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Genetic Theorizing and Schizophrenia*

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Schizophrenia research embodies a microcosm of the vexing problems that confront the behavioural sciences, but particularly those disciplines concerned with psychopathology. We are ignorant of the means to prevent schizophrenia because we continue to be ignorant about its aetiology. Despite recognizable descriptions of the syndrome in ancient Hindu treatises (*c.* 1400 B.C.) and 76 years after its designation as dementia praecox by Kraepelin (1896), we are still grappling with such basic issues as when and how to diagnose Eugen Bleuler's (1911) 'group of schizophrenias' (cf. Katz, Cole, and Barton, 1968). Despite brilliant advances in molecular biology, neurochemistry, and brain-behaviour phenomena generally, we cannot pinpoint any necessary biological defect in all or most schizophrenics. Despite selfless expenditures of time and energy by gifted psychotherapists and sophisticated social science efforts, we cannot specify any necessary life experience, either at the level of the family or of a culture, common to all or most schizophrenics. While there is obvious merit in casting the problem in an interactionist framework, aetiology still defies an easy solution because we must then isolate what element(s) in the genotype interact with what element(s) in the internal and/or external environment (as well as when and how) to produce the phenotype we recognize as a schizophrenic one.

The wish for a simple aetiology with a then obvious rational treatment and eventual prevention is ever present. The 'stuff' of which such dreams are made emanates from our coveting the successes with pellagra, paresis, tuberculosis, polio, and PKU. It may turn out that our ambitions are doomed to failure at this stage of our technology and theorizing; in that case the important tasks become the elimination of unprofitable lines of inquiry, the reordering of priorities for new research as a function of our current knowledge, and the generation of refined, sharply focused hypotheses which, *in toto*, will add enough strands to the network of information about schizophrenia to permit its ultimate comprehension.

Is it not anachronistic, in this age of molecular biology, to look at *whole* human beings and their *behaviour*? Simpson (1964) and Dobzhansky (1968, p. 1), among others, have observed that 'There are two approaches to the study of the structures, functions, and interrelations of living beings—the Cartesian or reductionist and the Darwinian or compositionist.' Dobzhansky did not mean that the biological sciences could be dichotomized in this way, only that biological phenomena have both Cartesian and Darwinian aspects, and further, that the two aspects are both necessary and complementary.

Mayr (1964), another eminent evolutionist, elaborated the analytical and systems approaches to biology another way. In his view the biologist studies systems of increasing complexity ranging from molecules through organ systems and individuals to populations, species, and species aggregates. It becomes obvious that a system at any level is composed of elementary units which are themselves the systems of the level lower down. Mayr goes on to conclude:

'On each level it is equally legitimate to study either the system as a whole or the elementary units of the system, but we will not get the whole truth unless we study both. It is fortunate, both for physics and biology, that systems at higher levels can be studied with profit long before the elementary units at the lower levels are fully

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understood. The past history of biology has shown that progress is equally inhibited by an anti-analytical holism or by a purely atomistic reductionism' (p. 1235).

Main Grounds for our Emphasis on Genetic Factors

In support of the position we are proposing for genetic factors in theories about the aetiology of schizophrenia, we cite the following:

1. Our species is extremely diverse genetically. It is logical to expect that this genetic variability will occasionally produce a combination of genes that results in a *phenodeviant* (Lerner, 1958) at the extreme of a distribution. The work of Lewontin (1967) on blood group antigens and of Harris (1970) on enzymes suggests that about 30 per cent of all human loci are polymorphic, i.e. two or more alleles at a given gene locus, each with frequencies greater than ·01 (hence not explainable by mutation). The findings imply that 16 per cent of the loci coding for the structure of proteins in any one person will be heterozygous; using conservative estimates for the number of such loci (50,000) we each of us have about 8,000 loci at which there are two different alleles, each locus resulting in a distinct protein. (Genes responsible for regulation and organization are excluded from consideration at this stage of our ignorance.) Harris calculated that the probability of two persons at random having the same type of enzymes at only eight loci was 1 in 200; the most commonly occurring types would be found in 1·8 per cent of the population. He called the kind of diversity already demonstrated merely the tip of an iceberg.

2. Many morphological and physiological traits are known to be under some genetic control. Behavioural traits such as intelligence, social introversion, and anxiety have an appreciable genetic component, with data for some of these traits coming from animal strain difference and selection studies as well as from work with twins and families. It would be a surprise if schizophrenia were altogether exempted from analogous genetic influences.

3. No environmental causes have been found which will invariably or even with moderate probability produce schizophrenia in subjects unrelated to a schizophrenic. When cases of *folie à deux* are examined carefully, a high prevalence of schizophrenia is found among the genetic relatives of the induced (Scharfetter, 1970), thus shifting the focus from the role of inducer as a cause to one of precipitator, and a consequent refocusing on the *predisposition* of the induced.

4. Schizophrenia is present in all countries that have been studied extensively. Table I shows that in many the incidence is about the same despite great variations in ecologies such as child rearing practices. Such observations detract from assigning 'culture' a major causal role in the aetiology of schizophrenia.

Table I

Expectation of schizophrenia for the general population (From Slater, 1968)

Date	Country	N (age-corrected)	Expectation (%)	S.E.
1931	Switzerland	899	1·23	0·368
1936	Germany	7,955·5	0·51	0·088
1942	Denmark	23,251	0·69	0·054
1942	Finland	194,000	0·91	0·021
1946	Sweden	10,705	0·81	0·087
1959	Japan	10,545	0·82	0·088
1964	Iceland	4,913	0·73	0·121

5. Within modern urban communities there is a disproportionately higher incidence and prevalence of schizophrenia in the lowest social classes compared to the highest. On the face of it, such observations provide strong support for the role of social stressors as causes of schizophrenia. Evaluation of the data (e.g. Goldberg and Morrison, 1963; Turner and Wagenfeld, 1967) suggests that downward social drift of the patient is the major explanation for the excess of schizophrenia in the lower classes; however, some genetically predisposed individuals might have remained compensated had they been in a more sheltered class. Paradoxically, social stressors can be both predisposing and precipitating at different times. Kay and Roth (1961) in their study of late paraphrenia noted that social isolation was initially the effect of the preferences of schizoid people and secondarily a cause of their decompensation in that isolation removed various resources for adjustment in old

age. Fuller and Collins (1970) provided a clear experimental model for such a phenomenon in mice susceptible to audiogenic seizures; sound as a stressor precipitated seizures in certain predisposed genotypes (DBA) on first exposure but not in others (C57BL); on a second trial 'sensitization-induced seizure susceptibility' was observed in 60 per cent of the C57BL mice but it was seen in even more (81 per cent) of the hybrids carrying half their genes from the DBAs. Even when the stressor predisposed the mice to seizures, it did so as a function of the genetic predisposition.

