

CHARACTERISTICS OF THE TWINS OF SCHIZOPHRENICS AS FALLIBLE INDICATORS OF SCHIZOIDIA

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Further advances in research into the etiology of schizophrenia will depend on the identification of an unambiguous indicator of the genotype associated with the development of schizophrenia. Such an indicator would permit accurate assessment of the relatives of probands as “affected” or not, so that the data generated in twin and family studies could be tested for the best fit to various genetic models that have been proposed. Schizoidia or schizoid personality has been considered by clinicians to be such an indicator, but it has been beset by semantic and logical difficulties. Most troublesome has been the extent to which the concept implies (merely) a phenotypic resemblance to schizophrenia, or a genotypic connection with it, or both. Four different but overlapping meanings for the concept of schizoidia are presented, in an effort to clarify the semantic and logic involved. Following Popper’s notions about the testability and refutability of theories, the authors, identified with both monogenic and polygenic theories, apply the definitions to their first-hand observations of the cotwins in the Maudsley-Bethlem Schizophrenic Twin Study. Pushing the concept to its limit, 91% of 22 MZ pairs and 45% of 33 DZ pairs contained “disordered” cotwins.

Theories, which combine correct and false facts, are more dangerous to science than complete errors; and hypotheses, which are only “justified in a certain sense”, always create confusion because the necessary reservations cannot always be stated. Clearcut concepts can only be formed if we ruthlessly reject everything that does not belong to them, regardless of whether we are dealing with simple problems or with entire theories.

[Eugen Bleuler 1950, p. 465]

Those admirable strictures and logical criterion for a concept were contained in a footnote in Bleuler’s 1911 classic. Would that we could adhere to them in 1977. The identification of a reliable clinical phenotype (exophenotype) is paramount to further progress in discovering the etiology of schizophrenia since behavior-genetic analysis requires such an indicator, one without surplus meaning. Schizoidia or schizoid personality has been considered such an indicator since 1909 (according to Essen-Möller 1946) when Gadelius commented on the unreasonableness and inaccessibility to argument that he saw in relatives of schizophrenics; he labeled such traits “pre-catatonic”. Although Kretschmer’s theories (since 1921) popularized the idea of a schizoid dimension continuous with normal personality but differing quantitatively, the term schizoid probably originated in E. Bleuler’s clinic. Kahn, an assistant to Kraepelin, used the term in 1921 (cf. Essen-Möller 1946); his 1923 study on the offspring of dual-mating schizophrenics (*The Schizoid and Schizophrenia in Heredity*) aimed to elucidate the two separate genetic components that he posited as necessary for the development of schizophrenia — one for schizophrenic psychosis and one for schizoidia. The problems of definition he faced are with us today but it is little consolation that we have the insight.

Given the justifiable interest in the schizoidia concept, how would we ever know when we had an indicator that Bleuler might have accepted as "clearcut"? It would have to be reliably measured and independent of the state or stage of the schizophrenic process itself (ideally, it could be determined prenatally, but then we would have left the realm of psychopathology). It should be distributed differently in schizophrenics compared to persons with other psychiatric disorders and compared to members of the general population unrelated to patients (cf. Meehl and Rosen 1955). The next step would be to carry out family and twin studies to see whether in fact the concept as defined could be used as a genetic marker of the predisposition to schizophrenia. A good genetic marker would be present in the identical cotwins of probands whether the latter were unaffected, affected, or in remission (*pace* genetic heterogeneity *pro tempore*). It should occur to a much lesser extent in fraternal cotwins and siblings, and other relatives in a way to conform to some genetic hypothesis. Further barriers to the detection of a good indicator of schizoidia arise because of the dynamic nature of both personality and of genes; thus it may require a certain stage of development or an ethical stressor to reveal a phenotype relevant to the genotype of interest, schizophrenia (cf. Gottesman 1974).

