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Clinical Genetics as Clues to the "Real" Genetics of Schizophrenia

(A Decade of Modest Gains While Playing for Time)

by Irving I. Gottesman, Peter McGuffin, and Anne E. Farmer

Abstract

Although a decade has passed since the genetics of schizophrenia was examined for the *Schizophrenia Bulletin,* the epigenetic puzzle of schizophrenia has not yielded its secrets to any scientific breakthrough. In this article we review a sample of the highlights relevant to enlightened genetic thinking, i.e., a broad diathesis-stressor framework with multifactorial causation assumed and with provision for the epigenetic interaction of psychosocial as well as neurobiological factors.

The clinical genetic epidemiologist needs to know the lifetime morbid risks generated by different definitions of schizophrenia, as well as the consequences for the familial risks generated by the various family, twin, and adoption strategies. Schizophrenia appears to occur through an interaction of a genetic susceptibility with some kind of environmental stress; the stress need not be an environment containing a person with a diagnosis in the schizophrenia spectrum; the genetic factors in schizophrenia have specificity as they do not increase the risk for major affective disorders or delusional disorder. Clearly, schizophrenia is clinically or phenotypically heterogeneous, but whether this variety is paralleled by etiological heterogeneity or to what extent is problematic. Once the existence of an important genetic predisposition to developing schizophrenia has been established, it becomes important to provide a theory (or theories) to account for its mode (modes) of transmission. Psychiatric geneticists have not yet solved the problem, in part because of the difficulty of specifying the appropriate phenotype to analyze and also because of the unknown degree of heterogeneity.

Genetic markers are a special category of biological markers. In addition to conventional markers, the advent of "the new genetics" of recombinant DNA has meant that many more genetic markers (probes) are now available and that the day is not far off when the human genome will be extensively mapped. Considerable optimism exists about the future usefulness of genetic markers in detecting major gene effects and resolving problems of heterogeneity in schizophrenia.

Although a decade has passed since the genetics of schizophrenia was critically, passionately, and minutely examined for the *Schizophrenia Bulletin* via an invited review (Gottesman and Shields 1976), together with invited and spontaneous commentaries (Dohrenwend 1976; Kessler 1976; Kety et al. 1976; Kringlen 1976; Lidz 1976; Matthysse 1976; Ødegaard 1977; Torrey 1977), the epigenetic puzzle of schizophrenia (Gottesman, Shields, and Hanson 1982) has not yielded its secrets to any scientific breakthrough. The controversies surrounding the causal roles for genetic factors continue unabated, with believers, disbelievers, and agnostics all beating a path to the podium (e.g., Lidz, Blatt, and Cook 1981; Pope et al. 1982, 1983; Abrams and Taylor 1983; Crow 1983; Grove 1983; Murray and Reveley 1983; Lewontin, Rose, and Kamin 1984).

In 1976 we noted that "Continuing uncertainty about the etiology of schizophrenia calls for periodic reappraisal of relevant data and conclusions, reappraisals guided by a

Reprint requests should be sent to Dr. I.I. Gottesman, Dept. of Psychology, Gilmer Hall, University of Virginia, Charlottesville, VA 22903.

beacon of modest doubt to avoid the distorted views of both the zealot and the skeptic" (Gottesman and Shields 1976, p. 360). In that spirit we shall review a sample of the highlights relevant to enlightened genetic thinking, i.e., a broad diathesis-stressor framework (Rosenthal 1963) with multifactorial causation assumed (Reich, Cloninger, and Guze 1974) and with provision for the epigenetic interaction of psychosocial as well as neurobiological factors (Gottesman, Shields, and Hanson 1982; Nicol and Gottesman 1983; McGue, Gottesman, and Rao 1986), from among the developments of this past decade. We shall also try to make some informed guesses about the best placement for continuously insufficient human and financial resources.

First, however, we must acknowledge with sadness the profound losses to our disciplines, through death or disease, of major contributors to our thinking about genetic aspects of schizophrenia. We therefore pay homage to Margit Fischer, Lennart Kaij, Hisatoshi Mitsuda, Ørnulf Ødegaard, David Rosenthal, James Shields, and Eliot Slater. Although no way can be found to compensate for the net loss of their experience and wisdom, the potential toll on further research advancement demands attention to the recruitment and training of appropriate scientists lest the infrastructure for genetic psychopathology crumble.

Overview of Schizophrenia—Relevant Reviews

Informative, specialized reviews with rich bibliographies should be consulted by readers who wish to explore in depth topics we can only treat summarily. Henderson (1982) updated the literature on human behavioral genetics, while Loehlin, Willerman, and Horn (in press) have assumed that heroic task for personality, psychopathology, and cognition. Kendler (1983) re-reviewed twin studies and confirmed our earlier conclusions about their essential validity. Propping (1983) compiled a scholarly collection of all those genetic disorders which, at times and to some clinicians, present as "schizophrenias"; thus these "genocopies" or genetic imitators of schizophrenia complement the classical treatment by Davison and Bagley (1969) of the phenocopies of schizophrenia, those schizophrenia-like psychoses associated with drug-induced and nongenetic disease-related organic disorders of the central nervous system. All research into the clinical and etiological heterogeneity, the psychopathology, and the pathogenesis of schizophrenia should be informed by the accumulating data on genocopies and phenocopies. For example, the symptomatic overlap between schizophrenia and some cases of Huntington's disease might be explained in part by the revelation of left globus pallidus abnormalities in blood flow measured by positron emission tomography (PET) (Early et al., in press), thereby implicating shared neuropathology (Bruyn, Bots, and Dom 1979).

