The Genetic Basis for Schizophrenia

By James Shields and Irving I. Gottesman, Ph.D.

When one talks about the genetics of schizophrenia, one can encounter a number of presuppositions in the audience. Many psychiatrists, psychologists, and sociologists today are skeptical whether genetic factors need to be considered at all. Lidz and his colleagues (1965), for example, believe that the existence of a genetic predisposition rests upon preconception and tradition, while evidence points to environmental and social factors. They regard schizophrenia as a deficiency disease, attributable to the faulty environment provided by the parents. Some geneticists are equally skeptical, not because they suppose heredity plays no part but because, on account of diagnostic and other complexities, they feel nothing can usefully be said at present about the nature or importance of heredity. Diabetes is a disorder with an established metabolic pathogenesis, and it has been described as a geneticist's nightmare (Neel et al., 1965); it is hardly to be wondered that some basic geneticists shy away from schizophrenia much as other people shy away from schizophrenics. For other geneticists, however, the problem is a challenge to be faced, and it is not one that any of us here can afford to ignore. Equally, it is not one which any of us can claim to have solved.

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Unlike mongolism or Klinefelter's syndrome or Turner's syndrome, schizophrenia is not caused by an extra or a missing chromosome. Unlike cystic fibrosis or the muscular dystrophies, it cannot be proved to be due to a single mutant gene or one of a number of such genes. For over 50 years it has been clear that the schizophrenic psychosis itself is not inherited as a simple Mendelian trait: fortunately for the families concerned, much fewer of the relatives of schizophrenics are similarly affected than the 50 percent of the brothers, sisters, parents, and children of patients with Huntington's chorea, a rare neurological disease of late onset which is inherited as a Mendelian dominant; and fewer, too, than the 25 percent of brothers and sisters in phenylketonuria, a rare form of severe mental subnormality due to a recessively inherited inborn error of metabolism. All simply inherited diseases are much less common than schizophrenia. It is very much an open question whether a simply inherited biological defect underlies all schizophrenics, while only a minority of individuals with the defect manifest the psychosis — certainly no such defect has been found as yet. The case for the existence of a genetic basis for schizophrenia must therefore rest partly on general grounds and partly on the exclusion of environmental causes as sufficient explanation of the findings. There is as yet no tie-up between the genetics and the biochemistry.

Among the general grounds for supposing that genetic factors make at least some difference to the risk of developing

schizophrenia are these (cf. Shields, 1968): first, the wide genetic variability in the population, leading to the virtually unique biochemical individuality of each person; second, the fact that no environmental causes have been found which will predictably produce schizophrenia in persons unrelated to a schizophrenic, or even significantly raise the risk; and third, the occurrence of schizophrenia with similar frequency in countries of different culture, the normal social class distribution of the parents of schizophrenics, the similar risks to the children of female and male schizophrenics, and the lack of any marked or agreed excess of schizophrenia associated with any particular birth order. With this third set of reasons, we are not implying that culture, class, maternal influence, or place in the family have no effect at all, merely that they are unlikely to reflect all important environmental causes of the disorder.

The more specific case for a genetic basis for schizophrenia rests on the combined evidence of many epidemiological, family, twin, and foster child studies of the disorder itself.

Incidence in Relatives

Let us now look at the various non-genetic hypotheses that have been put forward as alternative explanations at each step in the argument. The genetic case depends primarily on the raised incidence of schizophrenia in the relatives of patients. The first counter argument to be considered is that this supposed increased incidence is illusory: it could be that schizophrenia is much more frequent in the general population than is commonly realized and that the reported excess in relatives is the result of biased diagnostic practices. It is, however, generally accepted that there is good objective evidence of a significant familial clustering of cases.

The lifetime risk of someone from the general population becoming schizophrenic is about 1 percent. For the close relatives of schizophrenics it is about 10 percent, for second-degree relatives about 3 percent. These figures are based mainly on European studies which have been reviewed by Zerbin-Rudin (1967), Rosenthal (1970), Slater and Cowie (1971), and others. Table 1 shows the pooled data. (In America, different figures would obtain on account of a wider concept of the disorder.) Contrary findings have been exceptional. In 1963, in a study of all identical male twins born in Finland between 1920 and 1929, Tienari identified 16 schizophrenics, and none of their twin partners was similarly affected. Tienari (1968) himself has since reported a range of concordance rates from 6 percent to 36 percent in identical twins, depending on the criteria used.