Let us try to make it clear that we would not downgrade the part played by stress—it is after all half of the diathesis-stress model. We, as well as others, are unable to deal adequately with the concept of stress as an explanatory construct or as an intervening variable. Many of the difficulties plaguing the concept are confronted by Levine and Scotch (1970) and their colleagues and by Selye (1956). The simplistic flow chart

Stressor ⟶ Stress ⟶ Disorder

is all right as a starting point, but denies the important role we wish to assign to the '*stressee*'. Events which are apperceived as stressors depend on the genotypic *and* experiential uniqueness (e.g. intrauterine environment, perinatal hazards, learning history, exposure to CNS toxins, etc.) of the stressee; so do the kind and degree of stress responses, and so do the various disordered outcomes of the stress responses. The problems of specificity are far from solved and we don't yet have the answers. But why might the results of stress vary from hypertension to ulcer to schizophrenia?—perhaps because of the specific properties of the stressee.

6. There is an increasing risk of schizophrenia to the relatives of schizophrenics as a function of the degree of genetic relatedness, as can be seen in Table II. The familial distribution cannot entirely be due to environmental differences between families—the MZ concordance rate is higher than the DZ—or to gross differences within families such as sex or birth order. Table III presents the results of the earlier twin studies. These are simple pairwise rates without age correction and count as corcordant pairs in which the co-twin had any schizophrenic-like illness.

TABLE II

Expectation of schizophrenia for relatives of schizophrenics
(After Slater and Cowie, 1971)

Relationship	Total relatives (age-corrected)	Schizophrenic % (a)	Schizophrenic % (b)
Parents	7,675	4·4	5·5
Sibs (all)	8,504·5	8·5	10·2
Sibs (neither parent schizophrenic)	7,535	8·2	9·7
Sibs (one parent schizophrenic)	674·5	13·8	17·2
Children	1,226·5	12·3	13·9
Children of mating Schiz. × Schiz.	134	36·6	46·3
Half-sibs	311	3·2	3·5
Uncles and aunts	3,376	2·0	3·6
Nephews and nieces	2,315	2·2	2·6
Grandchildren	713	2·8	3·5
First cousins	2,438·5	2·9	3·5

(a) Diagnostically certain cases only.
(b) Also including probable schizophrenics.

TABLE III

The earlier twin series
(After Gottesman and Shields, 1966)

Investigator	Date	MZ pairs N	MZ pairs C	MZ pairs %	SS DZ pairs N	SS DZ pairs C	SS DZ pairs %
Luxenburger	1928	19	11	58	13	0	0
Rosanoff *et al.*	1934	41	25	61	53	7	13
Essen-Möller	1941	11	7	64	27	4	15
Kallmann	1946	174	120	69	296	34	11
Slater	1953	37	24	65	58	8	14
Inouye	1961	55	33	60	11	2	18

The more recent twin studies have usually been reported by the authors themselves as showing a range of rates, depending on what conditions are included as concordant. In our Maudsley twin study (Gottesman and Shields, 1972) we employed a diagnosis for both proband and co-twin which is based on the consensus of six diagnosticians from three different countries. They reached their opinions from summaries which did not refer to the diagnosis or zygosity of the other twin. The consensus diagnosis of schizophrenia, reflecting middle-of-the-road standards, gave better MZ/DZ discrimination

than attempts to apply very strict or very broad criteria, as Table IV shows.

The sampling methods in recent twin studies permit accurate use of the proband method in calculating concordance, which was not possible in some of the older studies and is theoretically more correct (cf. Allen, Harvald and Shields, 1967). Such rates show the proportion of independently-ascertained schizophrenics who have affected co-twins, i.e. are casewise rates. Table V shows our estimate of probandwise concordance in the recent research, using a criterion which approximates to the consensus diagnosis of our own study.

7. The difference in identical vs. fraternal twin concordance rates is not due to aspects of the within-family environment that are more similar for MZ than DZ twins although there are many such aspects. Studies of MZ twins reared apart as well as adoption and fostering studies show a markedly raised incidence of schizophrenia among relatives even when they were brought up in a different home by non-relatives. Heston's data are illustrative (1966) as shown in Table VI.

TABLE VI

Psychiatric disorders in foster home reared children
(After Heston, 1966)

	Mother schizophrenic (N = 47)	Controls (N = 50)
Mean age	35·8	36·3
Schizophrenia	5	—
Mental deficiency, IQ < 70	4	—
Sociopathic personality	9	2
Neurotic personality disorder	13	7

8. Such implicitly causal constructs as schizophrenogenic mothers, double-binding, marital skew, and communication deviance, have been found wanting (by others as well as ourselves), although we would not categorically deny them a role as possible precipitators or exacerbators of schizophrenia. The offspring of male schizo-

TABLE IV

Concordance in Maudsley schizophrenic twin study for consensus diagnosis and judges with the most extreme criteria for schizophrenia

	MZ	DZ	MZ : DZ
Judge with narrowest criteria			
Both twins first-choice schizophrenia	3/15 20%	3/22 14%	1·5
Consensus diagnosis of 6 judges			
Both twins schizophrenia, including ? schizophrenia ..	11/22 50%	3/33 9%	5·5
Judge with broadest criteria			
Both twins schizophrenia (including borderline schizophrenia) or schizotype	14/24 58%	8/33 24%	2·4

TABLE V

Concordance (proband method) in recent twin studies at a level approximating to the consensus diagnosis of schizophrenia

Investigation	MZ	DZ
Kringlen, Norway (1967)	31/69 45%	14/96 15%
Fischer *et al.*, Denmark (1969) ..	14/25 56%	12/45 26%
Tienari, Finland (1971)*	7/20 35%	3/23 13%
Allen *et al.*, U.S.A. (1972)*	52/121 43%	12/131 9%
Gottesman and Shields, U.K. (1972) ..	15/26 58%	4/34 12%
Total	119/261 46%	45/329 14%

* Male pairs exclusively.

