a critical review of recent adoption, twin, and family studies of schizophrenia: behavioral genetics perspectives*

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> . . . Modest doubt is call'd
> The beacon of the wise, the tent that searches
> To th' bottom of the worst.
>
> Shakespeare, *Troilus and Cressida*
> (Act 2, scene 2, line 15)

Continuing uncertainty about the etiology of schizophrenia calls for periodic reappraisal of relevant data and conclusions, reappraisals guided by a beacon of modest doubt to avoid the distorted views of both the zealot and the skeptic. This review does not set out to cover every possible aspect of the genetics of schizophrenia. It deals with data from recent family, twin, and adoption studies of schizophrenia rather than with theoretical issues—data primarily selected because they provide grist for one or another genetically "powered" mills. The conference entitled "The Transmission of Schizophrenia," held at Dorado Beach, Puerto Rico, in 1967 (Rosenthal and Kety 1968) is our point of departure, since it was there that the first reports were given of the adoption studies carried out in Denmark by Rosenthal, Kety, Wender, Schulsinger, and their colleagues (Kety et al. 1968 and Rosenthal et al. 1968). This is not to say there was no credible evidence in favor of genetic influences in schizophrenia before the adoption studies came along (Shields 1968 and Slater 1968); but the argument had been raised by those most skeptical of the genetic evidence that the environment, not the genes, provided by a schizophrenic, preschizophrenic, or otherwise abnormal parent might account for the occurrence of schizophrenia in his or her children. If this hypothesis is a strawman set up to be knocked down by the adoption studies, it was not one built by the geneticists. We (Gottesman and Shields 1972) are not the only genetically oriented investigators to acknowledge and to value the part played by external environmental and internal psychodynamic factors in the development of schizophrenia.

Earlier Genetic Studies

For those with only a cursory acquaintance with the subject, we will briefly outline the history of the genetic studies up to 1967. The first genetic family study of schizophrenia—or rather of dementia praecox—was carried out by Ernst Rüdin in Kraepelin's clinic before World War I and was published in 1916. Many other studies in different countries, by Rüdin's pupils and others (e.g., Schulz 1932, Kallmann 1938, and studies reviewed by Zerbin-Rüdin 1967), confirmed the higher rate of schizophrenia in the relatives of samples of schizophrenics (these schizophrenics were termed "probands" or index cases) than in samples of the general population. The earliest family studies did not question the general assumption of the time that there were genetic factors in schizophrenia. Their authors tended to be more interested in seeing whether the disease fitted a simple Mendelian mode of inheritance as

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Huntington's chorea did (it did not). These studies remain among the better sources of data on the empirical risk of the occurrence of schizophrenia in different kinds of relatives—important data for environmental as well as genetic theorists, and for genetic counseling. Systematic twin studies (Luxenburger 1928 and 1934) were at first undertaken to determine the "manifestation rate" of the supposed schizophrenic *anlage* or genetic factor rather than the relative importance of nature or nurture. This emphasis was based on the unrealistic assumption that the rate of expression of a gene or genes was a biological constant and not something dynamic depending on multiple factors, both external and internal (Slater 1939). For most scientists, however, the principal object of the classical comparison of genetically identical (monozygotic or MZ) and genetically dissimilar (dizygotic or DZ) twins brought up in the same home was to test the hypothesis that the genes really did make a difference and that familial aggregation of schizophrenia was not simply due to the shared family environment.

The largest of the earlier twin studies, published in the 1940's and early 1950's (Kallmann 1946 and Slater with Shields 1953), appeared amply to confirm the genetic hypothesis, since MZ pairs were much more often concordant (i.e., both twins schizophrenic) than DZ pairs. These twin studies, however, were strongly criticized in the late 1950's and early 1960's. The criticisms stemmed, first, from concern about the biological and psychological peculiarity of MZ twins and the patently more similar environments encountered by them than by pairs of DZ twins (Jackson 1960), and, second, from the belief that reported MZ concordance rates—as high as 86 percent in one study—might be misleadingly high for a number of methodological reasons (Rosenthal 1959, 1960, 1961, 1962a, and 1962b). In answer to the first criticisms, it could be shown that MZ twins as such were no more often schizophrenic than DZ twins, and that they did not need to be reared together to be concordant. But a new twin study (Tienari 1963)—one reporting a concordance rate of 0 percent in MZ pairs—appeared to bear out some of Rosenthal's criticisms, although we (Gottesman and Shields 1966a and 1966b) argued that properly understood, the old and the new twin studies could be seen as replications of the same experiment: Genetic and environmental factors were both involved.

It was against this background that Heston (1966) reported a higher prevalence of schizophrenia and other disorders in the children borne by hospitalized, chronic schizophrenic mothers, separated from them within the first 3 days of life, and reared in institutions or foster homes without contact with their mothers or their mothers' families. There was no schizophrenia and significantly less other psychopathology in a control group with nonpsychotic parentage and matched for type of rearing. Heston's study was followed by the elegantly designed adoption studies from Denmark (Kety et al. 1968 and Rosenthal et al. 1968), in which every effort was made to eliminate the possibility that knowledge of the diagnosis of one family member might influence the diagnosis of another (contaminated diagnosis).

Overview of This Review

This review starts with the adoption studies, and some of the problems raised by them since 1967, and proceeds to the recent twin and family studies, including those of the offspring of two schizophrenic parents (dual matings). We shall have cause to mention several of the many unsolved problems of the genetics of schizophrenia. The nature of the clinical disorders possibly connected with schizophrenia, raised by Eugen Bleuler in 1911 (see Bleuler 1950), crops up at once with the concept of a spectrum of schizophrenic disorders used in the Danish adoption studies (Kety et al. 1968 and 1975, Rosenthal et al. 1968 and 1975a, and Rosenthal 1975).

In the section on twin studies there are the questions of the nature of the environmental factors that interact with the genes, and there are pointers to possible underlying biological variables more directly inherited than the phenotype of schizophrenia. In the section on genetic family studies there is reference to theories of heterogeneity in schizophrenia (e.g., process vs. reactive schizophrenia) and its principal mode of inheritance—monogenic (one gene), several separate genes, or polygenic (many genes). We can only refer in passing to speculations as to how schizophrenia may have evolved and been maintained in the population on a genetic basis. Such uncertainties are not peculiar to schizophrenia, but are shared with many genetic and all common, partly inherited disorders. If one cannot identify individual genes in schizophrenia, neither can one do so in diabetes, hypertension, or "tallness."

It is difficult to do justice to all the family, twin, and adoption studies reported in one form or another (e.g.,

Bleuler and Angst 1971 and Bohman 1970) since the benchmark conference on the transmission of schizophrenia (Rosenthal and Kety 1968). Therefore, the focus of this report will be limited to our area of expertise—developments in genetically oriented research—but will exclude the prospective high risk studies of the children of schizophrenics since they have been described *in extenso* by Garmezy with Streitman (1974) and Garmezy (1974) in the *Schizophrenia Bulletin*. Much of what we shall report and discuss are extensions of the research in the 1968 volume edited by Rosenthal and Kety. The definitive version of Manfred Bleuler's (1972) longitudinal, multigenerational study of 208 schizophrenics has been published in German and an English translation by Yale University Press is underway. Likewise the final versions of more than one twin study have been completed. Further reports continue to appear on the Danish-based adoption studies (Rosenthal et al. 1975a and 1975b) with extensions to psychopathic (Schulsinger 1972), alcoholic (Goodwin et al. 1973), and criminal probands (Hutchings and Mednick 1975). Apart from these matured reminders of the Puerto Rico conference, Ødegaard (1972) has reported further data collected on the families of psychotics identified in the Norwegian Psychiatric Register, and there have been new twin (Allen, Cohen, and Pollin 1972, Hoffer and Pollin 1970, and Fischer 1973) and family studies (Kety et al. 1975, Lindelius 1970, McCabe et al. 1972, and Winokur et al. 1972) from both sides of the Atlantic.[1]

We shall critically discuss some of the main themes and problems of interpretation arising from these studies. We are in sympathy neither with the pessimistic views that there have been no advances in our knowledge about the origins and transmission of schizophrenia, nor with those perennial views asserting that the solution to the schizophrenia problem is close at hand.

Diagnosis

A fundamental theme throughout the recent literature is the disquieting variation in the definitions of what constitutes schizophrenia. Many of the disagreements in the data and about the conclusions formed from them flow from this variation. The problem encompasses both the issue of reliability and the deeper problem of validity (Carpenter, Strauss, and Bartko 1973, Carpenter, Strauss, and Muleh 1973, Cooper et al. 1972, Fleiss et al. 1972, and Klein and Davis 1969). (It would be easy to mandate a rigid, perfectly reliable research definition (cf. Feighner et al. 1972) of schizophrenia that had zero validity.) Even friends of the diagnostic enterprise have had difficulty in presenting a sanguine picture (e.g., Meehl 1973 and Spitzer and Fleiss 1974). Past attacks on the problem of the reliability and validity of the diagnoses of schizophrenia were based on diagnoses that lacked standardized input information on patients, lacked bona fide experts who could be harnessed to the task, and lacked cross-national reference points. Reasons for optimism about the diagnostic problem now come from the United States-United Kingdom Diagnostic Project (Cooper et al. 1972) and the International Pilot Study of Schizophrenia (IPSS) (Wing, Cooper, and Sartorius 1974 and World Health Organization 1973). We can illustrate some of these points with our clinical genetic study at the Maudsley Hospital in London of schizophrenics and their twins (Gottesman and Shields 1972). We used six diagnosticians of varying theoretical persuasions to derive a consensus diagnosis, and a Scandinavian view was obtained from Essen-Möller (cf. 1956) in Sweden. Subsequently, the case history summaries were processed by John Wing to obtain a classification from his computer-based Catego program (Wing, Cooper, and Sartorius 1974), and they were also used to elicit diagnoses from Joseph Welner at the Kommunehospitalet in Copenhagen. It was Welner who interviewed and described the 258 subjects in the Rosenthal et al. (1968) adoption studies in Denmark. We had hopes that the diagnoses he made using criteria traditionally employed in his own country as well as a second set of diagnoses employing the spectrum of schizophrenic disorders being explored by the Rosenthal and Kety group (Kety et al. 1968 and Rosenthal et al. 1968) would help us to build a bridge linking genetic studies of schizophrenia. Table 1 presents some of our data selected so as to illustrate the effect of varying individual criteria on the frequency of diagnosing the presence of schizophrenia in an extensively studied sample of 114 twins.

Our two Scandinavian psychiatrists, when operating within a traditional Continental European framework, had the lowest yield of schizophrenic diagnoses. We did not, however, table the fact that only 17 twins were

[1] Our references are intended to inform the reader about many of the recent developments in fields related to the topic under discussion.

Table 1. Frequency of schizophrenia (Sc) and probable schizophrenia (?Sc) diagnoses as a function of diagnostic standards.[1]

Essen-Möller, strict Sc	34	Six-judge consensus Sc or ?Sc	69
Welner, strict Sc	42	United Kingdom hospital diagnosis Sc or ?Sc	70
Catego, S, P, or O	52	Meehl, Sc or ?Sc	79
Slater, Sc or ?Sc	62	Welner, Sc spectrum	81
Mosher, Sc or ?Sc	63		

[1]Data presented in this table were either derived from Gottesman and Shields (1972) or are presented here for the first time.

categorized by the Wing et al. (1974) Catego scheme as class S+, a category defining a core or nuclear group of schizophrenics currently manifesting the first-rank symptoms of Kurt Schneider (1971). At all nine of the worldwide psychiatric centers in the IPSS (World Health Organization 1973), nearly all S+ patients had been clinically diagnosed as schizophrenics, but many who were not S+ were also clinically acceptable as "real" schizophrenics. We would have been unfair both to our histories and to Catego to have set the yield of only 17 alongside the much higher numbers in table 1. The histories were largely based on hospital records plus some verbatim interview material at the time of follow-up (often many years after hospitalization). Catego depends on input from symptoms elicited during an interview with current patients; the symptoms must have been present during the preceding month and must satisfy the criteria set out in a structured interview. We present the results for any of the Catego classes S, P, and O, each certain or probable, yielding 52 "hits." P represents paranoid delusional psychoses (e.g., ICD 297.0, 298.2[2]), while O's are clinically associated with diagnoses of catatonic, residual, or borderline schizophrenia. It is informative to note that Meehl, a Radovian-influenced therapist, called 69 cases chronic or acute schizophrenia, 8 borderline, and 2 schizotypes for a total of 79 schizophrenia diagnoses. Welner, after diagnosing only 42 cases as strict schizophrenia, shifted his orientation to that of the schizophrenia spectrum, and came up with a total indistinguishable from Meehl's, namely 81. Lest the range of values in table 1 be interpreted as evidence of unreliability, we hasten to point out that our panel of six consensus judges averaged 83 percent agreement as to whether schizophrenia was diagnosed (Shields and Gottesman 1972). The validity of any of these diagnostic concepts depends on various other considerations (cf. Kety 1974).

Until such time as the IPSS (World Health Organization 1973), together with its followup results, becomes part of the determining factors in worldwide diagnostic practice, the science of psychopathology will not be able to cope with the obstacles to defining the subjects of etiological and therapeutic-preventional research. Even such on-the-face-of-it simple tasks as reporting the prevalence, incidence, and lifetime risk of developing schizophrenia will have to be redone in the light of the new standards that emerge from the cross-national studies. Further barriers to communication among disciplines and between scientists and public health administrators/planners will still exist and deserve separate study and comment. Only one need be mentioned here in passing. Yolles and Kramer (1969), summarizing various prevalence rates for schizophrenia in the literature, report a lifetime prevalence from the study of Essen-Möller (1956) in rural, southern Sweden of 6.7 per 1,000 population. Essen-Möller himself and other psychiatric geneticists (e.g., Zerbin-Rüdin 1967) report a lifetime risk of developing schizophrenia of 1.12 percent (11.2 per 1,000) for the very same study. The difference stems from the difference in use to which the rates are put, and both schools of thought are correct for their own purposes. The testing and fitting of genetic models requires an age-corrected rate that uses a denominator of risk-lives observed. Yolles and Kramer considered a denominator of the total Essen-Möller sample, 2,550, while the investigator calculated that that total yielded only 1,515 risk-lives. Both used the same numerator of the number of actual schizophrenic cases. Such

[2]See the World Health Organization's (1967) *Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death.*

unheralded gaps in communication help to perpetuate skepticism about schizophrenia.