When the record keeping manuals for psychiatric taxonomy are consulted (on both sides of the Atlantic) the following phrases recur in connection with the glossary definition of schizoid personality: excessive shyness, excessive reserve, conspicuous aloofness, notably introspective, and eccentricity of conduct. On the face of it such a list suggests some kind of precision in the description of a personality type that may be at a greatly increased risk for developing schizophrenia. Recalling that the life time risk for the latter is close to one per 100 of the general population surviving to age 55 (Slater and Cowie 1971), the fallibility of the descriptors as predictors becomes apparent too soon. For example, the work of MacFarlane et al. (1962) with the behavior problems seen in *normal* children observed over a 14 year period in Berkeley, California, reports the following peak prevalences of traits selected by us for their overlap with the phrases above from the world of psychiatry:

Excessive reserve	59% of 10 yr. old girls,	52% of 11 yr. old boys
Excessive shyness	37% of 11 yr. old girls,	22% of 12 yr. old boys
Oversensitiveness	53% of 6 yr. old girls,	59% of 10 yr. old boys
Somberness	33% of 6 yr. old girls,	36% of 5 yr. old boys

Singling out the trait of oversensitiveness, the authors comment that it was like the common cold, almost everybody had it (p. 114). The conclusion is obvious: traits with such high base rates are useless in predicting an event that has a risk in the general population of 1%. The data on normal children make the data from the follow-up studies of shy, withdrawn children seen as patients in child guidance clinics less surprising. Morris et al. (1954) and Michael et al. (1957) found very few of such child patients grew up to be schizophrenic adults.

Given this latitude in the use of schizoidia, it is worth noting that investigators since Kahn differed widely in their reports of the prevalence of schizoid personality among relatives of schizophrenics. The rates for schizoid personality and schizophrenia in sibs of probands, respectively, were calculated as 3.6% and 11.5% by Luxenburger (1936) and as 31.5% and 14.3% by Kallmann (1938) (see Zerbini-Rüdin 1967, p. 499).

However, it is very important to distinguish between the prediction problem in the general population versus the one within the family of a schizophrenic proband. The point is made by Shields et al. (1974) with respect to Huntington's chorea.

"... let us assume that several children of parents with Huntington's disease are observed to be fidgety and that it is hypothesized that they are the carriers of the abnormal gene. It is predicted that the fidgety children *in Huntington families* will develop Huntington's chorea and that their siblings will not, but it is not predicted that all fidgety children in the general population are at risk for Huntington's disease. To the extent that fidgetiness is a common characteristic of children, the indicator will be an imperfect one. Some children of Hunting-

ton's patients may be fidgety for reasons other than the specific Huntington gene... It makes sense to us to see whether a high risk hypothesis, genetic or environmental, works in schizophrenic families without arguing that it must work equally well in the general population."

It is our contention that not all theories about the etiology of schizophrenia are equally meritorious. As clinicians with a genetic bent and a Popperian conscience, we believe that the theories should be pushed to their limits and hazarded to refutation, or, at the least, made ready for testing. We are enthusiastic about, but not committed to, two different genetic theories each of which provides for important contributions from the environment broadly defined (Gottesman and Shields 1967 and 1972, Heston 1970, Shields 1971, Shields et al. 1975). The balance of this paper shows the result of confrontation and compromise between polygenic and monogenic orientations towards the etiology of schizophrenia in the service of testability and refutation. Although we confidently expect our brethren in the fields of molecular biology and developmental genetics to administer the *coup de grace* to the Hydra-headed schizophrenia problem, their strategies will proceed most efficiently with guidance from psychiatric geneticists experienced in twin and family studies (cf. Shields and Gottesman 1973).

SEMANTIC CONFUSION VS. SEMANTIC CLARIFICATION

Semantic and logical problems have plagued the concept of schizoidia from the beginning. Most troublesome has been the extent to which the concept implies a phenotypic resemblance to schizophrenia, or, a genotypic connection with it, or, as Essen-Möller (1946) believed, both. We shall differentiate and define four uses of the term schizoid, three of which have no etiological implications:

Sd 1 Schizoid in the literal sense of resembling schizophrenia phenotypically but in a diluted fashion. This is how the word is used in the accepted diagnostic term *schizoid personality*, meaning shy, sensitive, aloof or eccentric (American Psychiatric Association 1968, General Register Office 1968). It does *not* imply a genealogical or etiological connection with schizophrenia. It shades into the normal. It can be extended to include paranoid personality. Though not standard usage, it could also be extended to cover persons such as those with a T score over 70 on the Schizophrenia scale of the MMPI or who score highly on a test of thought disorder that differentiates schizophrenics from others. It would not include depressives, criminals or the mentally retarded since they cannot generally be described as schizophrenic-like.