Zerbin-Rüdin (1980) has updated her definitive handbook chapter (1967), thus permitting continued contact with the non-Anglo-Saxon European literature (cf. *Schizophrenia Bulletin*, Vol. 12, No. 1, 1986). The carefully orchestrated Second Rochester International Conference on Schizophrenia has resulted in a collector's gem that will give joy for years to come (Wynne, Cromwell, and Matthysse 1978). Omnibus texts dealing solely with schizophrenia and giving a balanced hearing to genetic observations are well worth consulting (Neale and Oltmanns 1980; Cutting 1985). Edited works from conference proceedings often lack the kind of peer review seen in the better scientific journals, but they do permit one to keep up with work-in-progress by "visible college" members (Matthysse 1981; Nasrallah and Henn 1982; Alpert 1985; Sakai and Tsuboi 1985). An anthology of articles on schizophrenia covering more than a decade from the *British Journal of Psychiatry* has appeared (Kerr and Snaith 1986) with a wealth of thoughtful and provocative offerings.

A guide to the present and future contributions of molecular and mathematical genetics was edited by Gershon et al. (1981); it provides a blueprint, in part, for the next decade. Goldin and Gershon (1983), Cloninger, Reich, and Yokoyama (1983), and McGuffin and Sturt (1986) introduce us to the complexities of the new genetics, while Cloninger et al. (1985) review the contributions of genetic epidemiology. Faraone and Tsuang (1985) successfully accomplish the difficult task of reviewing for behavioral scientists the many modern attempts to apply mathematical genetic models to family data sets to explain the mode(s) of transmission.

Longitudinal prospective and retrospective high-risk research has achieved a respectable "yuppie-like" maturity since the strategies were outlined in broad brush strokes by Pearson and Kley in 1957. The interim and final yields from such projects will contribute important pieces to the final schizophrenia puzzle solution. Justice cannot be done to the material within the scope of the present review. Overviews of the progress, promises,

and disappointments can be tracked in the encyclopedic volume edited by Watt et al. (1984), in Garrone, Jablensky, and Manzano (1986), in Erlenmeyer-Kimling and Miller (1986), in the *Schizophrenia Bulletin*, Vol. 11, No. 1 (1985) for the continuing saga of the Israeli study launched by Rosenthal, and in Nuechterlein (1986).

Classification and Diagnosis

A schizophrenic is a schizophrenic is a schizophrenic? False, true, and cannot say! Our field needs an Einstein not a Gertrude Stein to straighten out the disordered, derailed, and ambiguous thoughts about the most valid way in which to diagnose the presence of schizophrenia and, eventually, the potential for developing it. Meehl (1986, p. 217) has succinctly stated the *sine qua non* for progress in research: "The pulling together of research data to give a coherent interpretation of an alleged psychiatric entity, whether taxonomic or dimensional in nature, presupposes the possibility of scanning the research literature with at least some reasonable confidence that patients called schizophrenic by one investigator are like those called schizophrenic by another." Such an innocent presupposition would endanger the health of your analyses and meta-analyses (see Andreasen, in this *Special Report*). Results from family, twin, and adoption studies of schizophrenia using an ICD (International Classification of Diseases) (World Health Organization 1967) diagnosis cannot be naively equated across or within such strategies with studies using RDC (Research Diagnostic Criteria) (Spitzer, Endicott, and Robins 1978), *DSM-III* (American Psychiatric Association 1980), or Catego (World Health Organization 1973), let alone with clinical diagnoses.

Trenchant critiques (Kendell 1975; Kety 1980; Eysenck, Wakefield, and Friedman 1983; Blashfield 1984) make it clear that the concept of schizophrenia is an "open concept" (Pap 1958; Meehl 1986) and a "fuzzy natural category" (Cantor and Genero 1986) whose validity evolves from changes in the information contained in its associated nomological network. Absent infallible indicators of schizophrenia and absent infallible validity criteria for evaluating the indicators, we face a necessary uncertainty in evaluating the genetic literature.

Dissatisfaction with the status quo for making psychiatric diagnoses is disquieting (Grove and Andreasen 1986; Millon and Klerman 1986; Zubin 1986). The decision to introduce a "midcourse correction" to *DSM-III* on the way to *DSM-IV* and the continuing negotiations over the form to be taken by ICD-10 (expected early in the next decade) have combined to destabilize confidence in one's diagnosis of schizophrenia (Brockington, Kendell, and Leff 1978; Endicott et al. 1982; Finn 1982). Rothblum, Solomon, and Albee (1986) bemoan the fact that the number of diagnostic entities has mushroomed from 60 in the first edition of the *DSM* to 230 in the present and project 400 by the end of the century. Disciples of Leonhard (1979, 1986) are enthusiastic about his 22 subtypes of schizophrenia.

In an exemplar of construct validation for nine definitions of schizophrenia, Stephens et al. (1982) applied the criteria sets to 283 patient charts after discharge with nonaffective, nonorganic psychoses "conservatively" diagnosed (i.e., based on observations of behavior as opposed to psychodynamic inferences). It is especially important to note here that, depending on one's views, schizoaffective, schizophreniform, borderline schizophrenia, and paranoid psychoses are arbitrarily excluded *or* arbitrarily included in the different concepts of schizophrenia. Only 7 percent of the patients were called schizophrenic by *all* nine systems. *DSM-III* criteria were met by only 37 percent of patients, the same yield obtained by applying the first rank symptoms (FRS) of Schneider (see Koehler 1979); however, they were not the same patients—77 percent of FRS cases were diagnosed schizophrenic by five or more systems compared with 94 percent of the *DSM-III* cases. Thus, the obvious difference in narrow vs. broad diagnostic orientation does not necessarily make the systems tested hierarchical ones, with all narrow systems being "nested" within all broader systems. Carpenter, Strauss, and Bartko's (1973) criteria (level 5) captured 53 percent of the sample compared to yields of 46 percent for RDC and 38 percent for St. Louis criteria (Feighner et al. 1972); all three criteria sets would be classified as narrow ones as would the FRS orientation.