Studies Using Adoption Strategies

After Heston's (1966) remarkable report that the offspring of severely schizophrenic mothers removed from them during the first 3 days of life still grew up to have schizophrenia at the same rate as those reared by their schizophrenic mothers, the dogma about schizophrenogenic mothers was called into question and the conventional psychodynamic establishment was temporarily rattled. When the Rosenthal et al. and Kety et al. landmark series of studies using Danish adoptees were reported in preliminary form in 1968 and shown to be in essential confirmation of Heston's results, the straw that broke the environmentalist's back descended on what had been a rather static domain of knowledge and uncertainty. Not only did the Danish adoption work amplify the usefulness of such a strategy, it also helped to usher in a renewed attempt by neurochemists and pharmacologists to take the schizophrenia disorder seriously as one worthy of their efforts at the interface between biology and clinical psychiatry. Perfectionism is the last refuge of the skeptic, and no amount of purified data can pierce that defense.

Since the 1968 reports, Kety has interviewed the relatives—parents, siblings, and half siblings of the biological and adoptive families—of schizophrenic and control adoptees in the field (Kety et al. 1975 and Paikin et al. 1974); he earlier had depended on psychiatric register information for assessments. The number of families providing probands has been expanded from 33 to 74 as he moved to cover not only the Copenhagen area but all of Denmark. He has also obtained a control group of 5,000 nonadoptees and from it determined data on the biological relatives of nonadopted (ordinary) schizophrenics.

Rosenthal likewise has increased his sample size of index adoptees (adoptees whose biological parents included a psychotic) from 39 to 79 (including 10 affective psychoses). The spouses of the schizophrenic parents have now been interviewed (Rosenthal 1975). A unique sample of 38 children of normal biological parents adopted by couples, one member of whom later became psychotic, provides an analogy to a cross-fostering design used by ethologists (Wender et al. 1974). With a further touch of elegance in psychiatric field research, Paikin et al. (1974) give details on those Rosenthal adoptees and controls, cross-fostered subjects, and nonadoptee controls (a total of 76) who refused to participate but on 56 of whom firsthand information was nonetheless obtained. The latter study also reveals that among the 258 subjects intensively and blindly interviewed by Welner for Rosenthal, 42 were nonadopted children of schizophrenics.

In general, the newest but still provisional data (Kety et al. 1975 and Wender et al. 1974) from the Danish adoption studies have confirmed the findings of the earlier reports. That is, there were more schizophrenia and schizophrenia-related disorders in the biological relatives of schizophrenic adoptees and in the adopted-away children of schizophrenic parents than in their control groups. As a guide to the discussion, table 2 presents our summary of the salient findings with regard to schizophrenia (i.e., omitting index manic-depressive parents or adoptees). The abbreviations B (definite schizophrenia) and D (uncertain schizophrenia) follow the investigators' usage in the latest published papers available to us as of June 1975 (see Kety et al. (1975) and Rieder et al. (1975)). The B1 category refers to definite chronic schizophrenia, B2 to definite acute schizophrenia, and B3 to definite latent or borderline schizophrenia. The categories D1, D2, and D3 correspond to B1, B2, and B3 but refer to cases in which the diagnosis of chronic, acute, or latent schizophrenia was uncertain.

In the last row of table 2, we have combined all sibling groups that are biologically *unrelated* to a schizophrenic adoptee and calculated the diagnosed prevalence of schizophrenia, whether definite (B) or uncertain (D). This procedure provides a group similar in age with whom the biological half siblings of schizophrenic adoptees may be compared. (Being adoptees, the index schizophrenics in the Kety study had only three full siblings, one of whom was schizophrenic; the full siblings were excluded from the table.) The 95-percent confidence intervals show the range within which we are 95 percent confident the true estimate of the prevalence will lie. The confidence intervals are provided as a caveat to those seeking "true" values of the prevalences, and as a reminder that most research in psychiatric genetics, however unique and elegant, is haunted by small sample sizes.

Table 2. Interim summary of the raw prevalence of schizophrenia, whether definite (B) or uncertain (D), in the Danish adoption studies.

Strategies	*N*	Percent schizophrenic (B or D)	95-percent confidence interval
Rosenthal:			
Children of schizophrenics, not adopted	42	([1])	
Children of schizophrenics, adopted-away index	69	18.8	10.4–30.1
Children of normals, adopted-away control	79	[2]10.1	4.5–19.0
Wender:			
Children ("purified") of normals, cross-fostered to schizophrenics	21	4.8	1–23.8
Kety:			
Biological parents of schizophrenic adoptees	66	12.1	5.5–22.5
Biological parents of control adoptees	65	6.2	1.7–15.0
Adoptive parents of schizophrenic adoptees	63	1.6	.0–8.5
Adoptive parents of control adoptees	68	4.4	.9–12.4
Biological half siblings of schizophrenic adoptees	104	19.2	12.1–28.0
All adoptive siblings plus full and half siblings of control adoptees	143	[2]6.3	3.0–11.9

[1]Not available in published reports.
[2]May be taken as an estimate of B or D (as they are applied) in the general population, that is, the "base rate."

Since the definitive versions of both the Rosenthal-led and the Kety-led adoption studies have yet to be written, a number of gaps in our information are inevitable, and the gaps frustrate an attempt at complete evaluation of the published data and interpretations. In the Rosenthal et al. (1975a and 1975b) work, the diagnoses and psychopathology ratings for the index adoptees and controls (258 interviewed subjects) have thus far been based only on a summarizing diagnostic or characterizing conclusion by J. Welner or the placement of such a summary in a 20-point forced platykurtic quasi-normal distribution (Wender et al. 1974) using the mean of three judges after the most discrepant fourth judge had been eliminated. Up to this time, Welner is still operating as a blindfolded contributor. The riches of the 3- to 5-hour taped interview with the adoptees covering 26 topics, a detailed mental status, and a psychodynamic formulation will also eventually be tapped (cf. Rosenthal et al. 1975a and 1975b).

Different problems arise in the case of the bases for the diagnoses of the index parents in the Rosenthal (1971, 1972, and 1975) work. The 69 schizophrenia spectrum parents were diagnosed by Rosenthal and Wender (and Kety for part of the sample) from English summaries of information appearing in the hospital charts of those parents on the Danish Psychiatric Register (number unspecified) among the 10,000+ parents in the starting sample. The original chart diagnoses and those by the Danish psychiatrist summarizer are not yet reported, and case history material has not been presented. It is difficult, therefore, to evaluate the team's diagnosis of schizophrenia and its prevalence among parents who give up their children for adoption.

Table 2 shows a rate of 18.8 percent of definite or uncertain schizophrenia (B or D) for the adopted-away children of schizophrenics reared in adoptive homes, a rate corresponding to the proportion in the upper quartile of the forced-normal distribution, that is,

points 16-20 (borderline schizophrenia and more severe, but not schizoid). A different and higher value would be obtained for this rate if diagnoses that the investigators called spectrum (Rosenthal 1972) were used (31.9 percent in index adoptees and 17.8 percent in adopted controls). Two of the rates in table 2 can be taken as an indication of the population base rate for what the Rosenthal and Kety team calls definite or uncertain schizophrenia (upper quartile criterion): One is 10.1 percent in the 79 adopted controls for the index adoptees and the other is 6.3 percent that we calculated among the adoptive full and half siblings of nonschizophrenic adoptees (Kety et al. 1975). The rates are remarkably high considering that they are not yet age corrected. Even for the adoptive parent groups (selected for mental health), the prevalences are 1.6 and 4.4 percent. Surprisingly, the higher rate applies to the control adoptive parents.

Although the major accomplishment of the adoption studies was to determine that numerous alleged environmental factors were neither necessary nor sufficient for the occurrence of schizophrenia, they provided a bonus by reawakening interest in the so-called schizophrenia spectrum. A reliable and valid indicator of a schizophrenic genotype in either relatives of schizophrenics (cf. Hirsch and Leff 1971 and 1975, Holzman et al. 1974, Iversen and Rose 1973, Marcus 1974, Mosher, Stabenau, and Pollin 1973, Wyatt et al. 1973a and 1973b, and Wyatt, Belmaker, and Murphy 1975) or in members of the general population who were not overtly affected with clinical schizophrenia would be a boon to etiological research and to therapeutic intervention. Data from adoption, twin, and family studies can be used in that search (Planansky 1972, Rosenthal 1975, and Shields, Heston, and Gottesman 1975). In the light of the latest reports, it is very doubtful whether schizoidia or schizoid personality as currently assessed belongs in the spectrum. It is even problematic whether the dividing line (threshold) should be placed to exclude borderline schizophrenia or to include it within the spectrum. The related problem of the place of acute schizophrenia (B2) will be addressed below. We earlier pointed out (Gottesman and Shields 1972) that schizoidia did not discriminate index adoptees from control adoptees in a previous (Rosenthal et al. 1968) report. (The discrimination came from the excess of definite chronic (B1) and definite latent (B3) schizophrenia in index adoptees, largely in those whose parents were themselves B1.) Schizoidia still does not discriminate in the Wender et al. (1974) or Kety et al. (1975) studies, except insofar as Rosenthal (1975) argues that more index adoptees have a spectrum disorder when they are offspring of a B1 parent mated with a spectrum (schizoid) spouse than when they are offspring of a B1 parent without a schizoid spouse. The numbers are small: six versus one in the index adoptees of the two B1 groups.

The place, if any, for sociopathy in the schizophrenia spectrum is an issue raised by the very different results of the Heston (1966; also, Heston and Denney 1968) and the Rosenthal (1975 and Rosenthal et al. 1968) studies of index adoptees. An unknown number of the Heston fathers were sociopaths, and at least nine of the Rosenthal fathers married to a schizophrenic were determined by interview ratings to have psychopathic disorders. Eight out of 30 male index adoptees in the Heston study were felons with prison records, while none of 35 male index adoptees in the Rosenthal study were known to have a criminal history. At the time the Rosenthal index adoptees were evaluated, however, the best source of information about criminality was not available to him, namely the Central Police Register. Hutchings and Mednick (1975) found that 16.2 percent of male adoptees consecutively registered in the same adoption pool used by Rosenthal and Kety (1968) had a criminal record at the Central Police Register. Furthermore, the general population risk for offenses more serious than a misdemeanor is about 8.8 percent. It is important to note that the rate of criminality in adoptees whose biological fathers were criminals but whose adoptive fathers were not was 21 percent in the Hutchings and Mednick study (p. 114), a rate not far from the 26.6 percent observed in Heston's male index adoptees with schizophrenic mothers but unexamined fathers. It is conceivable that the missing criminality data on Rosenthal's index adoptee subjects and Heston's fathers both would merge to reflect the heritability of criminality rather than provide evidence that sociopathy was in the soft spectrum as Rosenthal (1975, p. 203) suggests.

At various times, the adoption data have suggested to Kety, Rosenthal, and their collaborators that acute schizophrenia is different in etiology from chronic and borderline schizophrenia (and may have largely environmental causes). The suggestion derived from their finding no or little schizophrenia in the relatives of acute pro-

bands either when they were schizophrenic parents of adoptees or adoptees (Kety et al. 1968 and 1971). Lest their conclusion be taken more seriously than it deserves, the data supports need to be scrutinized. Two main points may be made: the definition of acute schizophrenia (B2) and the reliability of the findings. The criteria for B2 are admittedly restrictive—"one or two acute schizophreniform episodes without clear evidence of premorbid or residual schizophrenic pathology" (Kety et al. 1975, p. 153) and "Psychotic symptoms lasting more than one week, even with medication . . . Not more than one rehospitalization for recurrence of psychosis" (Rieder et al. 1975, p. 201). In terms of sample sizes, only four of the Rosenthal (1972) index parents were acute schizophrenics, and none of their children had any spectrum diagnosis; Kety et al. (1975) reported that only seven of their schizophrenic adoptees were acute schizophrenics and four of their biological relatives were uncertain latent schizophrenics (D3) on interview (a mother, a maternal half sibling, and two paternal half siblings). (Only one uncertain acute schizophrenic (D2) and no definite acute schizophrenic (B2) was diagnosed in the entire sample of 512 relatives.) The problem of where to place the acute, or remitting, or schizophreniform psychoses in our taxonomy is one of long standing and will require more research before we can reach an informed conclusion (McCabe and Strömgren 1975, Mitsuda and Sakai 1968, and Welner and Strömgren 1958). While some acute schizophreniclike episodes may well be nongenetic symptomatic psychoses (Davison and Bagley 1969), the same does not apply to all schizoaffective psychoses (cf. Perris 1974). We shall refer to this issue again in the section on family studies.

As the Danish adoption studies of schizophrenia have progressed, modifications have evolved in the original views about the schizophrenia spectrum. While once manic-depressive illness was thought to be in (Rosenthal et al. 1968 and 1971), now, more sensibly, it is excluded (Rosenthal 1975). Earlier, spectrum disorders were thought to be all the same genetically, with the form depending on the environment. Now it is noted that there is more definite chronic schizophrenia (B1) and more spectrum in the families of B1 probands, as we had pointed out (Gottesman and Shields 1972, p. 40). Currently, the spectrum is divided into hard and soft, with the latter including "schizophrenic personalities such as undifferentiated inadequate and subparanoid and schizoid personalities" (Rosenthal 1975, p. 202). Rosenthal (1975, pp. 202 and 204) is understandably ambivalent about whether definite and uncertain acute schizophrenia (B2 and D2) are soft spectrum; if not, there is some danger of self-fulfilling prophecy.

The principal conclusion that can be reached at this stage from the adoption work is that it disconfirms the widely held hypothesis that the high schizophrenia rate observed in the children of schizophrenics was due to an interaction between schizophrenogenic rearing and genetic predisposition, and, ipso facto, the cruder hypothesis that rearing by a schizophrenic parent was sufficient cause. An added bonus from this research is the demonstration that knowledge by the adoptive parents about the mental illness in one of the two biological parents could not have been important in the development of schizophrenia in the index adoptee. First hospitalization for schizophrenia in the Rosenthal et al. (1968) parents generally took place many years after the adoption process. This finding would appear to refute the criticism sometimes leveled at Heston's (1966) findings that the schizophrenias in adopted-away offspring could be accounted for by the possible knowledge about the schizophrenia in the mothers. Paradoxically, the burden of proof has shifted from showing that genes are important to showing that environment is important even though adoption studies cannot prove that environment is unimportant. Adoption studies are very useful but, like all strategies, limited in their resolving power and not necessarily the best for genetic research once the field of inquiry has been delimited by the findings. The candor of Wender et al. (1973 and 1974) about the limitations in their strategy is refreshing: Only certain biological parents gave or were permitted to give their children up for legal adoption; within-own-family placements were excluded; some of the adoptees were abnormal before placement, leading now to the additional usage of "purified" groups from which they have been excluded; adopting parents represented a restricted range of rearing environments on the good side of some distribution; a strong correlation between the socioeconomic status of biological and adoptive parents existed; and children who were fostered rather than adopted did not enter the initial pool of subjects. Moreover, the spouses of schizophrenics whose children are adopted are probably not representative of the spouses of schizophrenics in general since they include a higher proportion of socially inadequate

individuals. None of these problems erode the principal conclusion above. In one sense, the cross-fostering variation (Wender et al. 1974) on the adoption theme in the Danish studies can be said, after the fact, to gild the lily. Table 2 shows that of 21 "purified" children of normals who were reared by schizophrenic adoptive parents, 4.8 percent were B or D (upper quartile), a rate actually lower than the reported normal control values in that table—6.3 and 10.1 percent. Taken at face value, the cross-fostering finding does not strengthen a genetic argument so much as it weakens environmental ones. The 28 schizophrenic adoptive parents in the cross-fostering study were not really comparable to the 69 schizophrenic parents of the index adoptee cases in terms of severity of their illnesses; only 32.1 percent of the former compared to 60.9 percent of the latter were chronic schizophrenics. The Danish adoption results taken together with the Heston (1966) findings and the unique study by Fischer (1973) showing the usual high offspring rate of schizophrenia in the children of discordant (± normal) MZ co-twins of schizophrenics are all consistent and strong confirmation of the importance of genetic factors, so far unspecifiable.