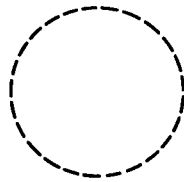
Sd 2 Psychiatric disorders occurring in the families (usually the twins or first degree relatives) of schizophrenics, *whether resembling schizophrenia or not*, and whether or not they occur more frequently in schizophrenic than control families. A genetic connection with schizophrenia is not implied. (These are the potential or eligible components for Heston's (1970) "schizoid disease".)

Sd 3 Disorders, whether occurring in a person who is the relative of a schizophrenic or not, that belong to a class found more often in the families of schizophrenics than in their controls. (These are akin to the "schizophrenia spectrum disorders" of Rosenthal and Kety's group, including those of the "extended" spectrum [Kety et al. 1974, Rosenthal 1975].)

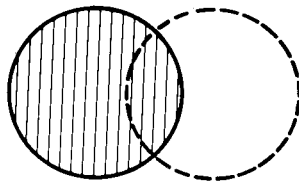
Sd 4 A diagnosis or behavioral trait or combination of traits, whether diagnosable as abnormal or not, which is believed to indicate either a probable carrier of the schizophrenic gene (monogenic hypothesis) or a high risk genotype (polygenic hypothesis). This usage resembles the schizotype of Rado (1962) and Meehl (1962, 1973), including the compensated schizotype, but is not necessarily wedded to Meehl's (1964) checklist of schizotypic signs or to a monogenic hypothesis.

Rather than arbitrarily modify the meaning of terms used by the DSM II, Heston, Rosenthal or Meehl, we shall refer to these uses of the term schizoid as *Sd 1*, *Sd 2*, *Sd 3*, and *Sd 4* respectively. *Sd 1*, 2 and 3 overlap to an extent that cannot be determined until much more extensive epidemiological and family investigations has been carried out using *Sd 1* and *Sd 3* as index cases.

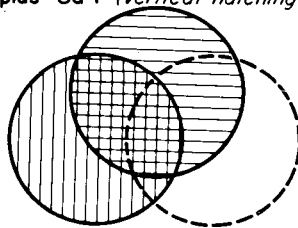
We shall illustrate the overlap of *Sd 1*, 2 and 3 schematically in a Venn diagram. Let us start with persons in a population who have *Sd 3* conditions. They are represented in the Figure by a circle



A. Persons with *Sd 3* conditions



B. Persons with *Sd 3* conditions (dotted outline) plus *Sd 1* (vertical hatching)



C. Persons with *Sd 3* conditions (dotted outline) plus *Sd 1* (vertical hatching) plus *Sd 2* (horizontal hatchings)

Fig. 1. Schematic of relationship between *Sd 1*, 2, and 3.

with dotted outline (A). These, then, are people with disorders of a kind found to occur more frequently in the relatives of schizophrenics than in controls. According to Kety et al. (1968) they would include criminals, and according to Heston (1966) some mentally retarded. Of course, which disorders are identified as *Sd 3* will differ from study to study, and their prevalence will differ from population to population. How far they may be related to schizophrenia genetically (*Sd 4*) is another matter. *Sd 1*, according to our terminology, means 'resembling schizophrenia'. While some *Sd 1* conditions, such as schizoid psychopathy according to the earlier investigators, almost certainly belong to *Sd 3*, other schizophrenic-like conditions may not necessarily distinguish schizophrenics' relatives from either other psychiatric or normal controls. Overinclusive thinking is one example (McConaghy and Clancy 1968); and it is unlikely that being *unmarried* (which some might conceivably call a schizophrenic-like condition) would be found in many studies to be a statistically significant *Sd 3* trait. Some overlap between *Sd 3* and *Sd 1* is illustrated in the Figure by the overlapping circles (B) in which *Sd 1* persons are represented by the vertically-hatched circle. The vertically-hatched area within the *Sd 3* circle brings out the point that only some *Sd 3* conditions resemble schizophrenia clinically.