Table 1

Expectation of Schizophrenia for Relatives of Schizophrenics

(after Slater and Cowie, 1971)

Relatives Relationship	Total (age-corrected)	Schizophrenic % (a)	(b)
Parents	7675	4.4	5.5
Sibs (all)	8504.5	8.5	10.2
Sibs (neither parent schizophrenic)	7535	8.2	9.7
Sibs (one parent schizophrenic)	674.5	13.8	17.2
Children	1226.5	12.3	13.9
Children of mating Schiz.xSchiz.	134	36.6	46.3
Half-sibs	311	3.2	3.5
Uncles and aunts	3376	2.0	3.6
Nephews and nieces	2315	2.2	2.6
Grandchildren	713	2.8	3.5
First cousins	2438.5	2.9	3.5

(a) diagnostically certain cases only

(b) also including probable schizophrenics

Identical and Non-identical Twins Reared Together

Accepting the raised incidence in relatives as genuine, we must next consider whether it could be due to family environment alone, that is, to characteristics perhaps of a cultural or social kind which distinguish

schizophrenics' families from others. This is where the classical twin studies come in. In these, the rate of schizophrenia in the genetically identical twins of schizophrenics is compared with that in the fraternal or genetically dissimilar twins, particularly those of the same sex. Both kinds of twins share the same womb, the same place in the family, and the same features of family social environment which differentiate schizophrenic from non-schizophrenic families. According to the family culture hypothesis as put forward to account for the disorder in uncles, aunts, parents, siblings, and children, the incidence of schizophrenia in co-twins of schizophrenic patients should be much the same whether they are genetically identical (monozygotic) or not. But if the genes are important, the concordance rate in identical twins should be significantly higher than in fraternal (dizygotic) twins.

On the face of it, the evidence from11 twin studies from eight different countries disproves the simple environmentalist hypothesis: in all but one, the identical concordance rate was at least three times the fraternal. This holds for the recent as well as the older studies. However, objections were raised to this conclusion. Twin studies are subject to various biases, biological, psychological, and methodological, and these, it was argued, resulted in spuriously high concordance rates in identical twins, particularly in some of the earlier studies (Table 2) reporting rates up to 86 percent.

Table 2

Concordance for Schizophrenia in the Earlier Twin Series

(After Cottesman and Shields, 1966b)

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

N = total number of pairs

C = number of concordant pairs

*The figures in Table 2 include Schizophrenic-like psychoses and information obtained on follow up. 4

It would be tedious to rehearse all the pros and cons of the twin method in general and of each schizophrenic twin study in particular, though later we shall say something about the more recent studies, including our own.

As regards the biological biases, many of these, insofar as they operate, would lead to an underestimate of the importance of nuclear genetic heredity compared with the postnatal environment: thus random errors in classifying twins as identical or fraternal would make genetic influences more difficult to detect; and prenatal differences between identical twins, such as those resulting from an unequal share of the cytoplasm or of the blood supply to the placenta, would make the twins less alike than they would otherwise have been. The psychological peculiarities of identical twinship, on the other hand, might make the identical twins more alike. Jackson (1960) argued that there was no nidus more favorable for the development of schizophrenia than being an identical twin, with its inherent problems of confusion of identity, weak ego formation, and the like. And many critics have pointed out that the environment is not quite so similar for fraternal as it is for identical twins: the latter might be treated more alike by parents, might themselves seek out more similar environments, and might more often influence one another. Such within-family factors, it was argued, might account for the closer resemblance of identical pairs. The first hypothesis - namely the supposed special schizophrenia risk for identical twins as such -is refuted by the finding, in several careful studies, that there is no excess of identical twins in populations of schizophrenics. To test the second hypothesis, we need to look at twins reared apart. There is now abundant evidence that concordance in identical twins is not entirely due to their having been treated alike in subtle ways by the same parents, or to their having lived together in a symbiotic relationship.

Identical Twins Reared Apart

Up until last month, the tally of pairs of

identical twins reared apart, at least one of them having schizophrenia, was 17, and of these 11 were concordant (Table 3), that is, both twins affected. This month, at the International Congress of Human Genetics, a Japanese psychiatrist, Inouye (1971), reported a further nine pairs; in three of them the second twin had a very similar severe schizophrenia, and in a further three a milder schizophrenic-like disorder. These 26 pairs (17 of them at least partially concordant) are not all as well documented or as representative as one would like, and some of Inouye's pairs were reunited in childhood; but the findings certainly do not suggest that concordance is any lower when twins do not share the same early childhood environment. However, Kallmann (1946) reported that adult twins who had been living apart for at least five years before the onset of schizophrenia in the first twin were somewhat less often concordant (78 per cent) than those who had been living together (92 percent).

Adoption and Fostering Studies

Some of the methodological biases believed to operate in twin studies derive from faulty sampling, contaminated diagnosis, and statistical errors, and these will be mentioned later when we come to our own attempts to avoid or evaluate them. Let us now take it that the case has been made for the importance of genetic factors in accounting for the difference between identical and fraternal twin concordance rates in schizophrenia, that is, in studies where the twins have been brought up together. Here many important environmental factors are held constant and the genotype varied. But what happens when the genotype is held constant and the environment varied? In addition to the mixed bag of identical twins reared apart to which we have referred, there have over the past five years been careful studies of parents and children, using the strategy of adoption and fostering studies. Biological parents normally provide their children with their early environment as well