Much more data are provided by Stephens et al., but we must defer an extension to such crucial issues as the sensitivity and specificity of the concepts tested and their reliabilities. The three-fold difference in yields between their narrowest (*DSM-III*, FRS, or St. Louis) and their broadest (hospital chart) concepts is the point we wish to emphasize here. The authors noted that had *DSM-III* and RDC allowed for schizoaffective and schizophreniform disorders to be included under the schizophrenia umbrella, the yields would have been close to 70 percent, the absolute agreement between the two, 89 percent with a

kappa (Cohen's index of agreement corrected for chance; see Bartko and Carpenter 1976) of .75.

In another paradigm for validating the definition of schizophrenia, Brockington, Kendell, and Leff (1978), using two English hospital samples of functional psychotics, tested 10 definitions including ICD 295 (schizophrenia including schizoaffective and borderline) and 297 (paranoia), three levels of Catego based on the (structured interview) Present State Examination (PSE) (Wing et al. 1974), Taylor, Abrams, and Gaztanaga (1975), a World Health Organization project diagnosis, and others overlapping with those mentioned above. They found an 11-fold difference in the yields from the narrowest (Taylor, Abrams, and Gaztanaga) to the broadest (Astrachan et al. 1972; New Haven Schizophrenia Index) concept in one sample. In the other sample of 134 psychotics, the highest yields were from the U.S./U.K. project clinical diagnoses (57) and from Catego (broad) (56), that is, counting all computer algorithm cases of definite or probable S, P, or O.

By following up this latter sample for an average of 6.5 years, the investigators had sufficient information from all sources to call 54/122 psychotics "final diagnosis" schizophrenics. With this as a criterion the initial diagnoses could be evaluated; the best true positive rates were from Catego (broad) and RDC (broad) with 40 and 37 hits, respectively (false positive misses were 16 and 7, while false negatives were 14 and 17). When employment status and social involvement at followup were accepted as a validating criterion, the clinical diagnoses, Carpenter (5), Langfeldt (1960), RDC (broad), and Catego (broad) proved superior to the base rate prediction for all 129 psychotic patients. The authors concluded that operational definitions were a step in the right direction.

The problems described so far are magnified within the context of clinical genetic research as the basic data consist of rates of affection with the same disorder in the relatives of various kinds of probands or index cases, be they twins, adoptees, siblings, or spouses. It is easy to envision a situation where the proband meets criteria for schizophrenia in one system and relative meets criteria in a different system. Such a "miss," repeated often enough, would prevent the detection of schizophrenia as a familial disorder.

Before the construct validity efforts described above, we had mounted a polydiagnostic approach to a benchmark data set consisting of the case histories of 114 twins (57 pairs), 62 of whom had a United Kingdom hospital chart diagnosis of schizophrenia. The histories have been judged or rated without knowledge of zygosity or cotwin status by numerous experienced clinicians from diverse schools of thought, by Catego, and by various older and newer operational definitions (Gottesman and Shields 1972; McGuffin et al. 1984; Farmer, McGuffin, and Gottesman 1984, in press; McGuffin, Farmer, and Gottesman, in press). One goal of these explorations has been to use the concordance rates generated in the twins by each definition of schizophrenia as a means to construct validation. Some of the yields from various criteria sets are shown in table 1. Individual judges' diagnostic orientations are briefly characterized in the table. A 27-fold difference in the yields from contrasting the most "generous" clinician when wearing his Danish adoption study soft spectrum hat (Dr. Joseph Welner) with the narrowest concept we have tried, the Type II schizophrenia of Dr. Timothy J. Crow (1985), who kindly guided our operationalizing of his concept for subtyping schizophrenia, can be seen in table 1.

Such a display of yields ranging from 3 to 81 hits from the criterion sample of case histories gives both pause and food for thought; the hits for the clinical judges included their probable schizophrenics and some 27 histories had a consensus from our six-judge panel of "within normal limits." We will not presume to reach a conclusion yet as to whether broader concepts are better than narrower or vice versa. Each concept can be used to answer empirical questions about its own validity. Given the constraints on the usual sample sizes available to genetic research strategies, low-yielding definitions cannot be recommended. The clinical genetic epidemiologist needs to know the lifetime morbid risks (age-corrected for the variable age of onset of schizophrenia) generated by each definition as well as the consequences for the familial risks generated by the various family, twin, and adoption strategies. Recall that we usually work with the assumption, based on the Western European studies of psychiatric epidemiology, that the lifetime morbid risk for an ICD-like definition is close to 1 percent (McGue, Gottesman, and Rao 1983; Jablensky 1986). The yield for *DSM-III* schizophrenia of 44 is considerably less than that for RDC (broad, 54), for the complex of Catego S, P, O (broad, 52), for the six-judge consensus (69), or for the United Kingdom hospital chart diagnoses (70). We can estimate that the last two would be approximated closely by ICD 295 plus 297. Others' uses of Feighner et al. criteria might not lead to our yield, which is comparable to Catego S, P, O (53 and 52), owing to the life-span nature of our histories which covered many

episodes and revealed the course of illnesses. We shall examine the consequences of some of the concepts for twin concordance rates below. The hierarchical nature of the concepts has only been partially explored (Carey and Gottesman 1978; Stephens et al. 1982).

Epidemiology for Genetic Research

We can now examine directly the lifetime morbid risks for schizophrenia defined along a continuum from broad to narrow and which may be used for extrapolation from the data in table 1. In a new collaborative study of schizophrenia and other severe mental disorders, the World Health Organization (Sartorius et al., in press) has interviewed with the PSE and diagnosed 1,352 first-contact psychotic patients from 13 geographically defined catchment areas in 10 countries, including 6 which had participated in the earlier International Pilot Study of Schizophrenia (IPSS) (World Health Organization 1973, 1979). Among the goals were the calculation by sex of incidence, prevalence, and lifetime morbid risk cross-culturally, and the testing of ideas about life events, expressed emotion, and determinants of outcome. Genetic and psychosocial theories about the etiologies of the schizophrenias will be critically informed by the results.