We shall now add another circle to represent psychiatrically abnormal persons (other than schizophrenic) found among the relatives of schizophrenics, that is, what we are calling *Sd 2*. Some of these persons will suffer from *Sd 1* or *Sd 3* disorders, but others will have conditions such as anxiety states which neither resemble schizophrenia clinically nor are generally found significantly more often than in a control group. They are shown by the horizontally-hatched circle in the Figure (C) that also shows that there may be many *Sd 1* and *Sd 3* individuals who are not closely related to a schizophrenic. It has been suggested that people classed as schizoid according to each of these definitions might provide a better phenotype for genetic analysis than schizophrenic psychosis, and might give an indication of what is inherited. However, with each the question arises as to how homogeneous the group is genetically. Are all criminals (*Sd 3*), or all overinclusive thinkers (*Sd 1*), or all anxiety neurotics related to a schizophrenic (*Sd 2*), predicted to be high-risk candidates for developing and transmitting schizophrenia; and if not, what proportion of them are hypothesized as *Sd 4*, that is, schizoid in the genetic sense? Opinions on these points differ and are not well formulated. The search with which we and others are concerned is for an identifiable characteristic, whether dimensional or categorical in form, which is the best attainable indicator of *Sd 4* in a defined population. While one would probably look for such a characteristic within *Sd 1*, 2 or 3, we may note that all schizophrenic genotypes do not reveal themselves easily; very few schizophrenics have a close schizophrenic relative, and a majority are not schizoid premorbidly in either the *Sd 1* or *Sd 3* sense. It is obvious that considerable caution is required before claiming to have identified a phenotype which can be substituted for schizophrenia in population genetic studies. However, persons who are schizoid in any of these senses may provide promising leads towards a better understanding of the development of schizophrenia at a biological or any other level. In particular, the relatives of schizophrenics remain a strategic population.

NORMALITY AND SCHIZOIDIA IN TWINS OF SCHIZOPHRENICS

Many kinds of data from different kinds of studies on the biological and adoptive relatives of schizophrenics could be used to illustrate the problems so far mentioned. In this paper we shall limit ourselves to the use of some recent twin studies including new analyses of our own Maudsley-Bethlem twins. In another paper (Shields et al. 1975) we shall examine the utility of *Sd 1*, 2, 3, and 4 in family and adoptee studies. With cotwins we can note what disorders were found (*Sd 2*), ask which ones were schizophrenic-like (*Sd 1*), and which ones occur more frequently than in control groups (*Sd 3*). Assuming that some of the disorders indicate a schizophrenic genotype, what we call *Sd 4*, do they fit some monogenic or polygenic hypothesis?

The newcomer to this field might believe that the cotwins of identical twins who are schizophrenic should provide *direct* information about what constitutes the range of *Sd 4* phenotypes indicating the presence of a schizophrenic genotype. Even if we ignored the relatively rare nongenetic symptomatic schizophrenias (cf. Davison and Bagley 1969), such a belief would be naive. It does not provide for the role of the environment at any point after fertilization in turning genes on or off differentially in the two members of our human clones, thus rendering their "effective genotype" non-identical. Reasons for many trait discordances observed in MZ pairs are manifold (cf. Gottesman and Shields 1972, Shields 1962) and cannot be detailed here. (Although random inactivation of the X chromosomes in female pairs and possibly of some parts of autosomes in all pairs may require some modification of the classical twin method, we will for now assume that all MZ cotwins of true schizophrenics will have a schizophrenic genotype coded in their nuclei and are *Sd 4*.)

In the face of these complications we can understand, on the one hand, Inouye's (1970) conclusion "... that where a monozygotic twin was affected with classical schizophrenia, its cotwin was usually distinctly deviated in personality. This agrees well with the early finding by Professor Essen-Möller, and accords with the well-known fact that there exists a peculiar personality deviation among family members of the patients affected with classical schizophrenia" (p. 95). And, on the other hand, Mosher et al.'s conclusion (1973) that "Our data from 'normal' and non-schizophrenic MZ cotwins

of schizophrenics do not support the hypothesis relating schizoidia to schizophrenia as we find a similar proportion of schizoid individuals in both groups" (p. 1175). Problems of sample size and follow-up (see especially Belmaker et al. 1974) aside, it is no wonder that in a landmark effort to restore descriptive psychiatry to its former credibility and to "scientize" it Wing et al. (1974) found no room for the term schizoid in their final list of 140 key symptoms to describe the "present state" from a psychiatric interview (they do have social withdrawal as one of their 140 but it feeds into a diagnosis of neurosis; schizoid personality *is* separately listed in their "Aetiology Schedule" as a kind of personality before first onset.)

In some studies the cotwins are as often neurotic as schizophrenic (narrowly diagnosed), and it is then sometimes implied (Kringlen 1967) that it is therefore only a tendency to mental disorder in general that is inherited. Do we then regard all neurotics as belonging to the schizophrenic spectrum? Clearly not. On the same argument, normality would be part of the spectrum too. In one study (Fischer 1973) 43% of MZ cotwins were clinically normal, a higher percentage than in any of the three other main categories employed.