Table 3 Schizophrenia and MZ Twins Reared Apart

Investigation	Age at separation	Number of pairs Concordant	Discordant	Source
Kallmann, Germany, 1938	Soon after birth	1	—	Daughters of schizophrenic proband
Essen-Moller, Sweden, 1941	7 years	1	—	In consecutive series of schizophrenic twins, followed up by Kaij (1960)
Craike and Slater, U.K., 1945	9 months	1	—	Single case report
Kallmann and Roth, U.S.A., 1956	Not stated	1	—	Index pair in series of preadolescent schizophrenics
Shields, U.K., 1962 Hospital twins	Birth	1	—	From consecutive series of Mauds ley
Tienari, Finland, 1963	3 years and 8 years	—	2	All twin births
Kringlen, Norway, 1967	3 months; and 1 year, 10 months	1	1	Index case in twin series
Mitsuda, Japan, 1967	Infancy	5	3	All investigated twins with psychiatric illness
		11	6	

as their genes. The parent-child resemblance in schizophrenia could result from the interaction of a faulty family environment with the predisposed genotype. Bring the child of a schizophrenic up in a different environment from that provided by his parents, and on this particular interaction hypothesis a lower incidence of schizophrenia would be expected to result. Two studies employing this strategy have been reported.

Leonard Heston (1966) followed up children born in Oregon State mental hospitals to chronic schizophrenic mothers and separated from them and their mothers' families at birth. The children were brought up in a variety of adoptive homes and institutions and, as adults, they were compared with a control group of non-psychotic parentage, matched for type of upbringing. Hes-ton's study included extensive personal investigation. From Table 4, it will be seen that schizophrenia was found only in the offspring of schizophrenics, and to an extent similar to that reported for the children of schizophrenics in general, for example, by Kallmann (1938). There was also considerably more abnormality of other kinds among the children of the schizophrenics. Much of this was of a kind that used to be described as schizoid psychopathy, but it is difficult to know how much of these other abnormalities might be accounted for genetically by the fathers, who may well have been of low intelligence or suffered from some kind of personality disorder, since they had impregnated women who were already chronic schizophrenics.

Table 4

Psychiatric Disorders in Foster Home Reared Children

(After Heston, 1966)

Mother Schizophrenic	**Controls**	
Number studied	47	50
Mean age	35.8	36.3
Schizophrenia	5	—
Mental deficiency, IQ < 70	4	—
Sociopathic personality	9	2
Neurotic personality disorder	13	7

The other study employing this strategy makes use of registers available in Denmark of adoptions, of mentally ill persons, and of changes of address. The work is a joint Danish-American enterprise, carried out by Drs. David Rosenthal, Seymour Kety, and Paul Wender of the National Institute of Health, and Dr. Fini Schulsinger and other psychiatrists and psychologists in Denmark. Extreme precautions were taken to avoid the hazards of contaminated diagnosis.

Table 5

Adoptees Study (Rosenthal et al., 1968) **Diagnoses of Adoptees (mean age 31.5)**

	Index cases	**Controls**
	Biological parent psvchotic	Biological parent not psychotic
Schizophrenia	3—i 21%. 2%	r-0
Borderline schizophrenia	5-"	M
Borderline schizophrenia	2	2
Schizoid, paranoid	3	4
Non-"spectrum" abnormality or normal	26	40
Total examined	39	47

Table 5 shows the provisional results of the study of which David Rosenthal was the first author (Rosenthal et al., 1968). The team examined children placed for nonfamilial adoption in Copenhagen between the years 1924 and 1946 where one of the biological parents was discovered to have become psychotic. At a mean age of 31, eight (or 21 percent) of the 39 children of psychotics were blindly diagnosed as having schizophrenia or borderline schizophrenia. This compares with only 2 percent of 47 control adoptees whose parents were not psychotic. You will see that the addition of "borderline, qualified", schizoid, and paranoid diagnoses did not help to discriminate between the groups. In other words, it would be misleading to suppose that it was just a schizoid or paranoid personality that was inherited, and that whether one then became more or less psychotic depended on

the environment. (Perhaps one ought to explain what "borderline, qualified" means. These are cases described in such terms as "pre-schizophrenic character, near borderline" and "borderline schizophrenia or pervert".)

In this study we are dealing with a wider concept of schizophrenia than in Heston's. The psychotic parents were not necessarily chronic schizophrenics, and indeed they included five manic depressives. The majority were not hospitalized until several years after their child was born, so the other spouses were probably more normal than were the fathers in Heston's study. So far as can be judged, the adoptive environments were less disruptive in the Danish study. These considerations might account for the relative absence of psychopathy in the children. Only one of the children had been in a mental hospital.

It may be noted that a more detailed analysis shows that the three unqualified schizophrenics among the offspring were all children of chronic or possibly chronic schizophrenic parents, and not of acute schizophrenic or borderline or manic-depressive cases. These conclusions are confirmed in a later report of the same investigation, based now on 76 index cases and 67 controls (Rosenthal, 1971).