Clinical genetic studies of schizophrenia require the lifetime morbid risk as a basic datum before the similarly age-corrected rates in different classes of relatives differing in genetic overlap (100 percent in identical twins, 50 percent in first degree relatives, and 25 percent in second degree relatives) can be further quantified for use in genetic model fitting (see below). Of universal interest and importance was the finding that the incidence rates of schizophrenia were very similar across such vastly different groups as rural India, Honolulu, Moscow, Dublin, and Aarhus (Denmark). The uniformity of case finding and definition may have resolved many earlier discrepancies and interpretations (Dohrenwend et al. 1979; Torrey 1980); some high density and some low density groups still remain a mystery. Four different but nested inclusion categories were used: (1) a clinical, ICD diagnosis of a nonaffective, nonorganic psychosis *or* meets criteria for Catego S,P,O; (2) Catego S,P,O; (3) the former, less doubtful cases of O; and (4) Catego S+ (i.e., omitting doubtful cases of S). Concept (2) corresponds to a yield of 52 and concept (4), a yield of 17 in table 1.

The narrowing of the concept from step 1 to step 2 reduced the study population to 86 percent; narrowing from step 1 to step 4 reduced the study population to 56 percent with "nuclear" schizophrenia (having one or more FRS of Schneider). Of most importance to the current discussion are the lifetime morbid risks generated by the concepts across the reported international field research centers, but especially those in Western Europe where so much of the genetic research has taken place. Combining sexes, the lifetime morbid risk for Aarhus and for Nottingham for the broadest concept (1) were 0.56 percent and 0.80 percent, respectively; the high-

Table 1. Yields of "schizophrenic" cases by clinicians' and operational criteria from the Maudsley-Bethlem twin sample (n = 114)

Clinician-based diagnoses	Yields	Operational criteria-based diagnoses	Yields
J. Welner (Danish adoption study "soft spectrum")	81	Research Diagnostic Criteria (RDC)—broad	54
P.E. Meehl ("Radovian" schizotypes)	79	St. Louis—broad	53
United Kingdom hospital charts	70	Catego S, P, O	52
Gottesman/Shields blindfolded six-judge consensus	69	RDC—narrow	49
E. Slater (neo-Kraepelinian)	62	Tsuang/Winokur paranoid + hebephrenic	49[1]
K. Abe (Postwar Japanese)	56	St. Louis—narrow	46
J. Birley (1960's Maudsley Hospital)	50	*DSM-III*	44[2]
J. Welner ("traditional" Danish)	42	Abrams/Taylor	39
E. Essen-Möller ("traditional" Swedish)	34	Carpenter et al.—5 cutoff	33
		Catego S only	17
		First rank symptoms (FRS)	17
		Crow, Type II	3

[1]Minimum estimate as it excludes "undifferentiated" cases.
[2]Excludes schizoaffective, schizophreniform, and delusional disorders (paranoia).

est rate reported was for rural Chandigarh (India) with 1.72 percent; the lowest, 0.50 percent, was for Honolulu. For the easily communicated concept (2), any S, P, or O, the lifetime morbid risks for Aarhus and Nottingham were 0.40 percent and 0.71 percent with the same cities above retaining the high of 1.40 percent and the low of 0.30 percent. Finally, for the narrowest concept (S+), the World Health Organization project reports all centers within the range 0.26 percent to 0.54 percent. The overall findings are quite compatible with the earlier literature, which has now been put on a much firmer footing.

Readers with a queasy stomach for tolerating uncertainty and open, fuzzy concepts should stop here and read no further. We will accept the perils, drawing on denial and repressive defense mechanisms, and will proceed to brief reviews and discussions of the recent clinical genetic literature, mindful of the hazards of building structures on uncertain foundations. In doing so, we reject diagnostic anarchy and explicitly advocate a polydiagnostic approach so as to prevent foreclosure on optimal definitions. Optimality will be judged post hoc by the successes which lead to mounting the stage in Stockholm later this century. We will have to accept the interim uncertainty just as do the physicists with their Heisenberg Principle.

Older Data Recycled, Reanalyzed, and New Data

The most prominent trend in the past decade with regard to the clinical genetic literature on schizophrenia has been the creative and sophisticated recycling and reanalyses of the hard-to-collect family, twin, and adoption studies that so influenced the field in the 1960's and since. Many of the reanalyses have been motivated in part by challenges to the validity of both the data and the conclusions reached from them in landmark studies. We have mentioned the prominent challengers above and caution against overreacting to messengers who may be bearing bad news as opposed to examining the "bad news" for its merits. Another major use to which the older data have been put is to explore the construct validity (Cronbach and Meehl 1955) and the genetic implications, if any, of suggested organizing schema (i.e., ways of cutting the schizophrenia pie) such as positive vs. negative symptom schizophrenia (Dworkin and Lenzenweger 1984; Andreasen 1985; Pogue-Geile and Harrow 1985), Type I vs. Type II schizophrenia (Crow 1985; McGuffin, Farmer, and Gottesman, in press), and familial vs. sporadic schizophrenia (Murray, Lewis, and Reveley 1985; Eaves, Kendler, and Schulz, in press). Many of the operationalized criteria for making reliable diagnoses have been tested with the Gottesman and Shields Maudsley-Bethlem twin sample (McGuffin et al. 1984; Farmer, McGuffin, and Gottesman 1984, in press).

Family and Twin Studies. The compilation in table 2 represents all published Western European family and twin studies of schizophrenia 1920 to 1978 with some exceptions. Adoption studies with their unique selection and diagnostic criteria are discussed later. Parents were omitted as a class as they have been selected for mental health and relevant personality traits, thus yielding risks that are not directly comparable with other first degree relatives in the table (Essen-Möller 1955; Risch 1983). As the concept of schizophrenia did not affect diagnostic practices until after Bleuler's (1911/1950) ideas were incubated, we also omitted grandparents and other ascendant relatives so as to preserve diagnostic homogeneity. Finally, studies using probands affected with complicating additional diagnoses such as alcoholism and mental retardation were omitted (cf. Gottesman, Shields, and Hanson 1982).