The complementary Kety-led studies (Kety et al. 1968, 1971, and 1975) summarized in part in table 2 clearly separate the findings in biological parents, first-degree relatives, from those in the important and uncommonly studied half siblings, second-degree relatives. The frequent combination of first- and second-degree relatives as "biological relatives" in the reports from this team can be criticized. It muddles information about the independent variable, genotype, in behavioral genetic studies, since first-degree relatives (parents, full siblings, and children) have 50 percent of their genes in common with the proband (parents and children have exactly 50 percent while siblings average 50 percent), but second-degree relatives average only 25 percent of their genes in common. The relationship between the "gene dosage effect" on the one hand and the rate of affectation on the other is what makes the experiments of nature into grist for our scientific mills. Kety et al. (1975) make some amends in their recent report by pulling out the biological paternal half siblings for separate analyses. Table 2 shows a 19.2-percent rate of B or D for the entire sample of 104 half siblings of schizophrenic adoptee probands, a rate higher than that shown for parents of those probands (12.1 percent) and as high as the rate in Rosenthal's index cases, 18.8 percent, despite the latter being first-degree relatives of schizophrenic probands and therefore having twice as much gene overlap with probands. Some MZ twin studies have reported even lower rates.

The importance of the data provided by the half siblings of schizophrenics leads us to set out a summary of the available information from the literature. Table 3 shows the data from the Kety et al. (1975) study and the two best other studies providing information on half siblings and also shows a breakdown of risks to half siblings as a function of the status of the shared parent. The pooled age-corrected rate from three older studies in the literature (see Zerbin-Rüdin 1967) for definite schizophrenia is 3.2 percent, the same as that reported by Bleuler (1972) for the largest such sample ever studied; 3.2 percent in half siblings may be compared with the pooled risk in full siblings of 8.5 percent.

The half siblings' rates for definite plus uncertain schizophrenia highlight the different diagnostic orientations between the Kety et al. (1975) results and the Kallmann (1938) and Bleuler (1972) findings. The 19.2-percent Kety et al. half-sibling rate would be even higher if it were to be corrected for age in the standard fashion. Even the rate of 19.2 percent generates impossibly high predictions for either monogenic or polygenic models of the transmission of schizophrenia (Gottesman 1975). It is worth remembering that neither Kallmann nor Manfred Bleuler has ever been associated with an exceedingly narrow view of what to call schizophrenia—as, for example, that associated with Schneider (1971). Kety (1974b) does report a measure of reliability for the concept of definite plus uncertain schizophrenia for three judges; the value of kappa (Fleiss 1971) is .61. (This may be compared with the reported kappas of .67 for definite schizophrenia and .58 for all spectrum disorders as well as with a value of .75 for schizophrenia plus probable schizophrenia in the Gottesman and Shields (1972) six-judge panel.)

The bottom of table 3 shows a valuable breakdown of the rates of schizophrenia in half siblings as a function of whether the shared parent was the one with or without schizophrenia and compares the results for Kallmann (1938) and Kety et al. (1975); the differences would be even greater if the Kety et al. data were to be raised by age correction. When the common parent is unaffected, we would expect the risk to approach the population base rate. It would closely approach the full-sibling rate (around 10 percent in most studies) only if there were

Table 3. Schizophrenia in the half siblings of schizophrenics.

Study	No. of half siblings	Prevalence (percent)		
		Schizophrenia, definite	Schizophrenia, definite and uncertain	Schizophrenia, schizoid personality, or spectrum
Kallmann (1938)	[1] 100	5.0	6.0	14.0
Bleuler (1972)	[2] 221	3.2	4.5	8.6
Kety et al. (1975)	104	9.6	19.2	29.0
	Common parent affected		Common parent unaffected	
Kallmann (1938)	[3] 24% of 21		[3] 1.7% of 57.5	
Kety et al. (1975)	[4] 53% of 15		[4] 13.5% of 89	

[1] Over age 20.
[2] Over age 18 (probably comparable to uncorrected Kety et al.).
[3] Age corrected (includes uncertain schizophrenia).
[4] Not age corrected (includes uncertain schizophrenia).

some very strong tendency for *the second spouse of a normal parent* of a schizophrenic to resemble the first spouse genetically. It is very difficult to reconcile the (minimum) 13.5-percent rate from Kety et al. with expectations. When the shared parent is affected, both studies agree in showing a much higher risk. One might have predicted a rate not far from the average of 17.2 percent found in other studies for the full siblings of schizophrenics when a parent is also affected. The 53-percent rate that Kety et al. report is of the order one would find in the case of Huntington's disease if it were to be studied in this fashion. No other data exist, however, to lead to a conclusion that the gene for schizophrenia is a dominant one with complete penetrance. In fact, the Kety et al. study shows no internal consistency in this respect in that fewer than 50 percent—namely, 12.1 percent—of the biological parents are known to be affected with definite or uncertain schizophrenia.

What might account for these very high rates for schizophrenia in the Kety et al. (1975) study, highest of all in the biological half siblings of the hard spectrum adoptees? Kety et al. showed that the high half-sibling rate could not be accounted for by intrauterine, perinatal, or early postnatal maternal effects, since the rate was even higher for the paternal half siblings than for the maternal half siblings. A further possibility that comes to mind is our old friend contaminated diagnosis. We must ask whether the initial selection of adoptee probands as schizophrenic could have been influenced by a knowledge of a family history of probable schizophrenia. The 34 adoptee probands were picked out of the 507 with psychiatric hospital records by three judges (Kety, Wender, and, in uncertain cases, Schulsinger) on the basis of their independent diagnoses followed by *consensual* agreement that an adoptee was a chronic, latent or borderline, or acute schizophrenic. These diagnoses were based (as described in Kety et al. 1968) on a checklist of symptoms prepared from the register records by a Danish psychiatrist, Dr. Willadsen, who also recorded her most probable diagnosis and the likelihood that the patient had schizophrenia. Willadsen had access to the entire hospital records that would have included information on relatives and their diagnoses as standard information. When Kety and Wender were in any doubt about an adoptee being anything other than definitely schizophrenic or definitely not schizophrenic, they further considered an abstract prepared independently by Schulsinger, who also had access to any information about relatives there was in the charts. The forms on which the judges based their diagnoses had, however, been edited to exclude information on mental illness in relatives.

Could the fact that Willadsen and Schulsinger had access to information about biological relatives contained in the register charts of the adoptees in about 1963

have influenced their diagnosing or summarizing habits (contrary to their training) in such a way as to influence, in turn, Kety, Wender, and (sometimes) Schulsinger's consensual diagnosis of definite schizophrenia so that out of the 50 adoptees on the register, they were enabled to pick 23 definite schizophrenic adoptees with 8 definite or uncertain schizophrenic parents (12 percent) who in turn had 15 offspring by another spouse, 8 of whom (53 percent) were definite or uncertain schizophrenics (interview diagnosis in 1973 plus registry information)? A conclusion of this sort seems unlikely in the extreme and based on a string of ad hoc assumptions. Remember that while some information about the biological family would be in the personal charts of the adoptees, this information would presumably be available only up to the time of the adoption some 16 to 39 years earlier.

It could, however, be argued that Willadsen and Schulsinger had been influenced in making a diagnosis by knowledge of preadoption admissions of parents, uncles, aunts, and grandparents. This could be so in only rather few cases, and it is difficult to see how it could account for the findings. It may not so much have been a *knowledge* of the family history as the *fact* of the family history that was important. The team's diagnoses would probably have been much the same whether Willadsen and Schulsinger knew or not.

It might perhaps be more plausibly argued that the high rates of definite and uncertain schizophrenia are in part accounted for by a high prevalence of personality disorder and other psychiatric illness in the biological families of Copenhagen adoptees at the time, a high heritability of many such disorders, and a wide concept of borderline schizophrenia on the part of the judges such as to include what might be called psychogenic psychoses, affective disorder, and personality disorder in other centers. The families of psychopathic adoptees (Schulsinger 1972) had an excess of relatives in the psychopathic but not the schizophrenic spectrum. What we are seeing, on this view, would be the largely independent genetic influences of both schizophrenic and other disorders, combined in some families of this sample of adoptees in ways that are not typical of schizophrenics in general. The suggestion is supported by the high proportion of reportedly abnormal co-spouses of schizophrenic parents in the Rosenthal (1975) study. A high heritability of personality disorder and affective disorder as well as schizophrenia would account for finding less abnormality in the families of control adoptees not on the psychiatric register than in the proband families.

Once again, the above view is conjectural. Maybe personality disorder is not sufficiently highly heritable to account for the findings in this way. The abnormality in the half siblings could have a considerable environmental component. We do not know whether they were also adopted. If they remained with "problem" biological families or were subjected to periods of institutional care, they might well be considered to be at risk for developing "inadequate" personalities that would be diagnosed definite or uncertain latent schizophrenia. Bipolar manic-depressive psychosis is the affective disorder with the highest heritability, but the chronicity by definition of the definite chronic schizophrenic and the definite and uncertain latent schizophrenic relatives does not lead us to suppose that the Kety et al. (1975) sample contains a high proportion of families that at other centers might be called bipolar manic-depressive families. The 10-percent rate for the control adoptees (Wender et al. 1974) is not explained, nor the 4.4 percent for adoptive parents of normal adoptees (Kety et al. 1975). A mental set not to miss possible schizophrenia-related disorders by the interviewers together with a consensus reached by the authors after discussion among themselves may be among the reasons for the high spectrum rates throughout these studies.

Some light on the unsolved problem should come from further studies in progress on the families of adoptees from outside the Copenhagen area, on those of affectively ill adoptees, and of schizophrenics reared by their own families. In this last group, the schizophrenia issue may not be so confounded with that of personality disorder as it is in the adoption studies, but the families will not be comparable as regards full and half siblings. The former will presumably predominate in the families of schizophrenics reared by their own parents, while half siblings will predominate in the biological families of adoptees. Genetic theory predicts a much higher risk for full siblings, as we have seen.

Up to now, the official chart diagnosis of the adoptees and the probable final diagnosis made by Willadsen are not available for comparison with the blind consensual diagnosis. Such information for all 507 hospitalized adoptees (and ultimately for their relatives) would permit a more detailed evaluation of the diagnostic problems in the Danish adoptee studies. For a fuller evaluation of the vexed problem of what is "in the

spectrum," one requires definitions of B3, D3, etc., that can be reliably applied by other investigators in representative family studies. The aim of such studies would be to report the incidence of all the relevant disorders (e.g., Catego S+, B1, B3, D3, schizoid personality) in the general population and in the families of probands of each type. In this way, one could test hypotheses as to which if any of these diagnoses represent threshold cutoff points of a continuously graded but otherwise homogeneous liability to a single disorder (cf. Cloninger, Reich, and Guze 1975, Falconer 1967, Fulker 1973, Mendell and Elston 1974, Reich, Cloninger, and Guze 1975, and Reich, James, and Morris 1972).

Before we leave the Danish adoption studies, it needs to be pointed out that the concept of assortative mating (Cavalli-Sforza and Bodmer 1971 and Rosenthal 1970) is an important one for population genetics. In the absence of contrary information, we assume random mating and use the formulas provided for that assumption. Up to now, this has been no problem for genetic studies of schizophrenia. Rosenthal (1975) reports that a very high proportion of the index schizophrenic parents in his study had spouses who could be diagnosed from interview summaries as spectrum (e.g., 45 percent of female co-parents). This finding may reveal a unique aspect of adoption research and thus limit its generalizability to studies using other genetic strategies. Bleuler (1972), even with his longitudinal familiarity with the spouses of schizophrenics, thought that only 3 of 120 marriage partners were schizophrenic or probably schizophrenic themselves, a rate not different from the normal population and one similar to that reported in three previous studies.

We are in debt to the Rosenthal and Kety teams for their role in reawakening interest in the genetics of schizophrenia in a heuristic fashion. As they work on patiently, we must also wait patiently for such details as those mentioned above: sex and age distribution breakdowns, case history summaries, the psychological and psychophysiological test findings (cf. Van Dyke, Rosenthal, and Rasmussen 1974), and the reactions of the interviewers when they are unblindfolded (cf. Slater's comments about the twins in Gottesman and Shields (1972) when unblindfolded). Taking their evidence at face value, chronic and borderline/latent schizophrenia—related in some as yet undefined way to schizophrenia as defined in the IPSS (Wing, Cooper, and Sartorius)—are diagnoses with a strong genetic component in their etiology. One of the important tasks for the near future is the confirmation or refutation of their findings in ordinary, more representative samples.

Recent Advances in Twin Studies

Adoption strategies hold an assumed genotype constant and then vary the environment of postnatal rearing, thus permitting a confirmation or refutation of certain hypotheses about the environment. The classical comparison of MZ and DZ co-twin concordance rates assumes that within-family environmental factors are controlled and, by permitting gene dosage to vary, permits the confirmation or refutation of certain genetic hypotheses. The seldom-appreciated fact that MZ twins per se are not at a higher risk for schizophrenia than singletons permits the use of the method for schizophrenia research. The old objection that elements of the shared environment "caused" the higher concordance rates in MZ twins should have been put to rest with the results of the adoption studies and the few pairs of MZ twins "reared apart" that show similar overall concordance rates. In schizophrenia research, the latter are curiosities to be collected (Prokop and Druml 1973) but do not provide the crucial data to solve the problem.