The N.I.H.-Danish group also used the adoption strategy in another way, this time starting with a schizophrenic adoptee, not a schizophrenic parent. In the study of which Seymour Kety was the first author (Kety et al. 1968), the group first identified 33 adoptees on the register who had become schizophrenic, and then proceeded to search for any psychiatric records there might be for their biological and adoptive relatives. Relatives included in the search were parents, full sibs, and half sibs. A matched control group of 33 normal adoptees was also selected, and the records of their biological and adoptive relatives were studied. Final diagnoses were made blind by a panel of four.

The main findings are shown in Table 6.

The highest frequency of what the authors call "schizophrenia spectrum" disorders was found among the biological relatives of the schizophrenic adoptees. Thirteen out of 150 relatives (or 8.7 percent) had schizophrenia spectrum disorders, and seven of these were "definite" schizophrenics. In addition, the biological parents of schizophrenics had an excess of personality disorders which the authors tentatively called "extended spectrum." This concept includes character disorder, delinquency, and suicide. When only those adoptees were used who had been separated from their biological parents in the first month of life, the difference between the groups was fully maintained. There was no more schizophrenic-like abnormality in the adoptive families of schizophrenics than in those of controls (2.7 percent versus 3.1 percent) and there was little such abnormality in the biological families of no schizophrenic adoptees. The authors concluded that their findings supported the importance of polygenic genetic factors in the transmission of schizophrenia. There was no evidence from this study that the presence of schizophrenia or related disorder in the rearing family was a relevant stress influencing the future development of schizophrenia. Thus, the foster-child studies failed to refute the genetic interpretation of twin studies, just as the twin studies failed to refute that of the family studies.

Table 6

Schizophrenia Spectrum Disorders*

(Data of Kety et al., 1968)

Subjects	In Biological Relatives	In Adoptive Relatives
Schizophrenic Adoptees	13/150 (8.7%)	2/74 (2.7%)
Control Adoptees	3/156 **(19%)**	3/83 **(3.6%)**

*Schizophrenia (incl. borderline schizophrenia), certain or doubtful; and inadequate personality.

Recent Twin Studies

When we reviewed the schizophrenic twin studies a few years ago (Gottesman and Shields, 1966b) we said that, properly un-

derstood, they could be seen as replications of the same experiment. Findings in the adoption studies have led some of those who were previously most critical of genetics and twin studies to reach the same conclusion. We shall, therefore, comment only briefly on the criticisms of the older twin studies and the reasons for the lower concordance rates generally reported in the recent studies. There is, however, a good deal of overlap. A Swedish study by Essen-Moller in 1941 reported zero concordance for strict schizophrenia in seven MZ pairs*, while the recent Danish and English studies give substantial concordance rates of over 50 percent when expressed in terms of the risk for the co-twin of a schizophrenic suffering from a schizophrenic-like psychosis.

Kallmann's (1946) much-cited figure of 86 percent used an unrealistic method of allowing for age in discordant identical twins which exaggerated the concordance: the crude rate for definite schizophrenia was 59 percent and including uncertain cases it was 69 percent. However, the objection that Kallmann might have changed his diagnoses according to whether he thought the twins were identical or not was shown to be unwarranted when we analyzed the information on hospitalization and diagnosis which Kallmann gave to Kety (Shields et al. 1967). A major reason for Kallmann's high rates may be that his sample was based in large part on chronic deteriorated cases in the New York State Hospitals; according to some theories, such twins might be expected to have a higher concordance than the general run of schizophrenic twins.

Advantages of the recent studies are that they could be based on wider and more thorough sampling methods and include blood groups as an aid in deciding zygosity, that is whether the twins were identical or not. Einar Kringlen (1967) in Norway and Margit Fischer in Denmark (Fischer et al., 1969) were able to match national registers of all twins born with national registers of psychosis, and supplement the findings with extensive personal investigation. In this country we do not have such registers, but over a 16-year period twinship was enquired about systematically in about 45,000 consecutive admissions to the large outpatient and short-stay inpatient departments at the Maudsley Hospital in London, and we followed up the 57 schizophrenic pairs identified (Cottesman and Shields, 1966a, 1972). As in many other studies, we found an increased risk of schizophrenia in the identical co-twin when the illness in the Maudsley proband was severe; for instance, on the severity criterion of whether the proband on followup had been out of hospital for at least six months and was working, concordance in mild pairs was 27 percent compared with 80 percent in pairs where the proband was severe. Similarly, the risk for the co-twin was higher when the premorbid personality of the proband was assessed as schizoid.

Table 7 shows the pairwise concordance rates in the recent twin studies and the range of concordance reported by the investigators themselves. The upper limits include doubtful and borderline schizophrenics of various kinds (when diagnosed), but not non-schizophrenic abnormalities, except in the final study from the U.S.A. (Pollin et al., 1969; Hoffer and Pollin, 1970) to which we now turn.