Table 1 shows the extent to which normality and nonschizophrenic disorders were diagnosed in seven twin studies. Normality could be paired with severe as well as mild schizophrenia. Differences

Table 1. *Pairwise MZ Rates for schizophrenia, schizoid and other psychiatric conditions, and normality in some schizophrenic twin studies. (After Gottesman and Shields 1972)*

Study	Numbers of pairs	% Schizophrenia and ?schizophrenia	% Sd 1 schizoid ^a	% Sd 2 other disorders ^b	% Normal
Luxenburger ^c (1936)	14	72	14	—	14
Rosanoff et al. (1934)	41	61	—	7	32
Kallmann (1946)	174	69	21	5	5
Slater (1953)	37	64	—	14	22
Kringlen (1967)	45	38	—	29	33
Fischer (1973)	21	48	5	5	43
Gottesman & Shields (1972)	22	50	9	18	23

^a So diagnosed by investigators.

^b Included as examples: alcoholic, psychopath (Kallmann); psychopathic; suicide (Slater); alcoholic, character neurosis (Kringlen).

^c Only includes cotwins of certain schizophrenics.

in the reported "normality" rates shown may depend partly on the extent of the investigation and standards adopted for what is within the normal range, but they probably also depend considerably on the varying use made by different authors of the ambiguous term schizoid and whether persons with a few schizoid traits were regarded as normal or not. In his original report Tienari (1963) described none of his 16 MZ cotwins as schizophrenic. Six had other psychiatric diagnoses and 10 were normal; 12 twins, many of them healthy, displayed schizoid traits. Essen-Möller's (1941) and Inouye's (1970) results are also difficult to tabulate. Both regarded all nonschizophrenic MZ cotwins as schizoid (Inouye) or as having a characterological trait genetically related to schizophrenia (Essen-Möller). Mosher et al. (1973) reported that only 6 out of 15 nonschizophrenic MZ cotwins were schizoid, either in the DSM II sense or in being rated highly in respect of the traits which Slater (1953) thought were distinctive in the abnormal relatives in schizophrenics' families. Employing a more liberal interpretation of schizophrenic-like, we considered from the data presented by Mosher et al. (1973) that at most 10 out of 16 of their cotwins could be so described. However, Mosher's twin sample was selected in a nationwide survey for MZ pairs where one member of the pair was an

undoubted schizophrenic and the other was an undoubted nonschizophrenic and with both parents alive and very cooperative. The selective biases thus introduced are hard to evaluate but one result must certainly have been that the cotwins were an unusually healthy group, as in fact they are compared to the systematically ascertained twins (but cf. Belmaker et al. 1974).

Nevertheless, it cannot reliably be claimed, even when using very liberal criteria, either that nearly 100% of MZ cotwins are disordered (*Sd 2*) or that 100% are schizophrenic or schizoid personalities (*Sd 1*).

The Maudsley Schizophrenic Twin Series

It may be of interest to examine at first hand the recent Maudsley Hospital twin study from London (Gottesman and Shields 1972) with regard to possible pointers to a schizophrenic genotype (*Sd 4*) in the cotwins. We shall ask how many MZ and DZ cotwins of schizophrenics could be conservatively or liberally termed *Sd 1* or *Sd 2*; and we shall discuss the findings in terms of "schizoid disease" and polygenic theories. The results are shown in Table 2.

Of 22 MZ pairs in which a proband was definitely or probably schizophrenic according to the consensus of six diagnosticians, 11 (50%) were concordant for schizophrenia, using the same criteria for the cotwin. As shown below, 6 cotwins had nonschizophrenic but psychiatric consensus diagnoses. This gives an *Sd 2* rate of 77%, using a conventional standard for "disorder". However, only 2 of these 6 cotwins had disorders resembling schizophrenia (*Sd 1*) or of a kind that would fall into the "schizophrenia spectrum" of Kety et al. (1968).