Despite the scrutiny and criticism to which twin studies of schizophrenia have been subjected, their major conclusions have held up remarkably well. They no longer have to bear the burden of advancing genetic ideas by themselves, but can be seen in a broader context of family and adoption studies as providing converging lines of evidence in support of a sophisticated detente known as a diathesis-stress theory. Advances have been made since the reports presented at the Puerto Rico conference (Rosenthal and Kety 1968) that will be chronicled below. Three of the modern twin studies (Fischer 1973, Kringlen 1967, and Tienari 1963 and 1971) were completed in different Scandinavian countries without a staff or significant budget. The Maudsley study (Gottesman and Shields 1972) was also a low-budget operation; almost 10 years elapsed between the onset and the book-length report of the study during which time we consulted geneticists and could involve a panel of expert, blindfolded diagnosticians. The Veterans' Administration (VA) twin study by Pollin et al. (1969) belongs in a different mold

from the remainder of studies in the literature. It is a chart study by a consortium of psychiatrists with major interests in psychodynamics and involves a giant sample of recorded materials on a population screened for mental and physical health by the armed forces induction procedures.

Kringlen's (1967) work based on Norwegian twins did not appear in monograph form until after his paper was presented at the 1967 Puerto Rico conference (Kringlen 1968). He has provided a limited distribution volume of useful case histories for his MZ pairs only (see his 1967 monograph for details). Although his Puerto Rico paper reported a failure to confirm our findings (Gottesman 1968 and Gottesman and Shields 1966b) on the positive relationship between severity and concordance, analyses stimulated by these findings have led him to reverse his earlier opinion so that we are concordant in his 1967 monograph. We are aware of an intended use of part of the Kringlen twin sample to test some of the ideas of Holzman (personal communication) about the usefulness of an eye-tracking/pendulum task in schizophrenia research (see Holzman et al. 1974). Both the Norwegian and the Danish twin studies are population based using a national register of twins. This basis has been misunderstood, however, to mean population-based studies are an improvement in accuracy over hospital-based registration of twin probands. Kringlen (1967) and Fischer (1973) both had to use national psychiatric hospital registers to identify which twins would be probands; their studies, therefore, are also hospital based. Neither followed up all twin births to see which would become diagnosable as schizophrenics. We know from both investigators that twins diagnosable as schizophrenic or schizophreniform were missed by their nations' psychiatric registers and did not appear until they did their fieldwork investigations. A finding-the-needle-in-the-haystack approach was tried by Tienari (1963, 1968, and 1971, to be described below).

Table 4 shows the results of the recent twin studies at two levels: a pairwise range of concordance rates reported by the investigators cited in the table and a set of probandwise concordance rates using a criterion of "affected" that approximates what our (Gottesman and Shields 1972) consensus panel of judges called schizophrenia or probable schizophrenia—that is, a functional psychosis with schizophreniclike features, one not likely to be an affective psychosis. The continued misunderstanding of the different kinds of concordance rates that can be calculated from the same twin data pool leads us to include an appendix to this article that can serve as a primer to the usage preferred by behavioral geneticists. Briefly, the pairwise rate expresses the degree of concordance as the percentage of all pairs in which both twins are schizophrenic, given a specified sample of twin pairs with at least one twin schizophrenic. The probandwise rate is the percentage of independently ascertained schizophrenic twins (the probands) who have a schizophrenic co-twin.

The studies summarized in table 4 are presented clearly enough by the authors so that we know how many twins were probands or index cases in their own right using each study's criterion. (In our opinion, recent investigators least interested in "pushing" a genetic argument are the ones who do not report their data in probandwise fashion; such rates are numerically higher than the pairwise rates.) Kringlen (1967) combined the pairs with schizophrenic (45) and schizophreniform (10) diagnoses to reach the tabled sample of 55 MZ pairs. As he used the diagnosis, schizophreniform turned out to be just as "genetic" as did schizophrenia. The lower end of the range of pairwise concordance rates, 25 percent, was obtained by dividing the number of pairs where both twins were hospitalized and registered as schizophrenic or schizophreniform (14) by the total number of pairs (55). The upper limit of 38 percent was obtained when Kringlen also counted as concordant those further pairs where the co-twin, though not on the register, was found by him to be either psychotic (3) or borderline (4). At the level of schizophreniclike functional psychosis, pairwise concordance is therefore (14 + 3)/55 or 31 percent. To convert this to a probandwise rate, we add the 14 MZ pairs where both twins appeared on the national psychosis register to both the numerator and the denominator to obtain a new fraction: (14 + 14 + 3)/(14 + 55) = 31/69 or 45 percent. This figure tells us how many of the independently ascertained (registered) twins with schizophrenia or schizophreniform psychosis (69 probands) had an affected partner. (If we had included cases that Kringlen diagnosed as borderline on interview, the probandwise rate would have gone up to 51 percent, 35/69.) This kind of embarrassment of riches in regard to the number of concordance rates that can be derived should be no cause for embarrassment, but rather, cause for pause and thoughtful deliberation.

Table 4. Concordance in recent twin studies.[1]

Pairs	Kringlen	Fischer	Gottesman and Shields	Tienari	Pollin et al.
Monozygotic:					
Pairwise range (reported by investigator)	25-38%	24-48%	40-50%	0-36%	14-27%
Number of pairs (used for consensus)	55	21	22	17	95
Probandwise concordance (our consensus)	45%	56%	58%	35%	43%
Dizygotic:					
Pairwise range	4-10%	10-19%	9-10%	5-14%	4-5%
Number of pairs	90	41	33	20	125
Probandwise concordance	15%	26%	12%	13%	9%

[1] Concordance rates are presented without age corrections.

Kringlen (1967) concluded that the genetic factors in schizophrenia were weaker than previously thought and were nonspecific. The first part of his conclusion must refer to lack of support for a monogenic position of the kind taken by Kallmann (1946), whose theory required very high MZ concordance rates and who reported an age-corrected rate (pairwise *not* probandwise) of 86 percent, more than twice as high as the rate calculated by Kringlen. However, low concordance rates can generate very high heritabilities (cf. Gottesman and Shields 1972 and Smith 1970). The second part of his conclusion is not supported by his own data that show a large amount of specificity. In fact, 16 of the 17 concordant MZ pairs were concordant for the very same subtype of schizophrenia. Kringlen's overall pattern of results is impressively like that of Kallmann's: there were no significant sibling-DZ, male-female, or same-sex-DZ/opposite-sex-DZ differences in concordance rates, all three "nulls" leading to an emphasis on autosomal genetic factors and a deemphasis on sex role and identification factors. In terms of the quality-quantity of sampling dimension, the Norwegian twin study is the best in the literature.

Fischer's (1973) Danish twin study was in progress at the time of Shields' (1968) summary of early returns. The published report was delayed by the author's commitment to the IPSS (World Health Organization 1973). Early reports of the concordance rates for schizophrenia in Danish twins by Harvald and Hauge (1965) have been completely superseded by Fischer's work that took up where they necessarily left off; for example, the 7 MZ pairs grew to 21. Her final MZ rates look very much like the others in table 4. On the face of it, her DZ probandwise rate of 26 percent looks anomalous. The most parsimonious explanation is in terms of sampling fluctuations, since the 95-percent confidence interval on her pairwise rate of 19.5 percent runs from 8.8 to 34.9 percent, thus suggesting that even her DZ rates are not significantly different from the others in the table. Her sample does differ from the others, though, in the proportion who were dead (35 percent) at the time of followup, a necessary consequence of the fact that the birth cohort of Fischer's twin sample covered the period 1870-1920. The low end of the MZ pairwise range, 24 percent, results from concordance for only those co-twins considered to be process (Kraepelinian) schizophrenics. The high value comes from counting as affected those co-twins she called grade 2 who "suffered from schizophreniform, paranoid, or atypical psychoses." Her concordance rate of 48 percent from this criterion is comparable to our rate for schizophrenia and probable schizophrenia but not to a value we reported earlier (Gottesman and Shields 1966b) for "grade 1 + 2." As in the Norwegian (Kringlen 1967) and Maudsley

(Gottesman and Shields 1972) studies in table 4, there were no conspicuous sex differences in concordance rates. It bears repetition that the Finnish (Tienari 1971) and Veterans' (Pollin et al. 1969) twin studies did not include female twins, a point that becomes important only if there are in fact real sex differences in the liability to developing schizophrenia.

One large advantage to the age at followup of the sample in Fischer's (1973) study was the view of concordance it gives us when no appreciable age correcting is needed. Her 56-percent MZ probandwise rate suggests that unthinking application of Weinberg abridged procedures for age correcting by twin researchers is unwise. On the other hand, while most concordant MZ pairs become so within a brief span, Fischer's long followup time revealed two pairs with differences in onset of 29 years and 17 years (cf. Essen-Möller 1970). In sum, some modesty is required in the presentation of "final" or "true" rates of concordance in any twin (or adoption or family) study. Fischer did not find a relationship between severity of schizophrenia in a proband and the risk of developing a psychosis in the co-twin that a number of other twin studies find. In part this could stem from such factors as a restriction in range of pathology from her initial criteria for process probands, a time frame before the phenothiazine era, and the common difficulties with small sample sizes. As in other studies, the schizophrenias of the concordant MZ pairs were not different in kind from those in the discordant pairs.

A careful consideration of the role of environmental factors led her to conclude that a variety of different factors may be partly responsible for the development of the disorder, but no single factor stood out. She found that childbirth precipitated some cases, but that the childless MZ co-twins were as concordant as the remainder of the sample. Interesting facts came to light when the rate of emigration in her sample proved to be higher than that in the general Danish population of that era. Eight MZ twins had emigrated, mostly to the United States, of whom six became schizophrenic within 5 years and were returned to their homeland. Any twin becoming ill more than 5 years after leaving would have been lost from the sample altogether. Fischer compares her findings with Ødegaard's (1932) on Norwegian emigrants and asks how far the trauma of separation from twin and family and how far the selective emigration of abnormal persons contribute to the findings. Since Kringlen's (1967) twentieth-century twins were not exposed to the temptation of earlier waves of Scandinavian emigration, elegant designs employing co-twin controls for genotype will have to remain fantasies, and displaced Vietnamese will have to provide tests of the relationships hypothesized.

One last unique feature of the Fischer work deserves attention. The mental status of the 71 children born to MZ twins was examined as a function of their parents' status—schizophrenic versus nonschizophrenic. After age correction, it was found that 3 out of 31.2 offspring in the former group compared with 3 out of 23.1 offspring of the latter group had schizophrenia and schizophrenia-like psychoses. The risks of 9.6 and 12.9 percent were not different from each other nor very different from the risks in the literature for the children of one schizophrenic. A variation on this analysis was the dividing of the parental sample of MZ twins into those from concordant and discordant pairs: the risk to offspring was 6.0 percent (1 out of 17.5) in the former group and 13.6 percent (5 out of 36.8) in the latter, a nonsignificant difference. Thus, both analyses suggest that the predisposition to schizophrenia is transmitted genetically with no appreciable genetic heterogeneity.

Tienari's study of Finnish twins with schizophrenia is best known for its early (1963) report of a 0-percent concordance rate in MZ pairs. By the time of the Puerto Rico conference (Tienari 1968), he had one fully concordant pair and a range of concordance rates that he thought best represented his findings. He had also published an important monograph on normal personality variation within twin pairs (Tienari 1966). In 1971 he published a brief followup report that provides the basis of our summary in table 4. The youth of Tienari's sample is highlighted by the fact that his birth cohort begins in 1920 (to 1929), the year in which Fischer's cohort (1870-1920) ended. Kringlen sampled from births during 1901 to 1930. The final story with the Finnish sample has yet to be written since a new followup was begun in 1969 of 1,432 twin pairs, a sample that augments his earlier one by 425 pairs who survived the beginning of the risk period for schizophrenia but for whom information on mental status was missing. On checking the registers of all Finnish mental hospitals, Tienari found that a second twin pair in his earlier reported series of 16 MZ pairs

was now concordant for schizophrenia, and he discovered three new MZ pairs, one concordant and two discordant, making a pairwise concordance rate for schizophrenia of 3 out of 19, or 16 percent. If we exclude the two previously discordant pairs where Tienari considered that the proband might have had an organic psychosis, and if we count one of Tienari's borderline co-twins as meeting our criteria for probable schizophrenia (Gottesman and Shields 1972), we reach a provisional pairwise concordance rate of 4 out of 17 (24 percent). Counting the twins in the first three concordant pairs as independently ascertained, we reach the probandwise rate of 7 out of 20 (35 percent) shown in table 4. We do not maintain this estimate is necessarily the most correct rate for the study. The findings will be subject to further change since the diagnosis and zygosity of all the 186 twins found in the hospital registers have not yet been completely sorted out.

The Maudsley Hospital based study of Gottesman and Shields (1966b and 1972) included case histories of both MZ and DZ pairs, blindfolded diagnoses of the 114 twins by a panel of six judges plus a Scandinavian viewpoint by Essen-Möller, and a critical afterword by P. E. Meehl (Gottesman and Shields 1972). Reports of the work before and at the Puerto Rico conference in 1967 (Gottesman 1968) made use of four operationally defined categories of disorder/normality that have been abandoned for the consensus diagnosis of the panel (see table 1). The complete reporting of details in Gottesman and Shields (1972) will permit further analyses and tests of competing or alternative hypotheses by others without the great expenditure of time and energy required initially to collect a sample from 16 years' worth of consecutive admissions to a regional psychiatric facility. Despite the emphasis on formal quantitative and population genetics as the framework for evaluating the data, attention is also directed to sociodemographic and hypothesized psychodynamic factors. The overly condensed summary of concordance rates in table 4 shows our work to be of a piece with the other recent twin studies. The fact that the probands came from about 45,000 consecutive admissions to both inpatient and (mostly) outpatient sources was given as one reason why the MZ concordance rates were somewhat lower than the earlier twin studies that had a large proportion of "standing" hospital cases. Extensive psychometric assessments by means of the Minnesota Multiphasic Personality Inventory, the Goldstein-Scheerer Object Sorting Test, and the Global Psychopathology Rating Scale added new dimensions to this twin study as did the tape-recorded interviews with most of the twins.

We (Gottesman and Shields 1972) explored a new way for testing the validity of various of our judges' individual and consensus diagnoses of schizophrenia by using a genetic criterion. We asked which concepts of schizophrenia preserved and maximized the difference in concordance rates between MZ and DZ pairs. Aside from the obviously greater reliability obtained for a consensus diagnosis for psychometric reasons, we found that either too narrow or too broad a concept for schizophrenia eroded the MZ-DZ contrasts—too narrow lowered the MZ rate to the value of the DZ rate and too wide raised both the MZ and the DZ rates to dilute an indicator of "biological specificity," the ratio of the MZ:DZ concordance rates. These findings are not unlike those of Carpenter, Strauss, and Bartko (1973), which showed the effects of too many or too few first-rank symptoms (Schneider 1971) on the number of false positive and false negative diagnoses of schizophrenia.