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phrenics are as much at risk for the disorder as are the offspring of female schizophrenics. When both parents are schizophrenic the risk to their children is about 46 per cent; it is difficult to account for the absence of schizophrenia in the rest of the children on environmental grounds given such a schizophrenogenic environment; in what might be perceived as an even worse environment, one where one parent is a schizophrenic and the other is psychopathic, the risk of schizophrenia in the offspring is only 15 per cent. Both sets of data are, however, compatible with genetic theories of aetiology.

We close this section with a reminder that, paradoxically, it is the data showing that identical twins are as often discordant as concordant for schizophrenia that provide the most impressive evidence for the important role of environmental factors in schizophrenia, whatever they may be.

Genetic Models for the Mode of Transmission

Once the existence of a genetic diathesis has been established, it becomes important to provide a theory for the mode of its transmission. In the first instance theories provide a scheme for systematizing diverse pieces in a jigsaw puzzle. In the second, they encourage the formation of testable and refutable hypotheses; ideally they should compete with each other in such a fashion that one theory is made more credible and another less so when subjected to a test. Different genetic models have different implications for the kinds of studies to be conducted, for the kind of molecular pathology involved and hence the rational treatment, for possibilities of detecting premorbid cases, and for recommendations about the prevention of schizophrenia, e.g. through genetic counselling.

Models for the genetic mode of transmission in schizophrenia can be roughly classed into three categories, which can in turn be divided. The broad classes are monogenic or one major locus, genetic heterogeneity, and polygenic. Monogenic theories can be divided into recessive, requiring homozygosity or a double dose of a gene at one locus (one from each parent), and dominant, requiring only a single dose of some necessary gene (from one parent). Genes themselves are neither dominant nor recessive; the terms only have meaning with respect to a particular phenotypic characteristic. John and Lewis (1966) introduced the useful distinction between exophenotype (external phenotype) and endophenotype (internal), with the latter only knowable after aid to the naked eye, e.g. a biochemical test or a microscopic examination of chromosome morphology. As endophenotypes have become more available, the distinction between recessivity and dominance has become blurred; in a sense all genes are 'dominant' (cf. sickle-cell anaemia vs. sickling trait) when we have a way of detecting gene action molecularly. Like most inborn errors of metabolism PKU is the result of an enzyme deficiency inherited in a recessive fashion (two doses of a gene), but the heterozygote (one dose of the gene) can usually be identified. Enzyme deficiencies can also be inherited in a dominant fashion, e.g. porphyria. The difference depends on how far the normal homozygous state produces an excess of the minimal level needed for health. To quote Harris (1970, p. 252), 'Dominant inheritance of a disease due to an enzyme deficiency is most likely to occur where the enzyme in question happens to be rate limiting in the metabolic pathway in which it takes part, because the level of activity of such enzymes in the normal organism will in general be closer to the minimum required to maintain normal function'.

Dominant gene theories of schizophrenia which provide for the modifying effects on the phenotype of genes at other loci or other alleles at the same locus (cf. the G6PD polymorphism) are in practice difficult to distinguish from polygenic models; Slater's (1958; Slater and Cowie, 1971) particular model will be discussed below. A simple monogenic theory for all schizophrenic psychoses where the gene is sufficient cause for the psychosis has no advocates.

Genetic heterogeneity means different things to many people. It can mean that schizophrenia, like low grade mental deficiency, is comprised of many rare varieties of different recessive or dominant conditions with the mutation rate at each locus maintaining the genes in the population. One form of genetic heterogeneity is one

we *can* agree with—the model is like that of mental deficiency throughout its range; a very small percentage of schizophrenic cases are due to different dominant and recessive loci, a further group is due to symptomatic phenocopies (e.g. epilepsy, or amphetamines, or psychic trauma), but the vast majority are segregants in a normal distribution of a liability towards schizophrenia.

Polygenic models can be divided into continuous phenotypic variation and quasi-continuous variation or threshold effect. Examples of the former are height and IQ scores where extremes of a distribution may be labelled as pathological (dwarf or retardate) at some arbitrary point in the distribution; individuals just to the other side of the point are not distinctively different. The most widely known polygenic trait models posit a large number of underlying genes all of whose effects are equal; with traits so determined we would expect the phenotypic correlation between relatives to be the same as the genetic correlation if the traits are completely heritable. We find, for example, that the parent-child and sib-sib correlations for height or fingerprint ridge count are very close to 0·50. A less well-known polygenic model of importance to our thinking about a model for schizophrenia permits the gene effects to be unequal. Thoday (1961, 1967) has shown that, although bristle number in Drosophila is under polygenic control, 87·5 per cent of the genetic difference between the means of a high and a low line could be accounted for by only five of the many genetic loci involved. The implications of such a weighted gene model for schizophrenia are to encourage searching by the usual methods of segregation analysis and linkage for some few handleable genes which may prove to mediate a large part of the genetic variation in the liability to schizophrenia.