Table 7

Recent Schizophrenic Twin Series

Range of Uncorrected Pairwise Concordance Rates for Schizophrenia or Related Disorder

	MZ Pairs		Same Sex DZ Pairs	
Investigation	Number	% Concordant	Number	% Concordant
Tienari (Finland)	16	6 - 36	20	5 - 14
Kringlen (Norway)	55	25 - 38	90	4 - 10
Fischer et al., (Denmark)	21	24 - 48	41	10 - 19
Gottesman and Shields (U.K.)	24	40 - 50	33	9 - 10
Pollin et al., (U.S.A.)	80	14 - (40)	146	4 - (11)

It may seem strange to cite a concordance rate of 14 percent as evidence in favor of genetic factors. Yet this is what the investigators themselves do, and rightly so. Identical pairs, they say, were 3.3 times as often concordant as fraternal pairs, a higher ratio than for any of the other 11 psychiatric or medical diagnoses included in their study. This study was based on over 15,000 pairs of twins where both twins had been fit enough to be called up to serve in the U.S. Armed Forces between 1941 and 1955. It is therefore selected for premorbid psychiatric health, and so one might predict a relatively low concordance rate. Yet when the rates are expressed in terms of the prevalence of schizophrenia in the twins of schizophrenics, compared with that in the total sample of 15,000 pairs of twins, the identical co-twins of schizophrenics were 24 times as likely to be affected with schizophrenia, and the fraternal co-twins 6.5 times as likely as an identical or fraternal twin picked at random. This may give some feeling of the importance of genetic factors even in this sample. These rates indicate high heritability of the predisposition to schizophrenia according to polygenic theory (method of C. Smith, 1970). Another possible reason for the low rate is that the diagnosis of schizophrenia may have been made more loosely in this study than in the others discussed here, and may include disorders of a kind where one would not normally expect the other twin to be schizophrenic. The upper range of concordance shown in the table, 40 percent and 11 percent in the two kinds of twin, include all co-twins known by the Veterans' Administration to have been psychiatrically treated; most of those with "other diagnoses" were hospitalized and so it is unlikely their illnesses were trivial. More recently, when schizophrenia was more carefully diagnosed, the MZ concordance rate increased (Allen et al., 1972; Shields and Cottesman, 1972.)

Diagnosis

We have more than once alluded to the problem of psychiatric diagnosis. It puts some geneticists off studying schizophrenia. It leads some critics to suspect contaminated diagnosis entering into concordance rates through the investigator being influenced in making his psychiatric diagnosis by his knowledge of whether a pair of twins is identical or not, or in deciding zygosity in the more doubtful cases by his knowledge of whether the twins are similarly affected. Some psychiatrists may lean over forwards in diagnosing schizophrenia or borderline schizophrenia in the twin - or a parent - of a schizophrenic, though maybe more lean over backwards in giving the twin the benefit of any doubt. Then there are the differing concepts of schizophrenia in the Scandinavian countries at the one extreme where they have very narrow and strict criteria, and in some U.S. centers at the other. How far do concordance rates differ according to the concept of schizophrenia used to select the probands and diagnose the co-twins?

It was in an attempt to tackle some of these problems that we invited psychiatrists from different countries and with different ideas about the importance of genetics and different concepts of schizophrenia to diagnose the histories of our Maudsley twins according to their own practice (Cottesman and Shields, 1972). This they did blindly from summaries of each of the 114 twins which did not mention whether the other twin was identical or schizophrenic. We can only mention the broad conclusions. Agreement as to whether a twin was schizophrenic, possibly schizophrenic, suffered from another diagnosis, or was normal, was close enough for a consensus diagnosis to be reached without difficulty. It was gratifying that (for instance) Dr. Eliot Slater, our former chief, and Dr. Loren Mosher, a psychodynamic psychiatrist from the U.S.A., agreed quite well about most of the schizophrenics and obtained similar concordance rates. The judges who deliberately used either very broad or very narrow standards agreed on a central core group, though they called it different names: the subjects diagnosed as having schizophrenia, questionable schizophrenia, or schizophrenia with two question marks by a British social psychiatrist

coincided very closely with those diagnosed as having chronic or acute schizophrenia (excluding borderline) by an American clinical psychologist. Greatest reliance can be placed on the consensus diagnosis of six diagnosticians. In our sample, the biggest difference between identical and fraternal twins was achieved with criteria, such as that of the consensus diagnosis, which would be regarded as fairly broad in this country and as fairly narrow in the U.S.A. Two pairs were rejected because they did not include a consensus schizophrenic. Counting the six cases of doubtful schizophrenia as affected, our consensus concordance rate was 11 out of 22 (or 50 percent) for identical pairs. This was 5.5 times as high as the rate of three out of 33 (or 9 percent) for same-sexed fraternal pairs. We have argued elsewhere (Shields, 1971) that classical schizophrenia remains a useful phenotype for genetic analysis. At present it appears that broadening the concept to include schizoid personality and other so-called spectrum disorders introduces increasing heterogeneity and many false positives. While some cases of neurosis or psychopathy or suicide may stem from a schizophrenic or schizophrenia-related constitution, it would be misleading to imply that most do.