Since the publication of our book in 1972, we have gone on to explore the concepts of schizoidia and the so-called schizophrenia spectrum (Shields, Heston, and Gottesman 1975) by using the expected and observed rates of various conditions in co-twins as a point of departure. One consequence of our joint paper with Heston was a revision of the latter's (1970) formulation that schizoidia was the basis of most schizophrenias and that schizoidia was caused by a dominant gene with complete penetrance. The revision was occasioned by looking at exactly what conditions it was necessary to include among DZ co-twins of the Maudsley schizophrenic probands before a 50-percent rate of affectation was achieved. It was obvious that a concept of schizoidia too wide to be useful outside of family studies was needed to retain the idea of complete penetrance despite the earlier formulation (Heston 1970) of twin and family data. We agreed to disagree on whether a dominant gene with incomplete penetrance (essentially Slater's 1958 theory; see also Slater and Cowie 1971) was any better or worse than a polygenic threshold theory wherein some genes could have large effects, especially since we had shown (Gottesman and Shields 1972) that

the predictions of the two theories led to indistinguishable differences with the empirically observed risks in relatives of schizophrenics (see table 9, p. 388).

It might be thought that the two kinds of theories, monogenic and polygenic, would generate very different research strategies. The monogenic theory should lead one to search for a specific biochemical abnormality, while the polygenic theory should necessitate a multivariate, statistical approach. Monogenic theories for schizophrenia, however, now require many factors in addition to the posited necessary gene, and polygenic theories, far from excluding biochemical genetics, would be consistent with schizophrenia depending mainly on a multifactorially determined quantitative abnormality in a single biochemical system. The consequences of the two classes of theories are not as distinct as was supposed before the revolution in molecular biology that incorporated gene regulation and before the advances in quantitative genetics that incorporated the concept of individual genes with much larger effects than others in a system (cf. Edwards 1972, Erlenmeyer-Kimling 1972, Harris 1975, and Shields and Gottesman 1973).

One recurring theme in our own writings on schizophrenia is that by construing the disorder as a polygenically determined one with a threshold effect, a number of heuristic benefits accrue to investigators. Models provided by *Drosophila* genetics (Thoday 1967), population genetics (Cavalli-Sforza and Bodmer 1971), and mathematical geneticists (Curnow and Smith 1975, Falconer 1965, and Smith 1972), and leads provided by researchers on such conditions as diabetes (Falconer 1967 and Maugh 1975) and even Huntington's disease become grist for the schizophreniologist's mill. We (Gottesman and Shields 1967) introduced psychopathologists to Falconer's (1965) concept of the liability to developing a threshold trait and calculated that the heritability of the liability to developing schizophrenia on present evidence is in the neighborhood of 85 percent; a naive determinist view of this value is not warranted (Brown, Harris, and Peto 1973, Gottesman and Shields 1973, and Shields 1971). Most other schizophrenia researchers have not chosen to differentiate between threshold and continuum models, even if they support a polygenic view over a monogenic one.

Unknown at the time of the Puerto Rico conference was the study reported in 1969 by Pollin, Allen, Hoffer, and Stabenau of the National Institute of Mental Health (NIMH) in conjunction with Z. Hrubec of the National Academy of Sciences/National Research Council Medical Follow-Up Agency that made use of computerized information on all pairs of male twins where both men served in the U.S. Armed Forces during the years spanning World War II and the Korean War (Pollin et al. 1969). The starting sample of 15,909 twin pairs from which their final sample of schizophrenic probands emerged was certainly impressive in size. The authors report that even a partial evaluation of the birth cohort from which their sample was selected revealed a large sampling loss: For 40 of the 50 States where vital birth statistics were compared, 23,000 pairs were identified where neither twin served and in a further 15,000 pairs only one twin served. Thus, some 70 percent of the male twin cohort was lost before their search for schizophrenics could begin. Table 4 shows one effect of this selection for mental and physical health in that the *upper* limits to the pairwise concordance rates, 27 percent MZ and 5 percent DZ, are the lowest of any of the recent twin studies. The probandwise procedure has the apparent effect of "undoing" the possible selective factors, and the final rates are much like those of the other studies. As reported by Pollin et al. (1969), the age of the twins in 1965, when the data were essentially up to date, ranged from 38 to 48 years.[3] The VA charts have been reviewed for the 420 pairs with a psychotic diagnosis, and the data in table 4 are based on reevaluations (not blindfolded) of that information by Allen, Cohen, and Pollin (1972). They report they found no difference in concordance rates as a function of the certainty of diagnosis of schizophrenia. It would still be of interest to see the actual rates for their three levels of certainty in case there is an expected trend.

In the study of veteran twins described above, no personal investigation of the twins has been conducted by the psychiatrist researchers, and it would be unwise to come to any final conclusion about the eventual results. Nevertheless, combining schizophrenic and schizoaffective groups (Cohen et al. 1972) gives the probandwise rates of 43 and 9 percent for the two twin types (assuming that all cases can be treated as probands). These prevalences in co-twins of psychotics can be compared with their very useful and unique data on the zygosity-specific prevalences in the entire VA

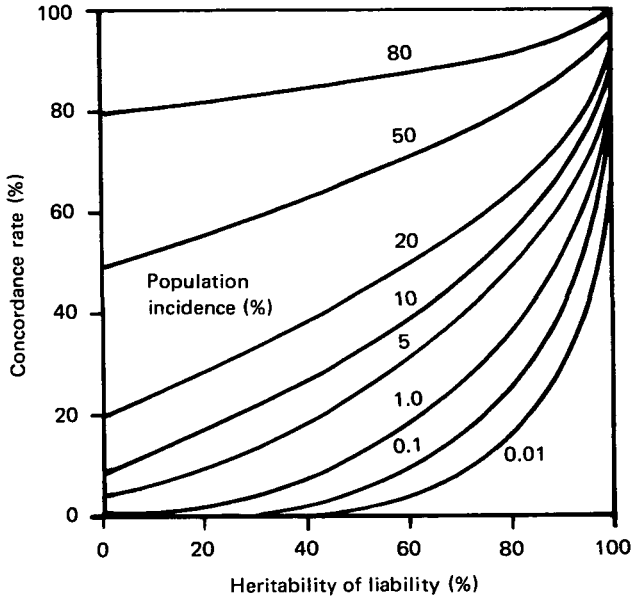
[3] Allen, Cohen, and Pollin (1972) report that 13 new cases were added "to the Veteran Twin Registry through 1970 as part of the ongoing updating process" (p. 940).

twin population, and the rates are some 50 and 10 times the corresponding rates. It should be noted that efforts of Pollin et al. (1969) to calculate the "heritability" of schizophrenia and to compare that with the values for other diseases and conditions cannot be taken seriously. They used a discredited formula derived from Holzinger (1929) for dichotomous traits that yields meaningless estimates (cf. Cavalli-Sforza and Bodmer 1971, Christian, Kang, and Norton 1974, and Smith 1974). They report a value of .373, whereas using the model of Smith (1970) their probandwise rates (given in our table 4) and their overall prevalence of .98 percent yield two independent estimates of heritability of the liability to developing schizophrenia of .83 and .80, indistinguishable from other values we have calculated using different classes of relatives besides twins.

Concordance and Heritability

As is apparent in table 4, there is reasonably good agreement among the recent twin studies of schizophrenia. In our own estimates of probandwise concordance (table 4), no MZ rates are now as low as 0 percent or even 14 percent. This is partly a consequence of using the proband method, partly the result of more thorough sample investigation or longer followup times in some of the studies, but largely because, in preparing table 4, we imposed diagnostic standards that were as similar as possible to the consensus diagnoses of schizophrenia plus probable schizophrenia that we had found so meaningful in the Maudsley twin study (Gottesman and Shields 1972). The differences between the classical studies of Luxenburger (1928), Slater (with Shields 1953), and Kallmann (1946) and the current work are less marked than was supposed at the beginning of the 1960's. Our current synthesis accords well with our statement a decade ago "that we are dealing with replications of the same experiment" (Gottesman and Shields 1966b, p. 815). It will still appear paradoxical that we and other geneticists can claim that the genetic factors involved in schizophrenia are of such major importance when the pooled MZ concordance rates are only about 50 percent. If one is willing to assume that the genetic and environmental contributions to liability are multifactorial and normally distributed, then the paradox is resolved by a study of the form of distribution of concordance rates in MZ twins as a joint function of the population prevalence of a disease and of the heritability

Figure 1. Expected concordance rate in identical twins given the population incidence and the heritability of liability.[1]



[1] **Reprinted from Smith (1970) with permission of *Annals of Human Genetics*.**

of liability to that disease. We reproduce Smith's (1970) projections in figure 1. It can be seen that with a population prevalence for schizophrenia of about 1.0 percent, the expected MZ concordance rate is only 13 percent when the heritability is 50 percent and only 37 percent when the heritability is as high as 80 percent. It follows that a low concordance rate in MZ twins cannot be taken as evidence that the degree to which the liability is under control of genes is also low.

The magnitude of heritability (symbolized as h^2) estimates for the liability to schizophrenia is much less informative about the importance of environmental factors for most schizophrenics than might be assumed. One of the reasons high heritability estimates do an apparent "injustice" to environmental factors is that heritability is a concept of population genetics according to which $(1-h^2)$ relates to the role of environmental differences over the population as a whole; the "what's left over" from genetic variance in liability thus becomes the "environmentability."

While environmental factors may contribute only about 20 percent (100 – 80 percent) to the variance of the combined liability to developing schizophrenia in the whole population, they will be critical in determining whether the individual with a genetic high risk breaks down. It is true that various lines of evidence reviewed so far converge to discredit shared family environment as important, but that still leaves as important for the individual those aspects of the environment not shared or those not experienced in the same way by others. Much of the work of social psychiatry, such as that of Birley and Brown (1970) and Brown, Harris, and Peto (1973), speaks to the role of such presumptive idiosyncratic stressors and objective "life events" of many kinds in precipitating onsets and relapses in some schizophrenics (cf. Dohrenwend 1973, Dohrenwend and Dohrenwend 1974, and Rahe 1968). Cases at the extreme tail of the distribution of genetic liability may infrequently have such objectively defined life events prior to developing the disorder—perhaps any environment would be sufficiently stressful for them. For the larger number of individuals who are not so extremely predisposed, however, these relatively gross events will presumably play a larger role (see Gottesman and Shields 1972, figure 10.4). The majority of the population, of course, do not develop schizophrenia even when exposed to severe and multiple stresses (cf. Kohn 1973, Lader 1975, and Hare, Price, and Slater 1972). Only those in the zone of combined liability near the threshold of overt schizophrenia may have their illnesses precipitated by the addition of liability from environmental sources. This reasoning makes it clear that although the genes may be necessary but not sufficient, the environmental contributions may also be necessary but not sufficient for "causing" schizophrenia.

Discordant MZ Twins as Pointers to Specific Stressors and Pertinent Endophenotypes

Although the study of discordant identical twins tends to be associated with the work at the NIMH of Pollin et al. (1966), it is a fact that all the systematic studies of MZ and DZ twins beginning with Luxenburger (1928) to the present paid special attention to discordant identical twin pairs for the value they had in highlighting environmental contributors to schizophrenia and for the suggestions they held in regard to etiological heterogeneity. Since the work reported at the Puerto Rico conference (Pollin and Stabenau 1968), the NIMH series has grown to 17 MZ pairs at first thought to be discordant and who have now been followed up (Belmaker et al. 1974). It would be a meaningless task to calculate the concordance rate for schizophrenia in such a series at any point in time since they were selected especially to be discordant. Discordant MZ pairs are ideal for revelations about specific stressors that precipitate schizophrenia, and they can be used to indicate endophenotypes that are not the result of the disease but that may be necessary for the disease or at least contribute to its etiology.

In the earlier reports on the NIMH series, intrapair submissiveness, birth weight, identification with parents, and a few other variables studied (Mosher et al. 1971a) were so intercorrelated that it was not possible to treat information on the variables separately. In the first 11 pairs (Pollin et al. 1966), the future schizophrenic was lighter at birth in every instance, if only by ½ ounce (one case). Of the current 17 pairs reported on by Belmaker et al. (1974), two had the proband heavier at birth. One pair has become concordant, and three, including a borderline case, possibly concordant. Of the 12 discordant pairs with available birth-weight information, 10 probands were lighter at birth. An unusual feature in an already unusual sample was the frequency of triplets (treated as if they were simply twins): much of the biggest weight differences were attributable to the "triplet twins," and in the eight discordant ordinary pairs and where the proband was lighter, the mean difference was 205 grams (less than ½ pound). Systematically ascertained twin samples do not support the hypothesized role of birth-weight differences in discordant pairs. Furthermore, the idea that either weight or other perinatal difficulties have a specific role in the etiology of schizophrenia in those at risk for it now seems unlikely (Hanson, Gottesman, and Heston 1976, McNeil and Kaij 1973 and 1974, McNeil, Persson-Blennow, and Kaij 1974, and Mirdal et al. 1974).

Intrapair submissiveness was more consistently related to discordance in both the NIMH and the other studies in table 4. Table 5 contrasts the data on both birth weight and submissiveness in regard to (pooled) discordant MZ pairs. From the analyses in table 5, it is clear that within-pair submissiveness was indeed associated with which of two genetically identical individuals became schizophrenic, and that lower birth weight occurred as often in the nonschizophrenic as

Table 5. Differential association of submissiveness and lower birth weight with schizophrenia in discordant MZ pairs.

More submissive twin is schizophrenic	Lower-birth-weight twin is schizophrenic
84/100 (84%)	43/87 (49%)

Note.—MZ pairs from studies by Slater (1953), Inouye (1963), Tienari (1963), Kringlen (1967), Fischer (1973), and Gottesman and Shields (1972), as analyzed by Gottesman and Shields.

in the schizophrenic member of such matched pairs. The first fact, however, does not lend itself to easy interpretation along the lines of therapeutic intervention. The reasons include the difficulty of distinguishing between cause and effect; the submissiveness could merely be an early sign of the schizophrenic process having started. Second, the entire discussion of submissiveness in the context of the dyadic relationship of twins makes use only of relative status on this trait vis-à-vis the other twin and may have no relationship to absolute levels (cf. Searles 1965 and Tienari 1966).

In principle, the study of discordant MZ pairs should be useful for detecting the role of neurologic dysfunction in causing or precipitating schizophrenia, even if it means using so-called soft signs (cf. Kessler and Neale 1974). The Pollin team (Mosher, Pollin, and Stabenau 1971b) made use of two blind neurologist raters and came up with admittedly inconsistent findings. Abetted by necessarily different standards for the presence of soft signs, only random agreement was reached between the two raters. Since followup showed 4 out of 17 possibly concordant pairs, the task of the neurologists was even more difficult than thought.