A polygenic model for handling discontinuous phenotypic variation, so-called threshold or quasi-continuous characters, also forms an important background to our thinking about schizophrenia. This model has made analysis of such traits as schizophrenia, cleft palate, diabetes, and seizure susceptibility feasible, provided one accepts the working hypothesis that the underlying liability is continuously and normally distributed. Falconer (1965, 1967), Edwards (1969), Morton *et al.* (1970) and Smith (1970, 1971) have illustrated the methods involved, and we (Gottesman and Shields, 1967) were the first to study psychopathology with such methods. Data on the occurrence of cleft lip with or without cleft palate, CL(P), in the relatives of probands can be used to illustrate the threshold model (Carter, 1969; Woolf, 1971). Schizophrenia is not present at birth like cleft lip so the analogy is wanting in this respect, but such elegant data for a disorder with both a variable age of onset and with the capacity for remission are not available yet.

The population incidence (q_g) of CL(P) can be taken as ·001 (Woolf, 1971). The risk in sibs is ·04, a low absolute value but a 40-fold increase over the population risk; in second degree relatives it is ·0065 and in third degree (first cousins), ·0036. The sharp falling off of incidence as one moves to more remote relatives is one of the tests for polygenic theory; a dominant gene theory calls for the frequency of affected relatives to decrease by 1/2 in each step. An important parallel between CL(P) and schizophrenia is that the risk to parents is about 1/2 that in sibs although both are classes of first degree relatives. In both disorders the reduced values probably represent the effect of social selection for who become parents; different values of q_g will be required to evaluate the significance to genetic theorizing of lower rates in parents when such selection is probable. Fig. 1 shows a diagram for the hypothetical distribution of the genetic liability to CL(P) or other threshold character, for the general population as well as first and third degree relatives.

The X axis is for normal deviate values of the posited polygenically determined predisposition or liability to the threshold trait. At a point on the X axis (not drawn to scale) corresponding to a value of ·001 (q_g) of the general population we can erect a vertical line (T) to represent the threshold value of liability beyond which all persons are affected; such a line would cut off 4·0 per cent of the sibs (q_r) and only 0·36 per cent of first cousins. The distances x/2, and x/8 in the figure are the increased means of the liability distributions for first and third degree relatives and are predictable from our general knowledge about genetic correlation between relatives, once A and G, the mean liability of affected persons, and of the general population, have been determined. A sharp threshold between the liability of affected and unaffected persons is artificial; the threshold model implies an increasing likelihood of

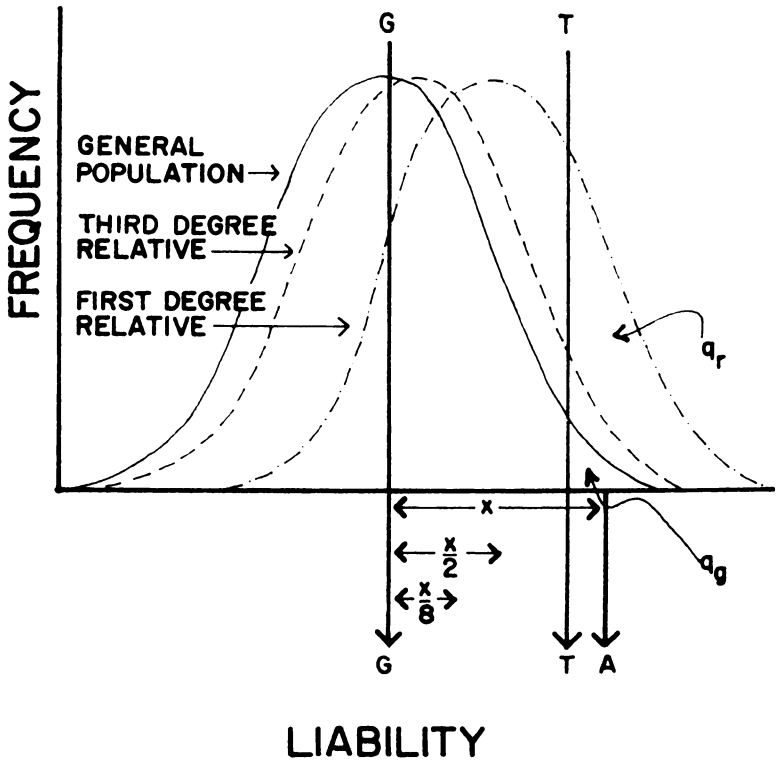

FIG. 1.—Model for polygenic inheritance of threshold characters: three distributions of the underlying liability in the general population, in first-degree relatives, and in third-degree relatives (see text for symbol definitions).

being affected as the polygenic predisposition increases (Edwards, 1969; Smith, 1970).

Support for the threshold model arises from a demonstration of a relationship between the severity of the defect in the proband and the risk to his relatives, based on the assumption that the more genes, the more severe the condition, and the more genes, the more the relatives will have when the amount is halved, quartered, etc. For CL(P) unilateral and bilateral affectation form two levels of severity; in the sibs of unilateral cases the risk is 3·83 per cent, in those of bilaterals, 6·71 per cent; and the generalization holds for other degrees of relatives. Further support for the theory comes from the demonstration that the risk to probands' relatives, say sibs, increases with the number of other relatives affected; i.e. families with two patients are more 'high risk' families than those with only one. In the case of CL(P), if no other relative is affected, the recurrence risk to a proband's sib is 2·24 per cent; if an aunt or uncle is affected, the risk rises to 9·91 per cent; finally if a parent is affected, the risk to the sib rises to 15·55 per cent. The malformation is too rare for there to have been extensive twin studies. From the available evidence Carter (1965, 1969) estimates the risk to the identical twin of a proband to be about 40 per cent.

From the above data estimates of the heritability of the underlying liability to CL(P) can be made. Heritability (h^2) is defined as the proportion of the total variability of the trait in the population that is due to genetic differences, in the absence of dominance and interaction between genes. The risks to MZ twins, sibs, and first cousins yield h^2 estimates (Smith, 1970) of 88 per cent, 92 per cent, and 100 per cent respectively, reasonably consistent values.