It is obvious that the environment plays an essential role in the development of the psychosis. Discordance in identical twins is the strongest piece of evidence that this is so. However, it seems at present that the environmental factors are neither clearly defined nor specific for schizophrenia. The stresses that predispose or precipitate the disorder vary from the ubiquitous to the idiosyncratic. The hope is that prospective studies on high-risk groups such as the twins of schizophrenics will eventually discover controllable environmental factors which will help to prevent the development of schizophrenia in those genetically most predisposed.

Mode of Inheritance

What can we say about how schizophrenia is transmitted genetically? There are three classes of theory, heterogeneity, monogenic, and polygenic. There is certainly some heterogeneity. It seems that some schizophrenias can develop on a non-genetic basis, for instance the schizophrenia-like psychoses associated with epilepsy in which Slater, Beard and Glithero (1963) found no excess of schizophrenia in the relatives. And within the bulk of schizophrenia for which it is hypothesized that the genes play an important part, every schizophrenic does not have the same constitution — different genes contribute to the total picture, particularly as between the various Kraepelinian and other subtypes.

The essential difference between monogenic and polygenic theory is whether or not there is the one necessary major gene for virtually all schizophrenics. The monogenic theory which fits the family data best is that which Slater put forward in 1958 and further developed in his recent book with Valerie Cowie (Slater and Cowie, 1971). Elston and Campbell (1970) have put forward a similar theory. According to Slater and Cowie, the gene should have a frequency in the population of 3 percent. All who inherit the gene in double dose, one from each parent, will develop schizophrenia. These homozygotes will account for 10 percent of schizophrenics. The remaining 90 percent will be heterozygotes, carrying the gene in single dose; but only 13 percent of heterozygotes in the population will develop schizophrenia. According to Elstonand Campbell, heterozygote manifestation will be as low as 6 percent or 7 percent. The model of schizophrenia as a balanced genetic polymorphism, which Huxley et al. (1964) put forward, assumed that Slater's monogenic theory was essentially correct.

Polygenic models assume that the genetic contribution to schizophrenia is the result of the combined effects of many genes, no one of which is essential, rather as in the genetic contribution to stature and intelligence. The genetic predisposition in the population is graded, and some schizophrenics will be more genetically predisposed than others. An individual becomes affected when the total

genetic and environmental predisposition or "liability" reaches a threshold, corresponding to that part of the distribution which accounts for the prevalence of schizophrenia in the population. Methods are now available for estimating how much of the combined "liability" in the population is genetic. These estimates can be independently derived from various classes of relatives - twins, siblings, second-degree relatives such as uncles and aunts, the children of two schizophrenics, and so on. Using the method of Charles Smith (1970, 1971), developed from that of Falconer (1965), we have shown (Gottesman and Shields, 1972) that for a population schizophrenia risk of 1 percent, the heritability estimates from all these classes of relatives, sharing different amounts and kinds of environment, agree quite well and are of the order of 80 percent.

Both Slater and Cowie and ourselves have tried to see whether the one model fits the data better than the other. But the tests of each theory by and large come out with such similar predictions as to be non-discriminative. To give one example, the theoretical schizophrenia risk for the children of two schizophrenic parents was calculated by Slater and Cowie as 37.1 percent for their monogenic theory, and by us as 40.9 percent for our polygenic theory. The empirically observed rate from the pooled data from five studies lies between 36.6 percent and 46.3 percent depending on whether questionably schizophrenic offspring are included. For the present it may be largely a matter of taste which model one prefers to work with. Neither rules out the other. Monogenic theory would lead one to look for the effects of the essential main gene in some simply inherited biological defect. Polygenic theory leads to a wider search for contributing factors rather than for a single cause, but there are grounds for hoping that major contributing biological factors are there to be found: it is good genetic theory to suppose that some few genes may be doing most of the work in a polygenic system (Thoday, 1967).

In practice, the way in which one would set about looking for essential, or contributing, biological factors, relevant for understanding the genetic basis of schizophrenia, would not be so very different for the two theories: one would look at relatives. The hope would be to identify an endophenotype - a stable biological characteristic - which would identify a high - risk genotype. It should distinguish schizophrenics from other psychiatric patients; it should, of course, be replicable in more than one laboratory; and the same type of abnormality should be found in all identical co-twins, discordant and concordant, and in a significant proportion of relatives. This may be a tall order, perhaps a naive suggestion.

We do not suppose there will be any more agreement amongst biological scientists where to look than there is amongst psychodynamic theorists as to what type of family environment would be most likely to raise the incidence of schizophrenia in persons unselected as to heredity. But the search might at least turn up some useful clues.