With some reservations, we believe the concept of schizophrenia relevant to the pooled lifetime morbid risks (LTMR) corresponds to an ICD 295 diagnosis, with or without the rare category of ICD 297 (paranoia). Thus, both schizoaffective and borderline or latent schizophrenics would have been included as "hits." The LTMR in the table are further quantified by converting them into appropriate correlations in the posited underlying liability to develop a threshold disorder (Cloninger et al. 1985); the necessary general population risks used in the calculations were 0.85 percent for the narrower and 0.99 percent for the broader of the two concepts. When the base rate is taken into account, the risks for the classes of relatives with the same and with different amounts of known genetic overlap can be compared in a meaningful way and will become data points for the genetic model fitting to be described below. The amount of overlap will be 0 percent for spouses, 100 percent for monozygotic twins, 50 percent for first degree relatives, 25 percent for half-siblings, nieces, and grandchildren, and 12.5 percent for first cousins who are third degree relatives.

As the studies pooled in table 2 were conducted before the heyday of structured interviews, operationalized lists, and grant-funded team approaches permitting blind-

Table 2. Pooled European family and twin studies of schizophrenia 1920–78

	Definite diagnosis				Definite + probable diagnosis			
	BZ[1]	Affected (%)	r^2	No. studies	BZ[1]	Affected (%)	r^2	No. studies
Spouses	399	1.0	.026	4	399	2.26	.128	4
Children	1678.6	9.35	.439	7	1254.3	12.84	.499	5
Siblings	7523.2	7.30	.381	10	7628	9.26	.418	10
Monozygotic twins	106	44.3	.853	3	261	45.6	.854	5
Dizygotic twins	149	12.08	.501	3	329	13.7	.515	5
Half-siblings (reared by common parent)	442.5	2.94	.198	3	267	5.99	.317	2
Nieces-nephews	3965.5	2.65	.179	6	2973	3.46	.202	3
Grandchildren	739.5	2.84	.192	5	382	4.97	.278	3
First cousins	1600.5	1.56	.092	3	1600.5	2.44	.141	3

Note.—Probands are definite cases; relatives are definite or definite + probable (after McGue, Gottesman, and Rao 1983).
[1]BZ = age-corrected sample size.
[2]Tetrachoric correlations calculated using lifetime risk of 0.85% for definite and 0.99% for definite-plus-probable.

folded interviews with probands (index cases) and their relatives, they were considered less than definitive by many of the critics mentioned above. Furthermore, few of the earlier investigators bothered to collect risks in normal or psychiatric controls using the same concept of schizophrenia as in the primary target group of schizophrenic probands; they had been content to use the available, seemingly appropriate risks compiled by dedicated psychiatric epidemiologists (cf. Strömgren 1950; Zerbin-Rüdin 1967). Recent efforts try to ameliorate the uncertainty, but we console ourselves that "perfectionism is the last refuge of the skeptic."

Kendler, Gruenberg, and Tsuang (1985, 1986) have revived and expanded the Iowa 500 research associated with Tsuang, Winokur, and Crowe earlier. Structured interviews and/or hospital charts and blind diagnoses using (earlier) St. Louis and newer *DSM-III* and RDC criteria provide defensible support for the pooled data in table 2, as do other family and twin studies to be summarized shortly. As with the twin "hits" in table 1, *DSM-III* reduced the 200 original schizophrenic cases to 173, to which were added 159 more *DSM-III* hits from consecutive admissions with schizophrenic chart diagnoses (310 "shrunk" to 159). By focusing on the 253 *DSM-III* probands with interviewed first degree relatives and similarly selected schizophreniform (n = 24), schizoaffective (n = 42), psychotic affective disorder (n = 19), and 261 controls, the authors discerned an informative pattern of *DSM-III* and RDC diagnoses. The LTMR in relatives of controls for *DSM-III* schizophrenia was only 0.2 percent, close to the World Health Organization figure for Honolulu using a concept known to be broader (S, P, O); the LTMR in controls' relatives for all nonaffective psychotic disorders, *DSM-III*, was 0.6 percent. What about the relatives of the psychiatric probands?

Among the large sample of first degree relatives of *DSM-III* schizophrenics, 3.7 ± 0.7 percent were likewise *DSM-III* schizophrenics, 18.5 times the control value; note that the absolute value of risk is often a misleading guide to the relative risk. The correlation in liability is a better indicator of the importance of familial factors and, with certain assumptions, of the weight of genetic factors; the data above generate a correlation of .38 and an estimate of broad heritability of .76; i.e., 76 percent of the variance in liability to develop schizophrenia is under gene control, and 24 percent is not. First degree relatives of *DSM-III* schizophrenics had a 7.8 ± 1.0 percent risk for the broader category "all nonaffective psychoses" as defined above, a value very close indeed to that reported for the pooled European studies in table 2 for children (9.35 percent) and siblings (7.3 percent) with a corresponding concept of ICD 295 + 297. Kendler et al. found 3.6 ± 2.1 percent schizophrenia in the relatives of schizophreniform disorders, 5.6 ± 1.9 percent in the relatives of schizoaffective disorders, and 4.3 ± 3.0 percent in the relatives of psychotic affectives (compared with 20 ± 6.3 percent for the same [homotypic] diagnoses). Interestingly, by shifting to an RDC framework, thus permit-

ting the separation of schizoaffectives into mainly schizophrenic vs. mainly affective, the investigators found that the risk for schizophrenia in the relatives of the former rose to 8.2 ± 3.2 percent and in the relatives of the latter dropped to 3.8 ± 2.2 percent. These new values from the Iowa family study can be compared with the earlier report based on clinical consensus of St. Louis-like criteria of 5.3 percent in relatives of schizophrenics and 0.6 percent in those of controls, a nine-fold increase.