Table 2. *Disordered (Sd 2) and possibly schizoid (Sd 1) cotwins of schizophrenics in the Maudsley Hospital Study*

Classification of cotwins		MZ pairs	DZ pairs
a. Schizophrenia or ?Schizophrenia (Consensus diag.)		11	3
b. Other diagnosis: Schizoid (clinical)		2	1
c. Other diagnosis: ?Schizoid (MMPI)		—	3
d. Other diagnosis: no evidence of schizoidia		4	5
e. Normal: ? <i>Sd 4</i> Schizoid (Essen-Möller)		3	—
f. Normal: ?Schizoid (MMPI and/or clinical)		—	3
g. Normal: No evidence of schizoidia		2	18
Total		22	33
<i>Sd 2</i> , consensus	a + b + c + d	17 (77%)	12 (36%)
<i>Sd 1</i> , maximum	a + b + c + e + f	16 (72%)	10 (30%)
<i>Sd 1</i> , maximum, or <i>Sd 2</i>	a + b + c + d + e + f	20 (91%)	15 (45%)

Probably Sd 1 schizoid disorder. MZ 14B, male, aged 20. Consensus diagnosis was Personality Disorder (inadequate, hypochondriacal). Some individual judges' diagnoses were (Meehl) pseudoneurotic schizophrenia, (Slater) inadequate personality, and (Essen-Möller) "schizophrenia-related personality". Psychotic appearing MMPI profile (8*56' etc.). He had quite fixed ideas about having ulcer disease for which he treated himself, but it has never been found after repeated examinations. His verbatim language from a tape recorded interview was scored for schizophrenicity using the methods of Gottschalk and Gleser (1969) by Arnold (1971); his G-G score was 5.58. The median score for all schizophrenics in our scored sample of twins was 6.5, for other psychiatric diagnoses, 3.0, and for normals, 1.4; only schizophrenics scored above 6.8.

MZ 16B, male, aged 44. Consensus diag. Personality Disorder (paranoid). Called a schizotype (Meehl) and schizophrenia-related personality (Essen-Möller). He refused both the MMPI and to have the interview tape recorded; was suspicious, resentful, humorless, irritable, showed little capacity for warmth but was married with one child and had never sought psychological help.

Probably not Sd 1 schizoid disorder. MZ 5B, female, aged 42. Consensus diag. Neurotic depression, anxiety. Schizoidia never suspected but her G-G score was 6.03 and her confession of lesbian interests was difficult to integrate with the rest of her personality. MMPI clearly neurotic (31'742' etc.). MZ 9B, female, aged 47. Consensus diag. Neurotic depression, anxiety. Schizoidia never suspected clinically, MMPI within normal limits. Her proband sister in our unblindfolded opinion had a symptomatic schizophreniform psychosis caused by a long history of alcoholism. MZ 18B, female, aged 37. Consensus diag. Personality disorder (hysterical), anxiety. Hospitalized 51 weeks for neurosis at age 20, and chronic attender at psychiatric outpatients since. Called pseudoneurotic schizophrenia (Meehl), inadequate personality (Slater), neither normal nor schizoid (Essen-Möller). Refused MMPI but her G-G score was 6.02. Two brothers were psychiatrically hospitalized but our information was inadequate to arrive at diagnoses. Her proband sister had a recurrent schizoaffective illness that responded to reserpine. MZ 24B, female, aged 40. Consensus diag. Post-partum depression. Hospitalized briefly at 31. Very normal at interview as was her MMPI. G-G score was zero.

The brief summaries above may underestimate the prevalence of *Sd 1*. In addition to the 2 cotwins with probably schizoid disorders, there were 3 psychiatrically normal cotwins who had schizophrenia-related personalities (*Sd 4*) according to Essen-Möller's review of their histories. That could bring the total with schizoidia, more broadly defined, up to 5. The 11 consensus schizophrenic plus the 5 possibly schizoid cotwins account for 72% of the 22 MZ pairs. In addition there was one cotwin (MZ 4B) of a mild schizophrenic who, at age 39, had an MMPI (98' etc.) that would have led to a suspicion of a schizoaffective disorder had she not appeared unremarkable clinically; later, however, her G-G score turned out to be 6.80, the only nonschizophrenic to score that high. The other normal MZ cotwin (MZ 20B) shows nothing of schizoidia at age 46, with a G-G score of 0.93 and a very normal MMPI. Her proband sister has, in our opinion, a symptomatic schizophreniform psychosis associated with thyroid disease; her G-G score was only 1.43 and her MMPI (4'etc.) did not even suggest *Sd 1* schizoidia.

In the Maudsley study the premorbid personality of the first (schizophrenic) twin was, so far as we could judge, schizoid or probably so in only 8 of 22 pairs. It is well known that many schizophrenias develop in personalities that are not *Sd 1* schizoid (Bleuler 1972); we should not expect all MZ cotwins of schizophrenics to be schizoid in the sense of *Sd 1*.