It would be unfortunate, especially in an Association such as this, to raise false hopes in schizophrenics or their relatives that the cause and the cure lie just round the corner. Yet we cannot help feeling that the relatives would do better to supply specimens for the laboratory bench than lie on the analyst's couch.

Conclusion

We have tried to show that there is a genetic basis for schizophrenia and not just for mental abnormality in general, but its existence rests on general considerations and on the occurrence of schizophrenia in relatives of patients in a way that excludes any reasonable alternative explanation. Recent twin and adoption studies have helped to place the role of genetic factors in perspective. No simply - inherited enzyme deficiency or other biological defect has been demonstrated in schizophrenia so far, and it may be that inheritance is polygenic, as in most common disorders. If it is agreed that the genes are necessary but not sufficient for the development of schizophrenia, it follows

that the environment is also necessary but not sufficient. At present it appears that the environmental contribution is less specific, and that the genes have the privileged status of what has been called the most uniformly potent cause (Meehl, 1970),

The conclusion that both heredity and environment play a part is trite unless an attempt is made to identify major genetic or environmental contributions and their interaction. It would be wrong to hold out false hopes, but the evidence is such as to warrant the continued energetic biological investigation of schizophrenics and their relatives.

REFERENCES

ALLEN, M. C, COHEN, S., and POLLIN, W.: Schizophrenia in veteran twins: A diagnostic review. Amer. J. Psychiat. 128, 939-945,1972.

CRAIKE, W. H., and SLATER, E., (with the assistance of George Burden): Folie a deux in uniovular twins reared apart. Brain 68, 213-221,1945.

ELSTON, R. C, and CAMPBELL, M. A.: Schizophrenia: evidence for the major gene hypothesis. Behavior Genetics 1, 3-10, 1970.

M

ESSEN-MOLLER, E.: Psychiatrische Untersuchungen an einer Serie von Zwillingen. Acta Psychiat. Neurol. Scand. Suppl. 23, 1941.

FALCONER, D. S.: The inheritance of liability to certain diseases, estimated from the incidence among relatives. Ann. Hum. Genet. 29, 51-76, 1965.

FISCHER, M., HARVALD, B., and HAUCE, M.: A Danish twin study of schizophrenia Brit. J. Psychiat. 115,981-990, 1969.

COTTESMAN, I. I., and SHIELDS, J.: Schizophrenia in twins: 16 years' consecutive admissions to a psychiatric clinic. Brit. J. Psychiat. 112,809-818, 1966a.

COTTESMAN, I. I., and SHIELDS, J.: Contributions of twin studies to perspectives on schizophrenia, in B. A. Maher (Ed), Progress in Experimental Personality Research, Vol. 3. New York. Academic Press, 1-84, 1966b.

COTTESMAN, I. I., and SHIELDS, J.: Schizophrenia and Genetics: A Twin Study Vantage Point. New York, Academic Press, 1972.

HESTON, L.: Psychiatric disorders in foster home reared children of schizophrenic mothers. Brit. J. Psychiat. 112, 819-825, 1966.

HOFFER, A., and POLLIN, W.: Schizophrenia in the NAS-NRC panel of 15,909 veteran twin pairs. Arch. gen. Psychiat. 23, 469-477, 1970.

HUXLEY, J., MAYR, E., OSMOND, H., and HOFFER, A.: Schizophrenia as a genetic morphism. Nature (Lond.) 204, 220-221, 1964.

INOUYE, E.: Similarity and dissimilarity of schizophrenia in twins. Proc. Third Internat. Congr. Psychiat, Vol. 1, 1961. University of Toronto Press, 524-530, 1963.

INOUYE, E.: Monozygotic twins with schizophrenia reared apart in infancy. Abstracts of papers presented at the 4th Int. Congr. Hum. Genet. Excerpta Medica, International Congress Series No. 233, 93, 1971.

JACKSON, D. D.: A critique of the literature on the genetics of schizophrenia. In Jackson, D. D., (Ed.), The Etiology of Schizophrenia, 37-87. New York, Basic Books, 1960.

KAIJ, L.: Alcoholism in Twins. Stockholm, Almqvist and Wiksell, 1960.

KALLMANN, F. J.: The Genetics of Schizophrenia. New York, Augustin, 1938.

KALLMANN, F. J.: The genetic theory of schizophrenia. An analysis of 691 schizophrenic twin index families. Amer. J. Psychiat. 103, 309-322, 1946.

KALLMANN, F. J., and ROTH, B.: Genetic aspects of pre-adolescent schizophrenia. Amer. J. Psychiat. 112, 599-606, 1956.

KETY, S. S., ROSENTHAL, D., WENDER, P. H., and SCHULSINGER, F.: The types and prevalence of mental illness in the biological and adoptive families of adopted schizophrenics. In Rosenthal, D., and Kety, S. S. (Eds), The Transmission of Schizophrenia. Oxford, Pergamon, 345-362, 1968.

KRINGLEN, E.: Heredity and Environment in the Functional Psychoses. London, Heinemann, 1967.