From a followup study of the St. Louis 500 by Guze et al. (1983) we learn how high the false negative rate of schizophrenia can be with St. Louis criteria applied cross-sectionally; the proband sample at index time of 30 schizophrenic or schizophreniform cases grew to 44 in the light of further information after 6 to 12 years. Operational criteria ("modified St. Louis"), a structured interview, and blind diagnoses of first degree relatives still revealed the familiality of schizophrenia. Among the relatives, 8.1 percent (prevalence not LTMR, therefore an underestimate) were definite or probable schizophrenics compared to 1.67 percent of the relatives of all other psychiatric probands (not normal controls).

Another American study, this time in New York City, used RDC to define schizophrenia from a Schedule for Affective Disorders and Schizophrenia interview and blind interviews with parents and siblings of 90 probands and their controls (acquaintances of the schizophrenics' well siblings). Baron et al. (1985*a*, 1985*b*) reported an LTMR of 8.7 percent among siblings of severe, early onset schizophrenics and 3.3 percent among their parents; control values were 1.2 percent and 0 percent, respectively. While exploring the spectrum concept of schizophrenia, they found an LTMR of definite schizotypal personality of 17.5 percent among sibs and 12.2 percent among parents; control values were 1.9 percent and 2.1 percent. Recalling that the latter diagnosis would be within the ICD 295 rubric, and allowing for the relationship between severity in the proband and risk in the relative (Gottesman, Shields, and Hanson 1982), we find that the combined risk in siblings of 26.2 percent might be reconciled with the earlier European data.

Scharfetter and Nüsperli (1980), working in the Zurich Clinic long associated with the names of Eugen and Manfred Bleuler, reported the risks of schizophrenia in the parents, sibs, and children of ICD-defined subtypes of schizophrenics as well as in unipolar and bipolar probands. Homotypical and cross-modal diagnoses were examined to see whether the subtypes "bred true" (they did not). Relatives were interviewed (70 percent of the living) using a checklist and diagnosed blindly with respect to the probands' diagnoses. Probands of each subtype had affected schizophrenic relatives with all of the other subtypes. Risks (LTMR) in the relatives of schizoaffectives and catatonics were 13.5 percent and 12.8 percent, while in the relatives of hebephrenics and paranoids they were 8.4 percent and 7.0 percent. A total of 180 schizophrenic probands and their 750 (age-corrected) relatives were examined so that the addition of such data would augment the data base in table 2 from other European studies. Relatives of the affective probands had a schizophrenia LTMR close to 3 percent, while the affective psychosis LTMR in relatives of schizophrenics was quite low overall (3 percent) but high (9.6 percent) among the relatives of the schizoaffective probands.

An interesting set of studies has appeared from Eastern Europe by a Hungarian psychiatrist using archival data from the Psychiatric Institute in Moscow for 350 schizophrenic probands and their parents and siblings all classified according to three different concepts—those of ICD, Leonhard, and Sneznevsky (continuous, shiftlike, recurrent). Schizophrenia was familial using the different concepts, with risks often resembling those described in this section (Ungvari 1983, 1984, 1985).

Although no completely new twin study has been published in detail, a major updating and clarification of the United States Veterans Twin Registry (Pollin et al. 1969) has been reported by Kendler and Robinette (1983) with a 62 percent increase in the number of schizophrenic probands after record review by the staff of the NAS-NRC Medical Follow-Up Agency using ICD diagnoses. Therefore the probands will include schizoaffective and borderline or latent categories. Sixteen years elapsed since the records were collected for the Pollin et al. project in 1965. The quality of the information in such a huge epidemiologic data set (31,848 individual male twin veterans) can be criticized, but maximal use has been made of the available recorded information. The built-in advantage of knowing the prevalence and LTMR of schizophrenia in the total twin sample, screened for mental and physical health as it was (Seltzer and Jablon 1974), permits the calculation of the appropriate base rate for evaluating the concordance rates quantitatively and making an estimate of the degree of genetic determination in the liability to developing schizophrenia (Gottesman and Shields 1972; Kendler and Robinette 1983).

Overall prevalences in monozygotic (identical) and dizygotic (fra-

ternal) twins for an ICD diagnosis of schizophrenia were not significantly different from each other, 1.63 ± .11 percent and 1.83 percent ± .11 percent. As the prevalence in the nontwin population of screened veterans is unknown, the data cannot be used to support earlier observations to the effect that twins do not have a higher risk than singletons; however, lack of monozygotic: dizygotic differences here argues in favor of no difference from singletons in that monozygotic (MZ) twins have a greater prenatal and perinatal frequency of birth complications, the supposed culprit in a hypothetical difference. The probandwise concordance rate for ICD schizophrenia in the enlarged, rediagnosed sample was 30.9 percent in 194 MZ pairs and 6.5 percent in 277 dizygotic (DZ) pairs (in 119 pairs with undetermined zygosity, the rate was 25.2 percent). Age correction made little difference in these values. Kendler and Robinette's rates stand in contrast to the 1969 pairwise rates reported for 80 MZ pairs of 13.8 percent and for 146 DZ pairs of 4.1 percent.

In the update the investigators estimated the effect of selecting out (at induction) of the twin panel different percentages of men "destined to become schizophrenic." They used a range of values to correct the probandwise concordance rates, from zero percent selection to 50 percent selection. Arguing by analogy from the known selection rate for diabetes mortality in the total of some 85,000 veterans of 53 percent (Seltzer and Jablon 1974, p. 370), we would select a 50 percent correction factor for schizophrenia in the twin rates. If correct, the net effect would be an extrapolation to an MZ rate of 47.2 percent and a DZ rate of 12.2 percent; both values are remarkably close to the recent literature from unscreened twin samples (Gottesman, Shields, and Hanson 1982). The Kendler and Robinette updating of the NAS-NRC Veterans Twin Registry appears to have consolidated the corpus of knowledge from twin study strategies and left it intact.