Of the DZ pairs, 3 out of 33 (9%) were concordant for schizophrenia. Nine cotwins (3 of them hospitalized) had other disorders; these were mostly anxiety or depression, sometimes mild and transient. They bring the *Sd 2* rate to 36%. Some of these other disorders, it was thought, could be accounted for by environmental stress or by depressive or other nonschizoid personality traits shared with the proband. Only one was generally regarded as a schizoid personality (DSM II sense), but 3 others among the 9 appeared to have a noteworthy schizoid element when the MMPI was considered. Among the normal cotwins a further 3 might be regarded as schizoid on MMPI and/or other evidence. The maximum concordance for schizophrenia or schizophrenic-like personality (*Sd 1*) is therefore 10/33 (30%) in DZ pairs.

The MZ and DZ concordance rates for *Sd 2*, 77% and 36% respectively, and those for *Sd 1*, 72% and 30%, fall short of the 100% and 50% required according to the dominant "schizoid disease" (Heston 1970) hypothesis, which makes an effort to avoid the introduction of "incomplete expression". However, if we count cotwins who either are "disordered" or are normal but with a possibly schizoid personality, maximum rates of 20/22 (91%) MZ and 15/33 (45%) DZ are achieved, which fall very little short of those predicated. The critic may say, however, that the prediction of 50% affected DZ cotwins makes no allowance for the frequency of a gene supposed to be associated with the abnormalities that gave rise to the maximum rates. For example, if the posited schizoid gene had a frequency in the population of 10%, the expected risk in siblings (including DZ cotwins) of schizophrenics would be 56% rather than the 50% expected with rarer dominant gene conditions. The maximum rates of 91% in MZ and 45% in DZ pairs reported in Table 2 should also allow for the possibilities of environmental phenocopies and of genocopies causing some of the wide range of traits counted as "affected". In other words, allowance should be made for false positive contributing to the nice fit with dominant gene theory.

The alternative polygenic model — even less disprovable, according to its critics, looks for a well defined measure which gives good discrimination between MZ and DZ concordance rates (*Sd 3*, MZ vs. DZ), or which gives consistent estimates of heritability (not necessarily 100%!) (Smith 1974) independently derived from different kinds of relatives. In the context of the Maudsley study best agreement with the model was achieved with the diagnosis of schizophrenic psychosis itself, using standards that would be regarded as narrow in the US and broad in the UK. Shields and Gottesman (1972) have argued that similar diagnostic standards also work well in other recent twin studies. The search now should be for important contributory etiological factors; on the genetic side there may be no *single Sd 4* indicator.

HOPES FOR AN ENDOPHENOTYPE

Despite the different diagnostic and strategic procedures and the contradictory findings and interpretations to which we have drawn attention in our discussion of twin studies, perhaps the most promising pointers towards *Sd 4* remain in the area in the Figure where our *Sd 1*, 2, and 3 circles overlap: it is the broadly schizophrenic-like disorders, such as schizoid character and borderline schizophrenia, which most consistently distinguish the relatives of process schizophrenics from appropriate controls. Beyond that little can be said. After stretching our resources to their utmost extent, we are no nearer to identifying other possible high risk genotypes in schizophrenics' families. In the absence of good objective criteria for schizoid character and other "borderline" conditions and the consequent lack of adequate epidemiological and family studies of such conditions, it cannot be claimed that we have an improved phenotype for population genetic studies.

At this point it might be helpful to see what can be learned from genetic diseases that are more completely known than schizophrenia. First, diabetes, which in its population genetics is remarkably like schizophrenia. As in schizophrenia, 45-50% of the MZ cotwins of affected persons are concordant. Then, if diabetes is defined as an abnormality in a glucose tolerance test (sometimes performed after an evocative stimulus), some of the remaining cotwins will be "chemically" diabetic (Gottlieb and Root 1968). Finally, if the plasma insulin response of cotwins who still seem normal is measured, it appears that nearly 100% will have a measurable abnormality (Cerasi and Luft 1967, Pyke et al. 1970). One problem here is that of genetic *expression*. What level of expression will we define as disease? What trait — overt diabetes, an abnormal glucose tolerance curve, or the plasma insulin response — is the best one for genetic analysis? Because severity of disease generally turns out to be important in medical genetics, perhaps all three traits will be useful depending on one's purposes. And even plasma insulin levels are removed from gene action so there will no doubt be other levels of trait definition to come. Although we think that the analogy to diabetes gives much to ponder that we will not make explicit, we will make the main points that expression of a genotype can vary widely indeed and that the comparatively extremely crude level at which the phenotype is assessed in schizophrenia is reason for humility and flexibility, not dogmatism.