Compatibility Between Theory and Data

We shall deal with monogenic theories first. Recessive inheritance for schizophrenia is diffi-

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cult to support, since sibs are not more often affected than children Most monogenic theories invoke a dominant gene. Slater's final version of the theory which he first proposed in 1958 fits the pooled family data best when the population life-time risk for developing schizophrenia is taken as 0·0085 and the gene frequency as 0·03. Ninety per cent of schizophrenics will then be heterozygotes, so the trait is basically a dominant one. Only 13 per cent of heterozygotes manifest the psychosis; however, manifestation is complete in the 10 per cent of schizophrenics who have inherited the gene in double dose (Slater and Cowie, 1971). Elston and Campbell (1970) proposed a similar theory, derived from the application of rigorous mathematical methods to the data of Kallmann. According to this theory, the manifestation rate in heterozygotes is only 6 per cent or 7 per cent, even lower than the 13 per cent 'penetrance' on Slater's theory. Clearly such theories are still viable and have the merit of simplicity. They suggest that the search for a simply inherited biological error underlying all cases may not be in vain. The problem of how the abnormal gene can maintain itself in the population in view of the low fertility of schizophrenics prompts a search for compensating selective advantage, such as an increased resistance to virus infections early in life (e.g. Carter and Watts, 1971). However, no mendelizing defect has so far been identified in schizophrenia—unless it is, the theory will remain implausible for many. Anderson (1972) has pointed out that 'it is difficult to estimate the degree of penetrance unless the variations in phenotype can be identified unequivocally, and unless there is independent information establishing the mode of inheritance'. If the mode of inheritance is independently established as due to a dominant gene there is no objection in principle to invoking very low penetrances; Sewall Wright himself (1963, p. 178) cited a penetrance of 2 per cent for a gene associated with a morphological character in hybrid guinea-pigs.

To avoid invoking greatly reduced penetrance Meehl (1962, 1973) and Heston (1970) have concerned themselves with a phenotype broader than schizophrenia, the schizotype and schizoid disease respectively. Heston considers most studies to have shown about 50 per cent of the first degree relatives of schizophrenics to have some mental abnormality. The difficulty is that there is no reliable way of defining schizoid disease without reference to relatedness to a schizophrenic. If the concept is defined broadly enough to encompass abnormalities in 50 per cent of schizophrenics' parents, sibs, and children, and then generalized, the population base rate will be exaggerated and include many false positives. Nevertheless, there is certainly merit in carrying out family investigations based on borderline schizophrenics, schizoid personalities and the like in order to test a Mendelian hypothesis.

Heterogeneity theories are less well defined, so it is more difficult to say whether they are compatible with the data or not.

One class of heterogeneity theory claims that in principle schizophrenia can be divided aetiologically, though not necessarily clinically, into two groups: (1) a high-risk genetic group comprising a large number of individually rare genetic disorders, each with a very high manifestation rate and inherited as recessive (Dewey *et al.*, 1965), or as dominant traits (Erlenmeyer-Kimling, personal communication); and (2) a residual group of sporadic cases with a low risk of recurrence consisting on the one hand of fresh mutations and on the other of a group of cases of environmental or complex aetiology. Deafness, blindness, low grade retardation, and the muscular dystrophies are conditions which belong to this class. The theory avoids the *ad hoc* assumption of low penetrance, though in practice there are few schizophrenic families in which the risk to sibs is as high as 25 per cent. If there were many recessive loci for schizophrenia (as there are for deafness), dual mating parents would be unlikely to be of the same type, hence less than 100 per cent of the children would be affected, as is the case; but, the observed rate in children, 13·9 per cent, when only one parent is affected remains unaccountable. The consequences of dominant gene heterogeneity are essentially the same as those of monogenic dominance for the recurrence risk in families; however, the theory accounts better for the continuing prevalence of schizophrenia in the population without invoking

either unrealistically high mutation rates, as pointed out by Erlenmeyer-Kimling and Paradowski (1966), or speculative selective advantages for the heterozygote.

There is increasing evidence (Davison and Bagley, 1969) that some cases—the symptomatic schizophrenias—develop on the basis of organic pathology, e.g. Huntington's chorea, Wilson's disease, temporal lobe epilepsy, and amphetamine intoxication. Slater *et al.* (1963) believe that the pathogenesis of such cases may give important clues to the pathogenesis of the more genetic forms of schizophrenia.

Tests of Polygenic Theory

In this section we shall muster some of the lines of evidence which can be brought to bear on the relative merits of polygenic theory in accounting for the data on schizophrenia. One indirect approach we have favoured in the past consisted of an effort to evaluate the compatibility and consistency of independent estimates of the heritability (h^2) of the liability to schizophrenia, after assuming it could be a threshold trait (Gottesman and Shields, 1967). We now present a summary in Fig. 2 of an updated version of this approach. We used Smith's (1970, 1971) improvements to Falconer's method, our own consensus diagnosis pairwise MZ concordance rate (50 per cent) and DZ rate (9 per cent), and the pooled rate for sibs (10·2 per cent), offspring of dual matings (46 per cent), and second degree relatives (3·3 per cent). Six different values of q_p, the population risk, ranging from 0·85 per cent to 3.0 per cent, were used so as to show the effects on estimations of heritability values. Probandwise twin rates might have been more technically correct here, but they would not change the overall impression; the pooled probandwise rate for MZ twins in the recent studies approaches 50 per cent.

For Fig. 2 we have taken the rates in relatives at the level including probable schizophrenia; again the overall impression would have been little affected had we only used 'strictly' diagnosed rates. Earlier questions we and others raised about the suitability of the Falconer method for MZ twin data have been resolved by Smith's refinements; and since the child regression on midparent is the same as that for one MZ twin on his co-twin (1·0), we can calculate the h^2 from risks to dual mating offspring.

It is the consistency of the estimates rather than their absolute values which is our main concern. Fig. 2 shows the results of this procedure; the results are most consistent at values of population risk of about 1 per cent, yielding heritability estimates close to 85 per cent. It can be seen that the MZ and dual mating data are least sensitive to changes in q_p, while the second degree data are very much aeffcted by changes in q_p exceeding 1 per cent.