The clinical, non-mental health professional applied diagnoses in twins not specially interviewed for research will not satisfy the critics. If the results from earlier twin studies could be attributed largely to clinical diagnoses based on unstructured interviews, we might expect the strong evidence in favor of the role of genetic factors to become weaker when such stipulations are imposed. McGuffin et al. (1984), McGuffin, Farmer, and Gottesman (in press), and Farmer, McGuffin, and Gottesman (in press) recycled the Maudsley-Bethlem schizophrenic twin sample (Gottesman and Shields 1972) so as to apply various objective criteria blindly to the original case histories including verbatim transcripts of semistructured interviews. The raw sample size yields were presented in part in table 1. Probandwise concordance rates generated by such concepts now become of interest.

RDC and St. Louis criteria, both at the probable level, preserved the MZ sample but excluded one third of the DZs, and resulted in comparable concordance rates: RDC MZ 45.5 percent and DZ 8.7 percent. The correlations in liability led to an estimate of the heritability of liability of .83. Applying *DSM-III* criteria led to probandwise concordance rates of 47.5 percent in MZ and 9.5 percent in DZ with similar sample exclusions to the RDC and St. Louis criteria. Requiring one or more Schneiderian FRS clearly present decimated the sample and produced, paradoxically, higher DZ than MZ concordance rates. Carpenter, Strauss, and Bartko's Flexible (5) criteria took a great toll on the sample size and produced no concordant DZ pairs. With Crow's guidance we were able to type the twins into pure Type I characterized by positive symptoms (delusions, hallucinations) and favorable response to medication; pure Type II characterized by negative symptoms, morphological brain changes, and treatment resistance; and a Mixed type. As shown in table 1, only three twins were Type II. Probandwise concordance rates for Type I were 53 percent (8/15) in MZ and 19 percent (4/21) in DZ, while for Mixed type they were 64 percent (7/11) and 0 percent (0/11). Our initial attempt to search for genetic meaning in Crow's typology yields mixed results but could be interpreted as reflecting a dimension of severity.

One of David Rosenthal's (1963) major contributions was the coordination of the story of the Genain quadruplets and its utilization as a microcosm of all schizophrenia research. The clone of four female schizophrenics differing in symptoms, course, and outcome is ideal for hypothesis generating. Some 25 years after their initial study at the National Institute of Mental Health, the women have been recalled and restudied with the modern armamentarium of brain-imaging, biochemical, and psychological devices reported in a series of three fact-filled articles (DeLisi et al. 1984; Mirsky et al. 1984; Buchsbaum et al. 1984). The major lesson taught concerns the clinical variability possible for one schizophrenic genotype cloned four times, thus highlighting the important roles played by psychosocial and nongenetic biological factors. PET findings suggested that frontal brain hypofunction was not familial and may be a state marker. Ventricle-brain ratio (VBR) appeared

to be familial but, contrary to expectation, the quads' computed tomographic (CT) scans did not show ventricular enlargement or cortical atrophy. One hope-filled finding was the lack of a downhill, deteriorating outcome in these drug-treated, cared-for chronic schizophrenic (3) and schizoaffective (1) quadruplets. The strategy of multiple biological and psychological assessments of MZ twins wholly or partially discordant has much to recommend it (cf. Johnston et al. 1983) for achieving insights to the processes of schizophrenia and is being pursued with a new nationwide sample of twins (E.F. Torrey, personal communication).

Adoption Strategies. When the parents who provide the genes to their offspring are not the same as the rearing parents, an opportunity exists for a better disentangling of the genetic and environmental rearing factors that predispose to the development of schizophrenia. Different adoption strategies have been used by Heston in the United States and by Rosenthal, Kety, Wender, and Schulsinger in Denmark in now classical studies, all pointing in the direction of major genetic contributions to the etiology of schizophrenia. The studies have been criticized for the same reasons noted above for family and twin studies, that is, dependence on clinical interviews and clinical, noncriteria-based diagnoses for both parents and adoptees. Some of these studies have been recycled so as to apply objective contemporary diagnostic criteria in a blindfolded fashion.

Lowing, Mirsky, and Pereira (1983) have subjected Rosenthal and his colleagues' Danish study of the adopted-away offspring of schizophrenic mothers and fathers to reanalyses with *DSM* criteria. Drastic changes in the entire sample were the results of removing parent probands who did not have unanimous *DSM-II* diagnoses of schizophrenia in the original study by Rosenthal and colleagues; 78 matched pairs were reduced to 39—27 ill mothers and 12 ill fathers. Of the 39 proband parents, 29 were judged to have chronic schizophrenia. Only 1 of the 39 index adoptees had a *DSM-III* diagnosis of schizophrenia (a prevalence, not LTMR, of 2.3 percent) while none of the controls had such a diagnosis. Ten index adoptees had schizotypal or schizoid personalities, while only four controls fell into these "spectrum" categories. As both the index and control adoptees were all still within the risk period for developing schizophrenia (35 pairs were under age 45), the final chapter on this study has yet to be written.

No additional followup information has been added to the reanalyses. One of the major effects of the imposition of *DSM-III* criteria on the index and control adoptees is to reduce the number of "false positives" for spectrum disorder in the controls, thereby increasing the statistical significance for the difference from the index adoptees. Rosenthal (1972) had reported spectrum rates of 31.9 percent in index and 17.7 percent in controls vs. the new *DSM-III* rates of 28.2 percent and 10.3 percent. The fact that only one child has been hospitalized for schizophrenia does support the idea that adequate adoptive rearing may prevent the realization of a schizophrenic diathesis.

The classical study by Kety et al. (1976, 1978) in Denmark using the unique strategy of examining the biological and adoptive relatives of adoptees who grew up to be schizophrenic and their normal controls has been subjected to *DSM*-izing by Kendler and Gruenberg (1984). Spectrum was redefined and refined to include not only *DSM* schizophrenia but also RDC schizoaffective—mainly schizophrenic, schizotypal personality, and paranoid personality. Schizophreniform disorders were excluded from the schizophrenia spectrum in this reanalysis. Only the Greater Copenhagen sample originally reported by Kety in 1968 has been reanalyzed by Kendler and Gruenberg (34 index schizophrenic adoptees and their relatives together with the control subjects) using both chart and interview data updated to the 1980's wherever available. Only 19/34 adoptees retained a spectrum diagnosis; a further five were called schizophreniform. Among the 69 biological relatives of the spectrum adoptees, 15 (21.7 percent) were similarly and blindly diagnosed compared with 3/137 (2.2 percent) of control relatives; the difference is reliable at the .000003 level. Restricting the analysis to only first degree biological relatives still resulted in a significant difference and an increase in the expected direction. Of the 17 such relatives of spectrum adoptees, six (35.3 percent) were also spectrum.