A second useful example is the Lesch-Nyhan syndrome. This bizarre X-linked syndrome features a severe neuromuscular disorder, self mutilation, and mental retardation. The defective enzyme (hypoxanthine guanine phosphoribosyltransferase) has about 0.005% of normal activity in the erythrocytes of affected persons. Now the activity of the same enzyme is deficient in an extraordinary range of other disorders found in Lesch-Nyhan families as well as families located through probands with one or another of those other disorders. Enzyme activity in the range of 0.01% to 0.5% of normal is associated with neurological disorders ranging from retardation to spino-cerebellar syndromes of variable severity. Levels of about 1% of normal are associated with gout (Kelly and Wyngaarden 1972, Seegmiller 1972). Certainly some of this clinical and biochemical variability will be associated with different mutations causing different amino acid substitutions in the same enzyme. Some variability can be attributed to differential modification of the enzyme's activity by environmental factors and by the balance of the genome. That the amount of protein translated from a mutant locus varies between families implicating modifying factors of the sort needed has been demonstrated

in the case of sickle cell hemoglobin (Nance and Grove 1972). The main point is a simple one. There would be no possible way on clinical grounds to group all of the clinical disorders associated with deficiencies in the activity of this one enzyme into one clinical syndrome, not even those disorders appearing in one family. Again, tentativeness and humility are prescribed, but there is the further point that familial clustering of disease provides a logical classification, even if the diseases are very dissimilar at the phenotypic level.

From what we have said about semantics, sampling, and other problems, we may not expect ready agreement about the most valid indicators of the schizoid state genetically (*Sd 4*). We should certainly strive for some better indication of "what is inherited" than a mid-Atlantic diagnosis of classical schizophrenia. But without further advances in the basic biological sciences, the testing of promising leads will be a laborious and, some might think, a fruitless proceeding. It involves the lengthy follow-up of strategic populations relevant to the transmission of schizophrenia. We have mentioned the desirability of prospective investigation of loosely schizophrenic-like (*Sd 1*) and *Sd 4*-suspect subjects (e.g., the thought-disordered or eccentric or physiologically over-reactive), to discover how many of them and their relatives develop definite schizophrenic psychoses; and we need to know what becomes of the offspring of the matings of couples both of whom suffer from suspected schizophrenia spectrum disorders, both in known "schizophrenic" families and in unselected samples from the general population.

Because doing such studies would expend prodigious labor to seek uncertain rewards, we think the best hope for the resolution of the schizophrenia problem may have to await the finding of a protein which differentiates schizophrenics from others. Short of that, close genetic linkage to a marker gene might be a possibility, despite the acknowledged difficulties (Jayakar 1970). However, the difficulty in distinguishing "affected" from "unaffected" family members, particularly in the younger age groups, would be likely to upset the arithmetic of linkage calculations (too many *Sd 4*'s who are not even *Sd 1* or *Sd 2*); the attempt might also founder because on a polygenic model there would be too many genes and on a monogenic model too many extraneous influences on expression.

Our hopes lie more with an endophenotype associated with the pathogenesis of schizophrenia. The characteristics of a good biological indicator of this kind have been outlined by Shields and Gottesman (1973). A biological advance may give us a better chance of solving some of the genetic problems in schizophrenia and the schizoid than distilling and juggling clinical categories and test scores. A reliable biochemical measure might help to decide between competing genetic models, discover what psychopathology should be described as schizoid, and identify individuals at high risk of developing a malignant psychosis. In principle, a better understanding of genetic etiology should lead to improved and rational environmental methods of treatment and prevention.

* It is in this sense that the concept has attracted the most attention. Scholarly reviews by Essen-Möller (1946) and by Planansky (1972) delineate much of the background against which our views should be considered. Despite the criticisms we level at the concept throughout this paper, we would not deny the heuristic value already proved for the term schizoid as a powerful explanatory variable in the hands of some investigators for some kinds of research closely related to our interests (e.g., Odgaard 1946 and Stevens 1969).

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