Despite high hopes, the study of discordant MZ pairs has not yet led to a big payoff in the identification of crucial environmental factors in schizophrenia. The problem is simply more difficult than we now can cope with: Environmental variation within twin pairs is limited to a relatively narrow range, sample sizes are small, the data needed are subject to retrospective distortions, and the "culprits" may be nonspecific, time-limited in their effectiveness, and idiosyncratic. Sophisticated efforts by Dohrenwend and Dohrenwend (1974), Rahe (1971), and Brown, Birley, and Wing (1972) that recognize individual differences in genetic background yield heuristic suggestions for further analyses of twin data.

Vistas appear more promising when it comes to using discordant MZ twins as a tool for identifying pertinent biochemical and physiological (including psychophysiological) *endophenotypes.* By the latter is simply meant phenotypic information that is not available to routine clinical examination and that is one step removed from behavior per se and thus one step closer to the genotype (albeit still a long way away). The NIMH Twin-Sibling Unit turned from environmental reasons for discordance to a careful look at some enzymes implicated in psychoses (Usdin and Snyder 1973 and Wise and Stein 1973); the Belmaker et al. (1974) followup was initiated to provide Wyatt et al. (1973a and 1973b) with useful blood samples. Enzyme activity connected with dimethyltryptamine was raised in the probands but not in the unaffected co-twins. This may or may not turn out to be an interesting biochemical finding, but there would be little point in testing the relatives for this enzyme: logic dictates that raised levels are an effect, not a cause. The results with platelet monoamine oxidase (MAO) levels were indicative of a pertinent endophenotype: Both the probands and their unaffected co-twins had low levels. On this basis alone it would make sense to follow the MAO lead and to examine relatives of schizophrenics for it. It is still unknown to what extent variation in levels is under genetic control (cf. Brockington et al. 1976 and Robinson and Nies 1973). The specificity of the finding in regard to schizophrenia has already been questioned by Friedman et al. (1974) who could not find differences among normals (23) and schizophrenics (26) and other

acutely hospitalized psychiatric cases (12). These authors concluded that MAO activity in platelets is not connected with psychiatric diagnosis but may be under hormonal, dietary, or genetic control (cf. Meltzer and Stahl 1974). Further, platelets are only assumed to be a model for what goes on in the brain catecholamine systems (Barchas et al. 1975).

Still the research with MZ twins discordant for schizophrenia is instructive for how the method of endophenotype searching can proceed and for how strategies can be developed whenever new methods develop (cf. Arnold 1971, Cazzullo, Smeraldi, and Penati 1974, Kety 1975, Omenn and Motulsky 1973, and Shields 1975). A number of individuals using such techniques have misleadingly labeled their particular endophenotype as a "genetic marker" of schizophrenia. The term should be reserved (see Giblett 1969) for the established genetic polymorphisms such as the blood groups where a particular endophenotype determined by a chemical reaction has narrow and fixed implications for the genotype of an individual. A more neutral term that could be used in this context is simply a "biochemical indicator" (of the liability to developing schizophrenia). True genetic linkage studies are difficult to conduct in the absence of large pedigrees fully studied for genetic polymorphisms, but interesting steps have been initiated (Elston 1973, Elston, Kringlen, and Namboodiri 1973, Fieve, Rosenthal, and Brill 1975, Renwick 1973, and Robertson 1973).

We are certainly not recommending the promiscuous embrace of just anything biological in connection with the search for endophenotypes of schizophrenia.[4] There has already been too much of a shotgun or cleaning-of-the-reagent-shelf approach (or psychological test locker). Our best hopes of advance for a genetic marker would be the identification of a protein (electrophoretically or otherwise) whose activity is related (rationally) to the biochemistry/pharmacology of schizophrenia (cf. Nicol, Seal, and Gottesman 1973, Kety 1974a, Kety and Matthysse 1972, and Snyder et al. 1974). It must also have the "right" amount of polymorphism to fit with clinical observations about probands and their relatives. If this ideal were not achieved, it would still be important to identify any polymorphism that might lead to prenatal detection (cf. Omenn and Motulsky 1975) of schizophrenia *potential* in probands' fetuses (another ideal), or to the ability to account for any appreciable variance in the liability to schizophrenia so that a different kind of high risk population might be identified from the general population of individuals not related to schizophrenics but who provide the vast majority of cases.

Family Studies

One of the consequences of the refutation of strong criticisms of the twin and adoption studies of schizophrenia is that we can focus with renewed confidence on genetically oriented family research. The advantages of family-based genetic research include ease of assembling a large and representative sample, freedom from the special problems associated with twins and adoptees, and a rich heritage of comparison studies in the human genetics literature. The number of family studies of schizophrenia in recent years precludes us from taking anything other than a general approach and providing appropriate citations for the consumer to follow up. We shall focus on the related problems of what disorders the affected relatives have, the genetic relationship of schizophrenia to other psychiatric disorders, and etiological heterogeneity within the schizophrenias. Attention to various within-family psychodynamic factors and between-family sociodemographic variables goes beyond the scope of this article.

One fact on which almost all the European-type family work agrees is an age-corrected risk of about 10 percent for schizophrenia in the siblings of probands (Bleuler 1972, Fischer 1974, Lindelius 1970, Ødegaard 1972, Stephens et al. 1975, and Tsuang et al. 1974). With the exception of Ødegaard, the cited studies found no excess of affective psychoses in siblings of schizophrenics. The consistency with the earlier European work (12 studies) summarized by Zerbin-Rüdin (1967) is comforting. Similar conclusions also apply to the recent studies on the risks to the other first-degree relatives—parents and children.

When we turn to American research, we find some exceptions. Winokur et al. (1974) reported quite low schizophrenia risks from .8 to 2.4 percent in the (adult) offspring of paranoid and hebephrenic schizophrenics, respectively. These risks contrast sharply with the finding reported by Cammer (1970) that 27 percent of the offspring of 273 manic-depressive parents were schizo-

[4] See the entire Vol. 2, No. 1, 1976 issue of the *Schizophrenia Bulletin* for a comprehensive review by many experts of the current state of the art in biological factors in schizophrenia.

phrenic. Reed et al. (1973) studied the pedigrees of 89 kinships first gathered at the Warren (Pa.) State Hospital before World War I. They enumerated more than 18,000 individuals in their total project. Diagnostic problems (e.g., old and brief State hospital charts, dead subjects) led them to analyze their data mostly in terms of functional psychosis. The risk of psychosis for the siblings of psychotics was (a quite high) 24.7 percent and for the children, 26.2 percent. Unexpectedly, only 1.7 percent of first-degree relatives of affective probands were similarly affected, while 15.0 percent had schizophrenia and 7.2 percent had other psychoses. Another atypical finding was an apparent maternal effect wherein the risk of psychosis for the children of psychotic mothers was 20.1 percent compared with 8.1 percent for those of fathers. Later onset cases (cf. Larson and Nyman 1970 and Zerbin-Rüdin 1975) in the offspring accounted for much of this difference. Part of the observed effect may well be due to less selection pressure against sick females than equally sick males. Reanalysis for schizophrenic parents only (Hanson 1974), however, shows that many of the females, unlike the males, had mates who were also psychiatrically abnormal. Like Kallmann (1938) earlier, Bleuler (1972) found no maternal effect—7.6 percent of the children of male schizophrenics were schizophrenic compared with 4.3 percent of female schizophrenics' children (not age-corrected).

Kraepelin (1974) was well aware of the complexity of the conditions determining psychiatric symptomatology: "no experienced psychiatrist will deny that there is an alarmingly large number of cases in which it seems impossible, in spite of the most careful observation, to make a firm diagnosis" (p. 28). He recognized that schizophrenic symptoms were by no means limited to dementia praecox. Though he was impressed by "the amazing similarity often found between the illnesses of close relatives" (p. 15), the first genetic study of schizophrenia by Rüdin (1916) found almost equal numbers of schizophrenic and affectively ill relatives in the families of schizophrenics. Though later workers of Rüdin's school thought that by selecting clinically homogeneous probands they could minimize the occurrence of psychoses of different types in the same family, the problem never entirely disappeared. Whereas Bleuler (1972) found no excess of manic-depressives among the siblings of his schizophrenic probands and only 2 percent among the parents, Ødegaard (1972) in further studies of the families of psychotic patients admitted to Gaustad Hospital in Norway found a mixed picture. While there is a significant degree of resemblance as to type of psychosis in pairs of psychotic first-degree relatives, neither severely deteriorating schizophrenia nor typical manic-depressive psychosis breeds completely true to type. Table 6 shows the percentage of psychotic relatives whose diagnoses were schizophrenia, reactive psychosis, or affective psychosis for six proband groups. Such findings do not fit easily into a view of distinct disease entities nor into that of a unitary *Einheitspsychose*, but might be consistent

Table 6. Diagnostic distribution of Norwegian index patients and their psychotic relatives.[1]

Proband diagnosis	No. of psychotic relatives	Percentage of psychotic relatives diagnosed as having:		
		Schizophrenia	Reactive psychosis	Affective psychosis
Schizophrenia, severe defect	109	78.0	7.3	14.7
Schizophrenia, slight defect	368	70.5	15.7	13.8
Schizophrenia, no defect (schizoaffective, etc.)	179	45.8	22.9	31.3
Reactive psychoses	82	28.0	47.6	24.4
Atypical affective psychoses	39	35.9	28.2	35.9
Manic-depressive psychoses	47	19.1	10.6	70.2

[1] Data presented in table derived from Ødegaard (1972).

with hypotheses between these extremes, such as correlated polygenic systems or genetic heterogeneity with phenotypic overlap (cf. Smith 1976).

Before turning from the relationship between schizophrenia and the other psychoses to the unity or diversity of schizophrenia itself, it may be useful to mention the types of nonpsychotic disorders that have been found among the relatives of schizophrenics. Lindelius (1970), in a Swedish study, found a high rate of alcoholism in the parents (16 percent) and children (10 percent) but not in the siblings (3 percent) of schizophrenics. Stephens et al. (1975), in their Newcastle-on-Tyne (United Kingdom) study, found an excess of nonneurotic personality disorders (psychopathy, paranoid and schizoid personality) in interviewed parents and siblings and an excess of heavy drinkers in all parents and siblings. Bleuler (1972), at the Burghölzli Hospital in Zurich, noted a variety of personality disorders in the siblings of schizophrenics and emphasized the point that these were not to be thought of as fixed constitutional traits; there was some excess of senile psychoses among the parents. Ødegaard (personal communication, 1974) found that the extent of psychosis in the parental generation of psychotic probands influenced the rate of "all psychiatric diagnoses" in the siblings, as well as the rate of psychosis itself. The nonpsychotic diagnoses were "serious cases of neurosis, most of them hospitalized, but not alcoholism." Conversely, Reed et al. (1973), as already noted, found that nonpsychotic abnormality in the spouse of a psychotic increased the risk of psychosis in the children. The variety of the findings in different settings and within different diagnostic frameworks highlights some of the problems over the concept of a schizophrenia spectrum and deciding what is in it (cf. Rosenthal 1975 and Shields, Heston, and Gottesman 1975).

Now we can begin to examine the degree to which the phenotypic heterogeneity of schizophrenia is paralleled by genetic heterogeneity. Currently the concern is whether the groups variously called reactive (as opposed to process) schizophrenia, schizoaffective, good prognosis, paranoid, acute schizophrenia, and so on are closely related genetically to nuclear ("true" or core) schizophrenia or are something quite different. We have already mentioned how the Rosenthal and Kety adoption studies led them to the view that unlike borderline cases, acute (B2) cases as they defined them should probably not be grouped along with the chronic schizophrenias. Welner and Strömgren had earlier (1958) excluded benign (at followup) schizophreniform psychoses from the genetic forms of schizophrenia, since they had been provoked by exogenous factors; genetic factors were nonspecific and related to general vulnerability. Clayton, Rodin, and Winokur (1968) group schizoaffective psychoses genetically with the affective disorders, while Mitsuda (1972) and Perris (1974) consider the atypical and cycloid psychoses to be separate mental disorders from either affective or schizophrenic ones and to segregate as Mendelian dominants (cf. McCabe and Strömgren 1975).

Data also exist to support the "lumpers" against the "splitters." Achté (1961), in Finland, compared schizophrenics with schizophreniform psychotics, carefully diagnosed, and found that parents of both groups were equally often schizophrenic. Using a division into good and poor prognosis probands (but the same strategy as Achté), Larson and Nyman (1974), in Sweden, found no differences between first-degree relatives. Bleuler's (1972) 208 probands contained 22 percent with acute onset ending in recovery. They had almost the same incidence of families with a positive history of schizophrenia (32 percent) as the other probands (38 percent), and there were many instances of good and poor outcome cases within the same family. A best-of-both-worlds opinion was provided by Angst (1966), who examined a group of 73 schizoaffective (mixed) psychotics. The family histories led him to conclude that they were a very heterogeneous group etiologically—some at least were schizophrenia related, since 7 percent of the siblings were schizophrenic.

A complementary issue is whether the classical pre-Kraepelinian subtypes, taken together, are genetically homogeneous or not. The status of paranoid schizophrenia has most often been questioned both in Kraepelin's time and since. Some forms of paranoid schizophrenia, such as Kretschmer's *sensitive ideas of reference*, might be psychogenic and unrelated genetically to nuclear cases, while others—indistinguishable from schizophrenia on phenomenological grounds—could be symptomatic organic psychoses (Davison and Bagley 1969) based on temporal lobe epilepsy or amphetamine poisoning (cf. Zerbin-Rüdin 1966). Apart from such possibilities, however, the general finding has been that cases of *all* subtypes occur in the families of *each* subtype, with only a modest tendency toward subtype resemblance within families. In addition, there appears to be more schizophrenia in the families of hebephrenic and catatonic cases than in those of paranoid and other peripheral

schizophrenics. Recently, Tsuang et al. (1974), in a study based on 60 probands with blind diagnosis of relatives, confirmed the tendency to higher rates in nonparanoid families, but found no tendency to family resemblance in subtype. Bleuler's (1972) findings reveal only a slight tendency to family resemblance in outcome or *Endzustand.* (He did not employ the hebephrenic-catatonic-paranoid grouping.)

The degree of resemblance found in twin and family studies led us (Gottesman and Shields 1972 and 1973) to consider that among the genes predisposing to the development of schizophrenia, some might have a greater influence than others, including some that affect the clinical picture. In other words, allowance would have to be made for some heterogeneity within the hypothesized polygenic system. Winokur et al. (1974), however, argued from provisional results from their "Iowa 500" study that there are two distinct genetic types of poor prognosis schizophrenia: hebephrenia, which may occasionally manifest itself clinically as paranoid, and paranoid schizophrenia in which there is a lower risk to relatives but in which an affected relative would suffer from paranoid schizophrenia only. We believe such a conclusion is premature (see the Editorial in *British Medical Journal* 1974) and gives the misleading impression that poor prognosis paranoid schizophrenia, hebephrenia, and good prognosis schizophrenia are distinct genetic diseases in the sense that Huntington's chorea and Alzheimer's disease are distinct.