When pooled data on the risk to parents are subjected to the procedure, we must take account of the lower value of q_p in a sample selected for mental health (cf. Mednick *et al.*, 1971); by halving a risk of 1 per cent to 0·5 per cent and entering Smith's nomograph with a risk q_r for parents of 5·5 per cent, we obtain an estimate of heritability of 72 per cent, not too much different from the values of unselected relatives at q_p = 1 per cent. The consistency of h^2 estimates across relatives sharing different amounts of environmental communality provides one line of evidence in favour of polygenic theory.

Risk as a function of the number of relatives already affected with schizophrenia provides a further test of polygenic theory; (a) the increase in risk to probands' sibs depending on whether a parent was schizophrenic or not and (b) to children depending on whether one or both parents were affected. Simple monogenic theory would predict no increase in the case of sibs and a rise from 50 per cent to 75 per cent for children. However current modifications of monogenic theory predict a considerable rise under both (a) and (b). Slater and Cowie (1971) have calculated the extent of these increases for Slater's theory. We have compared the increased risks with those predicted by polygenic theory (Smith, 1971) taking q_p at 1 per cent and h^2 at 80 per cent as the tabled values closest to our interpretation of Fig. 2. The risks are given in Table VII. For sibs, both theories are equally good at predicting the empirical risks. In the cases of children when one parent is affected the observed risks are too high for both theoretical predictions; if Kallmann's data were omitted, or

TABLE VII

Schizophrenia risk as function of parent status

Risk (per cent)	(a) To probands' sibs		(b) To probands' children	
No. of parents affected —	0	1	1	2
Observed, Table II ..	9·7	17·2	13·9	46·3
Predicted, polygenic ..	6·5	18·5	8·3	40·9
Predicted, monogenic ..	9·4	13·5	8·8	37·1

if the median empirical risk (9·7 per cent) were used as a criterion, the fit with both theoretical predictions would be much improved.

Other tests not discussed here (cf. Gottesman and Shields, 1967; Slater and Cowie, 1971; Ødegaard, 1972) include: (a) the drop in risk as one moves from MZ twins, to first degree and to second degree relatives; (b) the association between severity in the proband and the risk to the relative; (c) the occurrence in relatives of

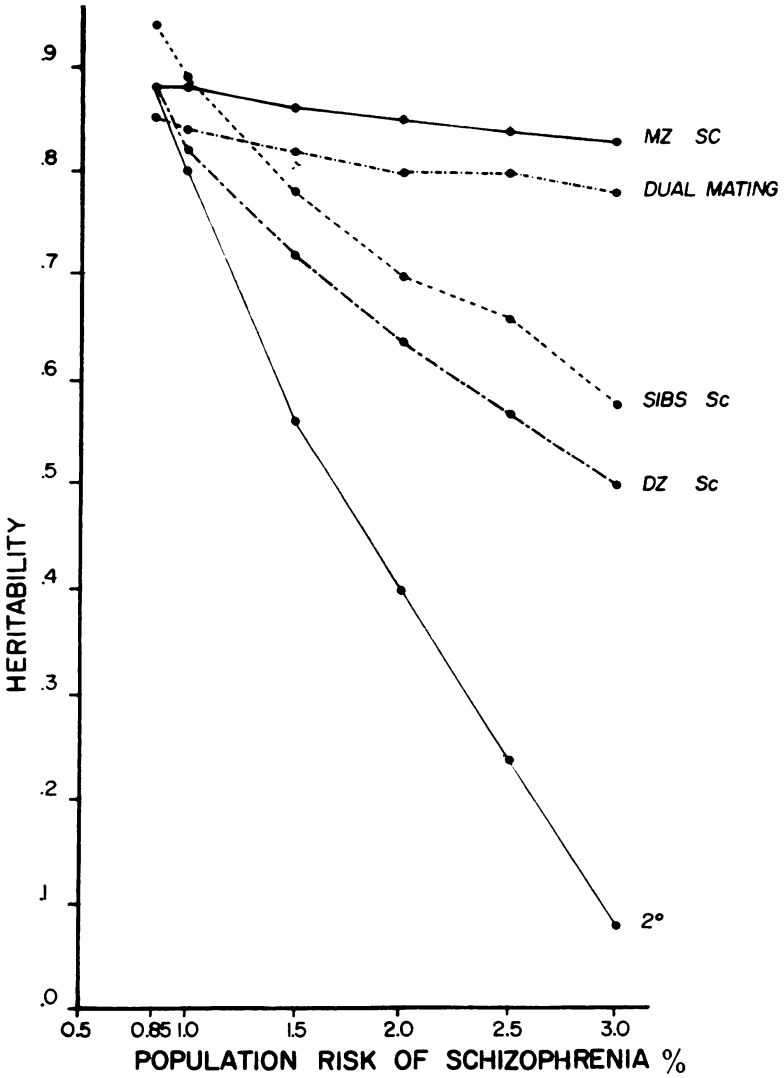

FIG. 2.—Heritabilities (Smith) of the liability to schizophrenia as a function of varying population risks (%), estimated from risks in different classes of probands' relatives.

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disorders other than strict schizophrenia, shading off into normality; and (d) the unilateral and bilateral familial distribution of affected relatives. The data are not free from ambiguity, but the first three tests tend to support polygenic theory, while the latter is consistent with a weighted polygenic as well as a monogenic model.