LIDZ, T., FLECK, S., and CORNELISON, A. R.: Schizophrenia and the Family. New York, International Universities Press, 1965.

LUXENBURGER, H.: Vorlaufiger Bericht tiber psychiatrische Serienuntersuchungen an Zwillingen. Z. ges. Neurol. Psychiat. 116, 297-326, 1928.

MEEHL, P. E.: Personal communication, 1970.

MITSUDA, H.: Clinical Genetics in Psychiatry. Tokio, Igaku Shoin, 1967.

NEEL, J. V., FAJANS, S. S., CONN, J. W., and DAVIDSON, R. T.: Diabetes mellitus. In Neel, J. V., Shaw, M. W., and Schull, W. J., (Eds), Genetics and the Epidemiology of Chronic Diseases, 105-132. Washington, DC, U.S. Department of Health, Education and Welfare, 1965.

POLLIN, W., ALLEN, M. G., HOFFER, A., STABENAU, J. R., and HRUBEC, Z.: Psychopathology in 15,909 pairs of veteran twins: evidence for a genetic factor in the pathogenesis of schizophrenia and its relative absence in psychoneurosis. Amer. J. Psychiat. 126, 597-609, 1969.

ROSANOFF, A. J., HANDY, L. M., PLESSET, I. R., and BRUSH, S.: The etiology of so-called schizophrenic psychoses with special reference to their occurrence in twins. Amer. J. Psychiat. 91, 247-286, 1934.

ROSENTHAL, D.: Genetic Theory and Abnormal Behavior. New York, McGraw-Hill, 1970.

ROSENTHAL, D.: Two adoption studies of heredity in the schizophrenic disorders. In Bleuler, M., and Angst, J. (Eds), The Origin of Schizophrenia, 21-34. Berne, Huber, 1971.

ROSENTHAL, D., WENDER, P. H., KETY, S. S., SCHULSINGER, F., WELNER, J., and OSTERGAARD, L: Schizophrenics' offspring reared in adoptive homes. In Rosenthal, D., and Kety, S. S. (Eds), The Trans-

mission of Schizophrenia, 377-391. Oxford, Pergamon, 1968.

SHIELDS, J.: Monozygotic Twins Brought up Apart and Brought up Together. London, Oxford University Press, 1962.

SHIELDS, J.: Summary of the genetic evidence. In Rosenthal, D., and Kety, S. S. (Eds.), The Transmission of Schizophrenia, 95-126. Oxford, Pergamon, 1968.

SHIELDS, J.: Concepts of heredity for schizophrenia. In Bleuler, M., and Angst, J. (Eds.), The Origin of Schizophrenia, 59-75. Berne, Huber, 1971.

SHIELDS, J., and COTTESMAN, I. I.: Cross-national diagnosis of schizophrenia in twins: The heritability and specificity of schizophrenia. Arch. Gen. Psych. 27, 725-730, 1972.

SHIELDS, J., COTTESMAN, I. I., and SLATER, E.: Kallmann's 1946 schizophrenic twin study "in "the light of new information. Acta Psychiat. Scand 43 385-3% 1967.

SLATER, E.: Psychotic and neurotic illnesses in twins. Med. Res. Coun. Spec. Rep. Ser. No. 278. London, H.M. Stationery Office 1953.*

SLATER, E.: The monogenic theory of schizophrenia. Acta Genet. (Basel) 8, 50-56,1958.*

SLATER, E., BEARD, A. W., and GLITHERO, E.: The schizophrenia-like psychoses of epilepsy. Brit. J. Psy-chiat. 109, 95-150,1963.*

SLATER, E., and COWIE, V. A.: The Genetics of Mental Disorders. London, Oxford University Press, 1971.

SMITH, C: Heritability of liability and concordance in monozygous twins. Ann. hum. Genet. 34, 85-91,1970.

SMITH, C: Recurrence risks for multifactorial inheritance. Amer. J. hum. Genet. 23, 578-588, 1971.

THODAY, J. M.: New insights into continuous variation. In Crow, J. F., and Neel, J. V. (Eds.), Proc. Third Inter-nat. Congr. Hum. Genet, 339-350. Baltimore, Johns Hopkins Press, 1967.

TIENARI, P.: Psychiatric illnesses in identical twins. Acta Psychiat. Scand. Suppl. 171, 1963.

TIENARI, P.: Schizophrenia in monozygotic male twins. In Rosenthal, D., and Kety, S. S. (Eds.), The Transmission of Schizophrenia, 27-36. Oxford, Pergamon, 1968.

ZERBIN-*RUDIN, E.: Endogene Psychosen. In Becker, P. E., (Ed.), Humangenetik, ein kurzes Handbuch, Vol. V/2,446-577. Stuttgart, Thieme, 1967.

'Reprinted in J Shields and I I Gottesman (Eds). Man, Mind, and Heredity Selected Papers of Eliot Slater on Psychiatrv and Genetics. Baltimore, lohns Hopkins Press, 1971