Even in diabetes, a disease much better understood pathophysiologically than schizophrenia and diagnosed on the basis of definitive tests rather than on subjectively recorded observations or self-reports of behavior, there is considerable uncertainty about the degree of homogeneity of juvenile and maturity onset cases. Expert analyses of available data have led to the conflicting conclusions (Maugh 1975 and Tattersall and Pyke 1972) that juvenile onset (before 40) cases are caused by viral infections; or, since they are early and the environment has less time to work its effects, they are even more heritable than maturity onset cases (Falconer 1967 and Smith, Falconer, and Duncan 1972); or they represent a different genotype; or they are simply more severe varieties of the one basic disease. The twin and family studies give some support to each of these interpretations, almost paralleling the schizophrenia saga. A recent analysis of some of the diabetes data according to multifactorial modeling (Smith 1976) concludes that the causes of early and late cases *are partly the same and partly different.* We feel comfortable with such a Solomonic stance vis-à-vis schizophrenia in its various clinical manifestations.

It is difficult to reach clear and definitive conclusions from the family studies reviewed in this section because of the inevitable heterogeneity of the disorder under study and because of the lack of consistency across studies that results from our old enemies diagnostic unreliability and invalidity. Further refinements must await a reliable and valid endophenotype. Some help can be expected from reanalyses of dual mating studies or from new dual mating studies designed to avoid the pitfalls of contaminated diagnoses of offspring after knowledge of parental diagnoses.

Dual Mating Studies

Since prospective studies of the offspring of schizophrenic parents have come to be called "high risk," it is necessary to distinguish the same kinds of strategies, but where both mother and father are schizophrenic, as "super high risk." Whereas the average risk to the children of one schizophrenic is about 13.9 percent, dual mating schizophrenics produce 46.3 percent definite or probable schizophrenic offspring (Erlenmeyer-Kimling 1968b and Slater and Cowie 1971). The strategy of studying offspring where both parents are affected need not be limited to the specific matings of two schizophrenics in order to add to our armament of data on the heterogeneity of schizophrenia and on the specificity of the components of any schizophrenia spectrum. It should be of crucial interest to see what kinds of psychotic children are produced and in what proportions when a 2 X 2 Punnet square (analogous to what geneticists call a diallel cross) is formed with maternal phenotypes on one edge and paternal phenotypes on the other while the children's phenotypes in each intersecting square are studied. In this fashion, one can search for differential maternal effects since both mother S (schizophrenic) and father BP (bipolar) and the reciprocal "cross" father S and mother BP would be examined. The Punnet square strategy is being pursued in Denmark with a large cohort of all psychiatric inpatients regardless of chart diagnosis by Fischer and Gottesman (see below). A classical illustration of the use of dual matings to elucidate the modes of transmission of a diagnostic syndrome was the

"group of deafnesses" (Cavalli-Sforza and Bodmer 1971, pp. 372-376): an unforeseen increase in assortative matings was brought about by special schools for the deaf. (Note that halfway houses and outpatient group therapy can have similar effects.) Conventional wisdom had it that most cases were recessive and some were dominant, but no one suspected the large amount of heterogeneity within both modes that was revealed by the dual matings' offspring. Briefly, matings between spouses with an apparent recessive form of deafness led to no affected offspring, while 100 percent affected had been expected from the mating of two homozygous recessive genotypes. Conclusion: Two different loci were involved. Blindness provides further examples (Fraser and Friedmann 1967).

The five classical studies involving dual mating schizophrenics were summarized by Erlenmeyer-Kimling (1968b) at Puerto Rico, and a study in progress in which she continued the work of Kallmann in New York was introduced. That so few studies exist can be taken as evidence of the rarity of such matings, especially those that are fertile, but Erlenmeyer-Kimling calculated that they were not rarer than MZ pairs with a schizophrenic proband. If one subscribes to the hypothesis of Searles (1965) that one schizophrenic can "drive the other spouse crazy" in a schizophrenic manner, dual matings would be a commonplace. Scharfetter (1972) studied just this problem of induced psychosis or *folie à deux* using nine of his own cases at the Burghölzli Hospital and 231 cases he identified in a survey of the literature (sources not detailed, however). His procedure for calculating morbid risks can be criticized, but even without age correction, the rate of schizophrenia among the first-degree relatives of the critical group of cases in whom a psychosis had been induced by a nonrelative was clearly raised to 9.1 percent (15/165). These results provide the strong suggestion that the seed had been planted in schizophrenic soil. Dual mating schizophrenics are not a commonplace, but some instances of induced schizophrenias (narrowly defined) in a spouse can suggest an unmasking of assortative mating for the predisposition to schizophrenia.

Elsässer's 1952 monograph was based on work done in 1936-38, but its publication was delayed by the war. A followup study of the children in 30 out of 38 families was carried out by Elsässer, with the help of three colleagues interested in psychodynamics, in 1955-59; the results of the followup by Elsässer et al. were published, in final form, in 1971. The 11 S X S families are described in detail, and the other kinds of dual matings receive abbreviated treatment. Depending on the age-correction procedure used, Elsässer's earlier (1952) 39 percent rate of schizophrenia is lowered to around 36 percent. The risks for other mating types do not differ much from this. Earlier, 20 MD X MD matings yielded 14 psychotics but only 1 was schizophrenic, and 19 S X MD matings produced 8 schizophrenic and 8 manic depressive offspring. A flaw in this research is that no diagnoses were made blindfolded. The authors conclude that at least one-third of the offspring of S X S matings become schizophrenic, that conflict situations and frustrations act as releasers of endogenous psychoses, and that particularly good or bad family environments appear to have no influence.

A new study of the offspring of dual matings has been reported in very preliminary form in Norway by Bastiansen and Kringlen (1972). They found that of the 70 offspring of 22 dual matings of psychotic parents, 19 percent were psychotic (a figure that went to 25 percent when age-corrected in an unstated fashion); 38 percent had other diagnoses; and 41 percent were called normal. In many ways the percentage of offspring seen to be normal in such studies is one of the most important pieces of benchmark information in the nomological network about schizophrenia. Bleuler (1972) only had three dual matings with a total of five children aged 30-54. None was schizophrenic, one was a schizoid psychopath, one was extremely neurotic, one had mild schizoid tendencies, and two were perfectly normal. He gives the case histories and comments about the three children who were useful citizens despite rearing by their parents: "Normal development can take place in the face of total neglect, copious 'teaching of irrationality,' and the total degeneration of the imaginative world of the parents." Elsässer (1952) too found 70 percent of the nonpsychotic children of S X S pairings to be perfectly healthy. Since it is obvious that we do not have a situation of matings between homozygous recessives, we can expect a great deal of genotypic variation in the offspring of dual matings: The high proportion of normality is evidence against the strong role that can be assigned to within-family environmental stressors as uniform causes of schizophrenia.

Ødegaard (personal communication) looked at the siblings of psychotics as a function of parental status. When both parents were psychotic, in addition to the proband, 35 out of 129 (27 percent) of the siblings were

psychotic. Including all diagnoses, mostly hospitalized, 50 percent were affected. In accordance with polygenic theorizing, the sibling rates (with both parents psychotic) varied according to whether uncles and aunts were also psychotic from 20 percent (undifferentiated psychosis rate in siblings, no psychotic uncles or aunts) to 61 percent (all-diagnosis rate in siblings, psychotic uncles or aunts).

A dual mating study conducted in Russia by Moskalenko (1972) provided the opportunity for the clinical observation of a large number of offspring of dual matings within the Soviet psychiatric framework, even though the research was not designed as a formal genetic investigation. The IPSS (World Health Organization 1973) permits a "cross-translation" of the Soviet nosology (e.g., shiftlike schizophrenia). Thirty S X S families were examined as were 44 in which only one parent was schizophrenic (but several of their spouses were said to be schizoid). Of the 57 children from dual matings, 33 (57.8 percent) were schizophrenic and, with the addition of 12 possible schizophrenics, that rate rose to 78.9 percent without age correcting. Only 5 of the 57 were considered to be within normal limits. In the unilaterally loaded families, as many as 50.7 percent of the offspring were schizophrenics or possible schizophrenics. These exceedingly high rates cannot be pooled with those in the literature for methodological reasons. Many of the families had been ascertained through their *already* schizophrenic children. Furthermore, unlike Ødegaard who dealt with the "siblings of probands," Moskalenko did not systematically exclude the schizophrenic probands when calculating the risk for offspring.

In Denmark, with the aid of both Danish and Scottish Rite Foundation support, Fischer and Gottesman are following up, both through the national registers and by personal interviews in the field, the approximately 400 adult offspring born to some 153 fertile couples where both parents had been inpatients in the Danish Mental Hospital system between 1920 and 1961—40 years of consecutive admissions. A further 45 couples were identified, but they had no children or none who lived beyond childhood. All of the parents and the so-far hospitalized offspring have yet to be blindly rediagnosed using IPSS standards. Twenty-five percent of the offspring, however, have already been hospitalized despite the mixture of chart diagnoses for the parents. The goal of this study is not to calculate the risk figures for various kinds of matings (although such data will be a byproduct of the study) but rather to use the information on all the offspring and all the parents taxonomically. That is, it seeks to know what goes with what. What kinds of matings produce schizophrenics? Can boundaries be drawn for the schizophrenia spectrum as a result of the disorders that occur to the children where, for example, both parents had a reactive depression or where a psychopath mated with a schizophrenic? Finally, are there any "antischizophrenia" genes that can be inferred by a lower risk of schizophrenia to the child of a schizophrenic than expected as a function of the other parent? When looked at in a probandwise fashion, the number of children to be examined in this study rises to almost 800.

We are very fortunate to be able to include an updated (July 1975) report on the status of the research on the offspring of dual mating schizophrenics from the laboratories of L. Erlenmeyer-Kimling (personal communication). Table 7 shows the current status of the three subsamples being followed as well as their status as reported by Erlenmeyer-Kimling (1968) at the Puerto Rico conference. As explained in the table, only the 70 children born to the 31 couples in group S are a "proper sample" from a sampling point of view. Table 8 presents for the first time the current status of the offspring who could be followed up. The crude percentage hospitalized is already 19.1 percent, and the age-corrected risk for psychiatric hospitalization is 32 percent. Not all of the hospitalized offspring were definite schizophrenics, but all carried a hospital diagnosis of "psychotic." The risk figure can be taken as a minimum one since it was impossible to follow all the children. We look forward to further information as this study proceeds.

The study of such strategic populations at the descriptive level still has much to offer at this stage of our ignorance about the genetics of schizophrenia. The studies already in the literature on the children of one schizophrenic cannot really be interpreted without some information on the other spouse. It was belatedly mentioned (B. Mednick 1973) that the Mednick and Schulsinger (see Mednick et al. 1974) 1962 high risk sample of children born to schizophrenic mothers included some fathers who were also seriously disturbed and hospitalized for disorders that included chronic schizophrenia. The attention that Rosenthal (1975) is now giving to the characteristics of the co-spouses in the adoption study may lead to a rapprochement between his and Heston's (1966) specific findings. The dual mating

Table 7. Number of dual mating pairs and children.[1]

Group[2]	From Erlenmeyer-Kimling (1968b)			Current revision		
	No. of pairs	No. of fertile pairs	No. of children[3]	No. of pairs	No. of fertile pairs	No. of children[3]
S	35	30	79	31	27	70
P	4	4	[4]21	5	5	[4]24
I	41	32	81	55	45	107
Total	80	66	[4]181	91	77	[4]201

[1] Data provided in table courtesy of L. Erlenmeyer-Kimling (personal communication).

[2] Group S = one of spouses located as an index case in a study of marriage and fertility of schizophrenic patients (Erlenmeyer-Kimling et al. 1969). Revised downward from 1968 report because of questionable diagnoses of four spouses. Group P = parents of index cases in the marriage and fertility study. One set of parents discovered to be a dual mating pair after the 1968 report. Group I = pairs located through inquiry. Seven pairs eliminated since 1968 report because of questionable diagnosis in one member of the pair, and 21 new pairs located since 1968.

[3] Total children ever born live. Excludes three stillbirths. Also excludes 40 children born to members of dual mating pairs in other unions.

[4] Excludes the index cases through whom group P families were located.

studies in progress, together with the results from other strategies, may altogether permit a better chance of defining the modes of transmission for the schizophrenias.

Mode of Inheritance

Most researchers in psychiatric genetics agree that genetic heterogeneity exists for schizophrenia but they do not agree on the proportion of phenotypes that can be accounted for with each posited genotype. It could mean that schizophrenia, like genetic cases of low-grade mental deficiency, comprises many (say 200) rare varieties of different recessive or dominant conditions, with the mutation rate at each locus maintaining such deleterious genes in the population. Another form of the genetic heterogeneity model is like mental deficiency *throughout* its range; a very small proportion of cases are due to different dominant and recessive loci, a further small group is due to schizophreniform phenocopies (e.g., associated with temporal lobe epilepsy, amphetamines, and head injury (cf. Davison and Bagley 1969), but the vast majority of schizophrenics would be segregants in a hypothesized normal distribution of genetic plus environmental liability to the disorder. So far no Mendelizing forms of schizophrenia have been identified. The remaining two broad classes of mode of transmission—monogenic and polygenic—are based on a strategy of lumping the phenotypes as if they were in fact homogeneous instead of splitting them.

Slater's (1958) monogenic theory (cf. Shields and Gottesman 1971), according to which virtually all schizophrenics have inherited the same abnormal gene in single or double dose, has been modified (Slater and Cowie 1971), and other investigators (e.g., Elston and Campbell 1970 and Kidd and Cavalli-Sforza 1973) have considered further modifications of the theory that result in variations in the posited penetrance of the dominant gene in the heterozygote. Heston (1970) hoped to avoid the ad hoc assumptions about penetrance of a hypothetical gene by focusing on "schizoid disease" as the phenotype for analysis. For his working hypothesis, he took all mental abnormalities of the kinds seen in about half of the first-degree relatives of schizophrenics as the schizoid phenotype. Difficulties with circularity and with the high base rate in the general population of the conditions required to give a 50-percent rate in relatives have led to the modification of the theory (Shields, Heston, and Gottesman 1975) described in the section on "twin studies." No monogenic theory can stand without some kind of support from such concepts as modifying genes,

Table 8. Current status of the dual mating children.[1]

Age	No. of children[2]	No. dead in infancy or childhood	No. adopted away	No. remaining[2]	No. in mental hospital[2]	No. with other problems[3]
Dead	16	16	–	–	–	–
45 years or over	43	–	1	42	14	1
15-44 years	132	–	16	116	18	16
Under 15 years	10	–	1	9	–	2
Total	[2]201	16	18	[2]167	[2]32	19

Note.—Crude percent hospitalized = 32/167 or 19.1 percent; age-corrected risk (Weinberg abridged method) = 32/100 or 32 percent.
[1] Data provided in table courtesy of L. Erlenmeyer-Kimling (personal communication).
[2] Excludes the five index cases in group P (described in table 7).
[3] Includes 10 in psychiatric treatment; 1 suicide attempt; 1 vagrant, "peculiar"; 2 classified "sick" by social workers and relatives; 1 behavior disorder of childhood; 2 mentally retarded; 2 Down's syndrome.

penetrance, or expressivity. A two-locus theory put forward at the Puerto Rico conference by Karlsson (1968) has since been withdrawn (Karlsson 1973 and 1974) in favor of a Slaterian monogenic theory.