We agree with Anderson (1972) that it is not too helpful to rely on evolutionary theory in deciding among genetic models; we simply do not know enough about how any human behaviour evolved (cf. Gottesman and Heston, 1972). However, data on the fertility or Darwinian fitness of schizophrenics are interesting and important in their own right. The question of how a disadvantageous genetic condition can be maintained in the population over time despite the greatly reduced fitness of both male and female schizophrenics (e.g. Slater, Hare and Price, 1971) can perhaps be answered more readily by polygenic than monogenic theory. The former would obviate the need to find a selective advantage in gene carriers hypothesized by the balanced polymorphism theory of Huxley *et al.* (1964). Response to natural selection against a polygenic trait associated with lowered marriage and fertility rates would be very slow. Genes in the system would only be eliminated from the gene pool when they were present in the rare individual at the tail end of the distribution, while those below the threshold would not be subject to negative selection. Schizophrenics could be thought of as part of the genetic load, the price paid for conserving genetic diversity. In passing, we may note that high heritabilities suggest that the traits concerned may not have been objects of directional selection pressures and so may be irrelevant to the evolution of our species.

The evidence we have adduced in favour of polygenic threshold inheritance shows that it is an equal contender with current monogenic theories. On general grounds polygenic inheritance appears more likely to us; the commonest disorder for which single gene inheritance has been established, cystic fibrosis of the pancreas, is about 20 times rarer than schizophrenia. However, there is considerable overlap between the two principal models, and the tests proposed for differentiating between them are far from efficient. As Slater and Cowie (1971) say, 'Two genetical models are available, either of which provides an adequate framework for the observations, so that the worker is entitled to choose the model which suits his purposes best.' To these we would add heterogeneity theories. Our own preference for a polygenic framework leads us to look for specific and important contributing factors on both the diathesis and the stressor sides of the model. Refutation of a polygenic theory would come about by the discovery of an endophenotype which segregated in a monogenic way in all schizophrenics.

Factors Contributing to Liability

It would be both defeatist and incorrect to assume that because a trait such as the liability to schizophrenia is inherited polygenically the search for cause has ended and relevant specific genetic loci are undiscoverable in principle. The genes underlying continuous variation are not qualitatively different from those associated with discontinuous traits at the molecular level —both are subject to the same rules of inheritance because they are chromosomal and thus segregate, show dominance, epistasis, linkage, and genotype-environment interactions (cf. Penrose, 1938). From the beginning of this century geneticists have succeeded in identifying specific loci in polygenic systems and in locating them on specific chromosomes by linkage with major genes; however, the feats were accomplished with genetically tractable organisms such as wheat and *Drosophila* (Thoday, 1961, 1967). It is heuristically important to us to learn that whenever polygenic variation has been studied under *laboratory conditions* (e.g. inbreeding, backcrossing, availability of chromosome markers), 'a few handleable genes have proved to mediate a large part of the genetic variance under study' (Thoday, 1967). One locus in wheat accounted for 83 per cent of the variance in ripening date, with three others jointly accounting for 14 per cent. Such 'weighted genes' for bristle number were mentioned, but we must add the striking fact that separable components of the complex character permitted their study as more or less discontinuous variables. Wright (1934 a, b) concluded

that three or four major factors (genes) controlled the threshold character polydactyly in inbred lines of guinea-pigs.

Encouraged by the demonstration that the genes in polygenic inheritance need not be and often are not roughly equal in their effects on the phenotype, and bolstered by our clinical observations on what appears to be 'excess' similarity between pairs of affected relatives on the simpler equal effects assumption, we hazard the speculation that there are a few genes of large effect in the polygenic system underlying many schizophrenias. In other words, we view the aetiology of schizophrenia as being due to a weighted kind of polygenic system with a threshold effect. Some of the heuristic implications of our speculations about high value genes in the polygenic system underlying schizophrenia include a focusing on partitionable facets of the syndrome such as catatonia, paranoid features, protein polymorphisms in brain and blood, and neurophysiology, on the chance that family studies will reveal one or more of the high value genes. There are already suggestions in the human genetics literature that a gene associated with a biochemically different insulin in juvenile diabetics may be identified as one of the polygenes causing early-onset diabetes (Falconer, 1967), and one facet of congenital dislocation of the hip, joint laxity, may segregate as a Mendelian trait (Wynne-Davies, 1970).

The contribution of specific genetic factors to the genetic liability to schizophrenia analogous to the specific contributors in the diabetes and hip examples above forms only part of the picture in respect of the *total* liability to schizophrenia. General genetic contributors which serve as modifiers or potentiators, together with general environmental contributors which serve as modifiers or potentiators, each define dimensions of liability which combine with the specific genetic liability to determine the net liability and the position of an individual *vis à vis* the threshold at a particular time.

Diathesis-Stress and the Unfolding of Schizophrenia

A static depiction of schizophrenia is not very satisfying when it comes to communicating knowledge about the changes over time which add to or subtract from the combined genetic predisposition to schizophrenia. A dynamic picture of an individual's trajectory through life is needed to do justice to the concept of a genetic diathesis interacting with stress to produce the varieties of schizophrenic phenotypes (cf. Bleuler, 1968). Fig. 3 presents a trial scheme which incorporates the ideas of changes in the combined liability over time from environmental sources and from the environmental triggering of genes that had not been switched on at birth. The time axis starts with zero time at the moment of conception. Both chance (random) factors and ontogenetic constitutional changes will influence the trajectories, leading to both upward and downward inflections. Environmental stressors coming close together in time would be expected to exert a cascade effect and have more effect than the same stressors spread out in time.

G_1 is intended to indicate the trajectory of a person with a low (for schizophrenics generally) combined *genetic* liability to schizophrenia; over time environmental contributors to liability, say first the death of a spouse and then the onset of deafness, cause upward deflections of his trajectory to the threshold (T), culminating in a late-onset paraphrenia. The dashed line at the bottom of the zone of the so-called schizophrenic spectrum disorders (Kety, Rosenthal *et al.*, 1968) is intended to convey the idea of a possible need for a second threshold in our model; Wright (1934b) invoked a second threshold to account for the imperfectly formed fourth digit seen in crosses between a high and a moderate line of guinea pigs with liabilities to polydactyly.

G_2 could be the divergent trajectories of a pair of MZ twins; only the A-twin encounters the sufficient factors over time leading to schizophrenia for a person with his genotype. The B-twin at the time of observation is discordant for schizophrenia, but close to the threshold of schizophrenic spectrum disorders. Sub-threshold values of combined liability make it clear why so many first degree relatives can have normal MMPIs (Gottesman and Shields, 1972) and why two phenotypically normal parents are typical for the vast majority of schizophrenics. The A-twin is shown to have an acute onset with

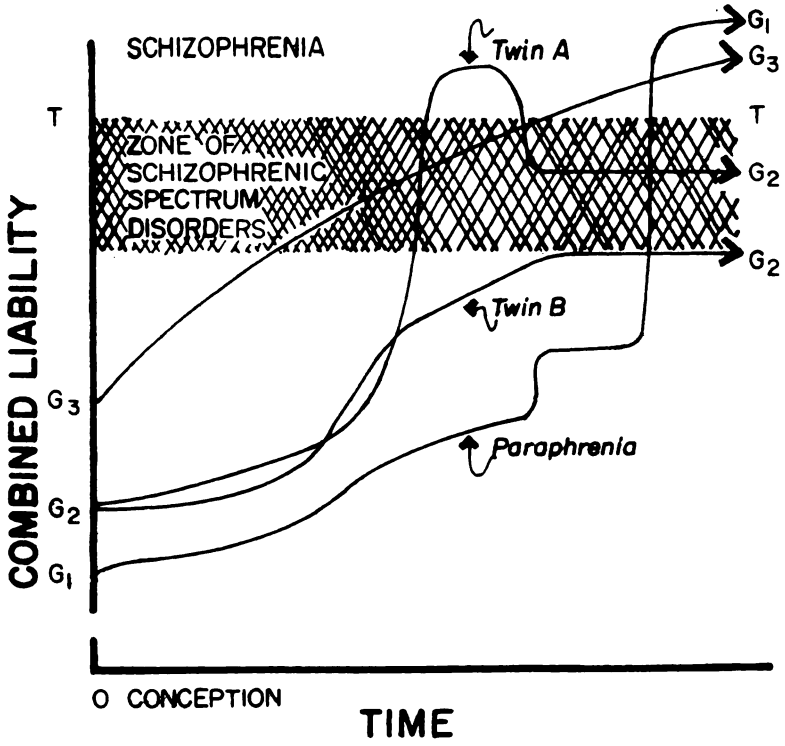

FIG. 3.—Schematic proposal for how diathesis interacts with stress in the ontogenesis of schizophrenia.

an undistinguishable premorbid personality, and a remission from schizophrenia into a chronic schizoid state.

G_3 is the posited trajectory of a person with a high genetic loading needing very little in the way of environmental contributors to make him schizoid; he is shown as having a poor premorbid personality, an insidious onset, and a deteriorating course. Many other life trajectories could have been drawn to illustrate the unfolding of schizophrenia. It is easy to see how the hospitalization data in pairs of twins and the fascinating histories of the Genain quadruplets (Rosenthal, 1963) would augment the total perspective about the pathogenesis of schizophrenia.

CONCLUSIONS

At the present time the case for a genetic basis for schizophrenia rests on the compatibility of the pattern of elevated risks to relatives with certain genetic models, together with the continued exclusion of any particular environmental factor as a sufficient cause. Ordinary Mendelian models will not do for explaining the mode of transmission for mental disorders since we find almost no families with 25 per cent or 50 per cent segregation ratios, and the population rates are so high as to make each condition 'common' by the standards for Mendelian diseases. Dominant gene models with incomplete penetrance, genetic heterogeneity models, and polygenic models are all viable contenders in the explanatory arena.

A satisfactory *corpus delicti* for the biochemical geneticist or cytogeneticist is not yet at hand. This does not mean that specific genetic factors play no part, or even that we must compare progress in the genetics of mental disorders unfavourably with that in other fields. In the first

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Annual Review of Genetics Robertson (1967) pointed out that, after years of control over such characters as milk yield in cows and egg size in poultry, we are surprisingly ignorant of the real biochemical or physiological differences between inbred lines. One of the most exciting challenges of the near future will consist of the best ways to synthesize the empirical facts about twin, family, and adoptee studies so as to lead to testable hypotheses.

Methods developed by Falconer, Edwards, and Smith permit the estimation of the heritability of the underlying predisposition or liability to developing a mental disorder, once the assumptions about the model being appropriate are accepted. Independent estimates from various classes of relatives lead to the convergence on a heritability value of about 80–90 per cent for the liability to schizophrenia. A weighted polygenic model (cf. Thoday on bristle number in *Drosophila*) offers hope that some facets of the schizophrenic phenotype will be shown to segregate or to have detectable biochemical or neurophysiological consequences.

It is important to understand the implications of finding that a trait such as the liability to schizophrenia has a high heritability. In the samples so far studied, it means that environmental factors were unimportant as causative agents of the schizophrenias. However, and this cannot be emphasized too strongly, these data do not permit the conclusion that curative or preventive measures will be ineffective. As Falconer (1965, p. 69) has pointed out, 'The environmental factors proved to be unimportant are those operating in the population sampled and these do not include special treatments or preventive measures. *No prediction can be made from a knowledge of the degree of genetic determination about the efficacy of curative or preventive treatments. All that could be said in such a case is that one will have to look outside the range of normal environments experienced by the untreated population.*' (Italics added.)

The beauty of a diathesis-stressor theory, or philosophy if you will, is that it fills the chasm between geneticism and environmentalism. Our preferred model for construing the syndrome of schizophrenia permits the clearer separation of aetiological and phenomenological considerations. It comprises a network of events connected by sequential causal arrows. A chain of consequences is set into motion by a variable, polygenically caused predisposition and culminates in a set of symptoms recognizable as schizophrenia. Feedback loops and chance have important roles in the total picture. Our construction clarifies how psychotherapy or phenothiazines or a good mother may each contribute to symptom amelioration without necessarily casting light on aetiological questions. It is our hope that a heuristic genetic theory about the aetiology of schizophrenia will hasten the day which brings it under man's control.

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