Polygenic models of inheritance can be divided into continuous variation (cf. Elston and Gottesman 1968), and quasi-continuous variation or so-called threshold models. Examples of the former include height and IQ, and of the latter, diabetes, pyloric stenosis, and ulcer. By analogy, and given the ways in which we diagnose the presence or absence of schizophrenia, the threshold variant of the polygenic model seems most appropriate. Reich and coworkers (Reich, Cloninger, and Guze 1975 and Reich, James, and Morris 1972) have proposed variations of a single-threshold model in the hope it might better distinguish between monogenic with incomplete penetrance and single-threshold polygenic models. Like sophisticated monogenic models that provide for background effects, the threshold models (one, two, or three thresholds) are multifactorial models (cf. Curnow and Smith 1975). The particular combination of multiple causes will vary from one case of schizophrenia to the next. Earlier models of polygenic inheritance assumed that the contributing genes were equal and indistinguishable in their effects, and that an indefinitely large number of genes were involved. Polygenic traits analyzed in more tractable species such as wheat, guinea pigs, or fruit flies, however, showed that a large proportion of the variance in the traits was often due to a few loci with larger effects than the other loci involved (cf. Haseman and Elston 1972 and Jayakar 1970). Further, it appeared that some of the loci of large effect were associated with different facets of the phenotype. Our application of the methods devised for threshold traits (Falconer 1965 and Smith 1971) showed a satisfactory compatibility between the data and a threshold model (Gottesman and Shields 1967 and 1972). Other thoughts about other possible genetic models are included in the book *Genetic Factors in "Schizophrenia"* (Kaplan 1972). Even to insiders there would appear to be an excess of genetic model building; one reason for such proliferation may be that there is no penalty for being wrong.

It is difficult to choose among models even if one wants to (Curnow and Smith 1975 and Slater and Tsuang 1968). At the present time the predictions from a threshold polygenic model and a monogenic model with incomplete penetrance are not distinguishable from one another, as shown in table 9. The polygenic predictions assume a population prevalence of 1 percent for schizophrenia and a heritability of its liability of 80 percent (cf. Gottesman and Shields 1972, p. 328).

The kinds of data provided by us (Gottesman and Shields 1972) on the relationship between severity and concordance in twins and by Ødegaard (1972) on the relationship between number of relatives affected and the risk for mental disorder favor construing some kind of polygenic model. Tsuang et al. (1974) believe that analyses using a method devised by Slater (Slater and

Table 9. Monogenic (Slater and Cowie 1971) and polygenic (Gottesman and Shields 1972) predictions of schizophrenia as a function of parent status.

Item	Risk[1] to probands' siblings		Risk[1] to probands' children	
	No parent[2]	One parent[2]	One parent[2]	Two parents[2]
Empirically observed	9.7	17.2	13.9	46.3
Polygenic prediction	6.5	18.5	8.3	40.9
Monogenic prediction	9.4	13.5	8.8	37.1

[1] In percent.
[2] Indicates number of parents affected with schizophrenia.

Tsuang 1968) to fill a gap in this problem area—the side-of-family technique—favor a monogenic model or perhaps explanations using genes with large effects. Slater and Cowie (1971), Smith (1976), and, based on table 9 above, we do not believe a basis exists yet for choosing between these two leading models.

Related technical problems about the relative fertility (e.g., fitness) of schizophrenics and hypothetical selection pressures (cf. Carter and Watts 1971) that perpetuate the disorder are discussed in monographs by Stevens (1969), Lindelius (1970), and Gottesman and Erlenmeyer-Kimling (1971), and in such papers as those by Erlenmeyer-Kimling (1968a), Kidd (1975), Moran (1972), Larson and Nyman (1973), and Buck et al. (1975). The question of how a disadvantageous genetic condition can be maintained in the population over time despite the greatly reduced fitness of male (about 0.5 children per patient) and female (about 0.9 children per patient) schizophrenics can perhaps be answered more readily by polygenic than by monogenic theories.[5] The former would obviate the need to find a selective advantage in gene carriers as required by the "balanced polymorphism" theory put forward in the now-famous letter to *Nature* in 1964 by Huxley et al. 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 gene distribution, while those below the threshold would not be subject to negative selection. Recent work (Buck et al. 1975 and Larson and Nyman 1973) has not confirmed the hypothesized increased fertility in the siblings of schizophrenics. Schizophrenics could be thought of as part of the "genetic load," the price paid for conserving necessary genetic diversity in our species.

An appreciation of the concept of the *liability to developing schizophrenia* highlights what power the diathesis-stressor model has for resolving conflict and for perpetuating the necessary ambiguity about model choosing at this stage of our understanding. Five contributors to the combined liability to developing schizophrenia can be denoted. The first three—specific genetic liability, general genetic liability, and general environmental liability—each can have components with different weights, and all combine in some fashion to push an individual toward the threshold of overt clinical schizophrenia. To obtain the net liability at any point in time, the last two (negative) contributors—genetic assets (cf. Jones 1973 and Jones and Offord 1975) and environmental assets—each can have components with different weights and must be subtracted from the total of the liability factors. This kind of flexibility in the construing of the liability is made even more flexible by allowing for the dynamic aspects of life events and their effects on personality and brain functioning, and for the dynamic effects implied by our knowledge about gene regulation

[5] We can only touch on the complexities involved in this area of theoretical population genetics. Fertility in the subset of schizophrenics who get married is not conspicuously reduced; they have their families largely before their first hospitalization. The proportion of schizophrenics who do marry is markedly reduced—54 percent of females and 33 percent of males in recent times. See Cavalli-Sforza and Bodmer (1971, p. 308), Kidd (1975), and Slater, Hare, and Price (1971).

in lower organisms. What this all can be taken to mean is that an analogy to the Heisenberg uncertainty principle in physics must apply to human trait unfolding. We must operate within a field with a necessary amount of uncertainty.

Conclusions and Opinions

Schizophrenia research ought to be avoided by those individuals who cannot readily tolerate ambiguity and uncertainty. Our present knowledge does permit a strong statement about the obvious involvement of genetic factors in schizophrenia and probably allows us to conclude that some of the factors are specific and that the factors as a whole are important. By specific we mean that some genes, whatever other (so-called pleiotropic) effects they have on other traits, contribute to the development of schizophrenia rather than or more than they do to, say, blood pressure, affective psychoses, or eye color. The specific schizophrenia-related genes are posited to be differentiable from the general genetic contributors to the total liability; the latter contributors serve as modifiers or potentiators. No individual schizophrenia-related gene has yet been characterized biochemically or biophysically. It may bear repetition that both the genes and environment (also as yet unspecified) are each necessary but not sufficient for developing schizophrenia. Efforts aimed at finding good endophenotypes and true genetic markers of the vulnerable genotypes should be encouraged as should basic research on how the brain works and how drugs empirically therapeutic in the treatment of schizophrenia may give clues to its pathophysiology. We are far from a dead end so long as we avoid repeating mistakes or following leads that careful prior study of the literature would show to be unprofitable.

We can think of no better philosophy to endorse in regard to research on the genetics of schizophrenia than to let many flowers bloom. Such a philosophy must be tempered by the hope that administrators and editors informed by the kinds of data we reviewed in this far-from-definitive report will be able to discriminate between flowers and blossoming weeds.

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appendix *

The Calculation of Twin Concordance Rates

Different Kinds of Concordance

The concept of concordance has led to a certain amount of confusion. There are a number of different ways in which the term may legitimately be used, and these need to be clearly distinguished (Allen, Harvald, & Shields, 1967). We shall illustrate the main sources of confusion by means of our earlier data on hospitalization and diagnoses of schizophrenia in MZ twins [Gottesman and Shields 1966b].

Concordance: Complete and Partial, Narrow and Broad

The concept of concordance implies dichotomy, and dichotomies can be drawn arbitrarily. Therefore concordance, though it is usually taken to denote the occurrence of the *same* condition, e.g., schizophrenia, in both twins, as in our Grade I, can also usefully be reported in such a way that it includes pairs where the second twin has a lesser, or less certain, degree of abnormality, than the proband along some dimension not easily quantifiable. For instance, pairs may be reported as concordant, or *partially concordant*, in which one twin is schizophrenic and the other is doubtfully schizophrenic, "borderline" or even schizoid.

It may also be relevant to ask whether twins are similar in respect of a less specific category. It is sometimes claimed that it is not so much schizophrenia that is inherited as a more general and nonspecific tendency to psychiatric abnormality. A *broader type of concordance* may therefore be reported so as to include abnormalities in the second twin of a kind apparently different from that by which the original case was selected. For instance, pairs in which the first twin was schizophrenic and the second twin psychopathic, neurotic or even mentally retarded, may be regarded as concordant, both being abnormal on the broad dimension of *psychopathology*.

Our Grade II concordance includes pairs where both twins were *hospitalized*, not necessarily for the same or even related conditions: they are concordant in respect of the category of psychiatric hospitalization. As stated in Chapter 2 [of Gottesman and Shields 1972], the purpose remains to contrast one rate with another, especially MZ:DZ, so as to permit an inference about the role of genetic factors.

Casewise and Pairwise

Concordance may refer to the proportion of cases with an affected partner (casewise rate) or the proportion of pairs in which both twins are affected (pairwise rate). For a given set of data, casewise and pairwise rates are related to one another in a constant manner, since *each concordant pair consists of two cases.* If the casewise rate is defined as $C/(C + D)$, where C = the number of cases with affected partners and D = the number with unaffected partners, the corresponding pairwise rate will = $\frac{1}{2} C/(\frac{1}{2} C + D)$. Our MZ Grade I pairwise rate of 10/24 (42%) has as its corresponding casewise rate 20/34 (59%); the 24 pairs included 34 schizophrenics, 20 from concordant and 14 from discordant pairs. However, all schizophrenics did not come to notice independently.

The Proband Method

Probands are the index cases of a genetic investigation, the cases having been independently ascertained in a defined manner. Confusion arises in some studies over whether concordance has or has not been calculated according to the proband method.

The kind of problem which the proband method of Weinberg (1912, 1928, and Crow, 1965) was originally designed to tackle was how to estimate the incidence of a disorder in a sibship in order to discover how closely it approximated to the 25% expected in the offspring of two heterozygotes under a recessive hypothesis. Some early attempts to estimate parameters of such a kind had fallen into the naive error of pooling sibships and calculating the proportion of affected to unaffected members without first excluding the cases by which the sibships came to be ascertained; inflated rates were thereby produced. The proband method omits probands from the calculation, but if there is more than one proband in the sibship the family will enter more than once. The method need not, of course, imply

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the testing of recessivity or any other monogenic hypothesis, but is applicable to all data where independent ascertainments of affected individuals had been recorded. In twin studies, concordance calculated by the proband method is intended to give an unbiased estimate of the ratio of affected to normal in the twins of given cases: twin pairs are treated as sibships of two.

The proband method is not a device thought up by wicked geneticists to make a condition appear to be "more genetic" than it really is by the unwarranted double counting of pairs in which both twins are probands. The proband method rate should not be thought of as the inflation of a pairwise rate, but as the reduction of a casewise rate. The method does not, strictly speaking, count pairs twice at all, but co-twins. Probands are omitted from the calculation unless they also happen to be co-twins in their own right. The obtained concordance is a rate in co-twins, and as such it may be compared with rates in other relatives or in unrelated controls. Provided the probands in a study are representative of cases in a population, the proband method rate will approximate the casewise rate for twins in the population.

It will be clear that concordance calculated according to the proband method expresses the proportion of probands who have affected partners. In other words it is a *casewise rate, corrected for mode of ascertainment.* We ascertained via our twin registration system not 34 but 28 schizophrenics from MZ pairs. Of these, 14 had affected co-twins and 14 had unaffected co-twins. The proband method rate is therefore 50%. If all the 34 schizophrenics observed by us had been ascertained as probands, the proband rate would have been the same as the directly observed casewise rate. If no pair had included two probands, it would have been the same as the directly observed pairwise rate. In fact, as we have already reported, four out of the ten concordant MZ pairs consisted of twins both of whom were independently ascertained as schizophrenic probands on our register. The proband method rate lies in between the two direct rates of 42% and 59%.

The pairwise rate which corresponds to the (casewise) proband method rate cannot be directly observed, but is estimated indirectly by halving the number of probands (cases) with affected co-twins, as in the formula shown in the previous section (Allen, 1955). The usefulness of the indirect pairwise rate, which is the estimate of a population parameter, appears to have limited value for our purpose.

The relationship between casewise and pairwise on the one hand and directly observed and proband-based on the other hand can be seen in Table A-1. The nomenclature of the four kinds of concordance generated is also shown.

In our own study we shall normally report the direct pairwise rate. It has the merit of simplicity and it is the only rate based on the raw number of pairs observed, from which the number of degrees of freedom is calculated. It may be regarded as a conservative estimate of the proband method rate. However, when it is appropriate, some analyses will be given in terms of co-twins of Maudsley Hospital probands, i.e., probandwise. Slater and Cowie (1971, Appendix C) have shown how the proband method has the advantage of taking into account pairs where neither twin is affected, and V. E. Anderson (personal communication) has shown that this conclusion holds independently of the probability of ascertainment (π) (cf. Crow, 1965).

Table A-1. Four different MZ Grade I concordance rates uncorrected for age.

		Calculations based on:	
		All schizophrenics observed	**Ascertained schizophrenic probands**
Casewise	$\frac{C}{C+D}$	**20/34 = 58.8%** **Raw casewise**	**14/28 = 50.0%** **Proband method**
Pairwise	$\frac{\frac{1}{2}C}{\frac{1}{2}C+D}$	**10/24 = 41.7%** **Direct pairwise**	**7/21 = 33.3%** **Indirect pairwise**

Age-Corrected Concordance

Estimates of the morbid risk for co-twins have to take account of their age because the disorder has a variable age of onset and the sample is a current one. Various methods, none of them entirely satisfactory, have been suggested for age correcting. They involve reducing the denominator in such a way as to allow for the proportion of the risk period for the condition not yet lived through by the co-twins (see Chapter 6 of Gottesman and Shields, 1972, and Appendixes D and E in Slater and Cowie, 1971).

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