For the first time the LTMRs for schizophrenia per se have been calculated for the first and second degree biological relatives of the adoptees from whom they have been separated. It was 10.5 ± 9.9 percent in the former and 6.7 ± 6.5 percent in the latter; the severe winnowing process has led to very large standard errors so that the extension to the nationwide sample will be awaited. The reanalyses of Kety et al. by Kendler and Gruenberg have altered the substance but not the substantive conclusions reached earlier. Schizophrenia appears to occur through an interaction of a ge-

netic susceptibility with some kind of environmental stress; the stress need not be an environment containing a spectrum person as none of the adoptive parents had such diagnoses; the genetic factors in schizophrenia have specificity as they did not increase the risk for major affective disorders or delusional disorder.

A completely new adoption study examining the offspring of schizophrenic mothers (the strategy of Heston and Rosenthal), some of them prospectively, has been launched in Finland by Tienari, Wynne, and colleagues (Tienari et al., in press). Early results, still quite preliminary, are available; they are especially interesting to the field of psychiatric genetics as the investigators are known for their psychodynamic orientation to schizophrenia and for their healthy skepticism about the weight to be accorded to genetic factors. Hospital diagnoses of schizophrenia and paranoid psychoses (influenced by a Langfeldtian tradition) are being used initially but will be supplemented by RDC and *DSM* criteria eventually. So far 184 offspring of 171 schizophrenic mothers have been identified, with 49 offspring still under age 20. Of the 112 index adoptees with information including some telephone interviews and all hospital charts, eight are psychotic (five schizophrenic, two paranoid, one bipolar manic) compared with two schizophrenics in 135 control adoptees. The 6.25 percent prevalence (not LTMR) for nonaffective psychosis is in agreement with the literature in psychiatric genetics. The new "wrinkle," however, comes from the report that based on clinical assessments of the joint family interview by a psychiatrist, the adoptive family mental health has been rated as seriously disturbed for every one of the seven schizophrenic adoptees. If and when such soft data become "hardened" by further quantification, they would exemplify the diathesis-stressor model for schizophrenia and provide data about the relevant psychosocial stressors. It will be from such a research program that the stuff of prevention will be extracted.

Although not strictly a family study or an adoption study, the project begun in Israel by Rosenthal, Nagler, and colleagues examines the prospective effect of high-risk children of schizophrenic parents being reared by their ill parents vs. being reared in a kibbutz environment with patently less exposure to their ill parents. First examined between the ages of 8 and 15, 50 high-risk children (half kibbutz reared) and their controls are now reported on 15 years later by Mirsky et al. (1985), after a SADS-L interview and *DSM-III* diagnosing. Schizophrenia only appears in the index children (three in the kibbutz and two in town), as does schizoid personality (three in the kibbutz and one in town). Although the subjects are still well within the risk period, the decreased exposure to an ill parent does not appear to have reduced the appearance of schizophrenia spectrum disorders; the authors suggest that the kibbutz may have actually produced an excess of psychopathology in this high-risk group.

Heterogeneity—Phenotypic and Genotypic

Clearly, schizophrenia is clinically or phenotypically heterogeneous with respect to phenomenological subtype, age at onset, course, outcome, positive family history, and brain morphology and function. Whether this variety is paralleled by etiological heterogeneity or to what extent is problematic. In light of the earlier discussion about phenocopies and genocopies, questions about etiological heterogeneity are paramount in all past and future research into schizophrenia.

In his catalogue of mendelizing (clearly dominant, recessive and X-linked) genetic disorders, McKusick (1986) favors the view that what is called "schizophrenia" is a mixture of different entities. However, he earlier noted (McKusick 1969) that the leading principles of genetic nosology include not only the idea of heterogeneity, but also *pleiotropism*. Pleiotropism is the phenomenon of a single etiological factor (for example, a single gene) having multiple effects. A nice example with psychiatric relevance is the demonstration of the various (biochemical, morphological, and behavioral) phenotypic manifestations of the phenylketonuria gene. However, we can broaden the notion of pleiotropism to include nongenetic medical conditions, and here syphilis and systemic lupus erythematosis provide excellent examples of how a specific pathogenic process can have clinical manifestations that are many and various, often leading to diagnostic error and perplexity.

In cases of late syphilis, the contrasts in presentation between one patient and another may be quite disparate, whereas in schizophrenia, classification and differentiation of syndromes is based on comparatively subtle differences, and moreover on differences that are liable to state dependency. McKusick's (1969) warning that when dealing with heterogeneity, purely phenotypic differences may provide "the most treacherous basis for decision" must be taken seriously. Against this, it must be allowed that progress in medicine has depended

to a large extent on teasing apart broad clinical syndromes and on the delineation of specific, narrower disease entities.

As with other subtyping systems described above, we have reexamined the clinical abstracts for the Gottesman and Shields (1972) schizophrenic twin series and have reclassified affected individuals as paranoid vs. nonparanoid and with Crow's typology. Pure Type II cases are rare in this series, but once again we see a tendency toward homotypia which is incomplete. Furthermore, there is some suggestion that the mixed form is a "more genetic" condition than is Type I schizophrenia in that there is a very marked difference between MZ and DZ concordance rates where the proband has a mixed type disorder.

Unfortunately, such a small amount of data does not permit any definite conclusions about the Crow subtypology, and we are unaware of any other familial data that might help clarify the issue. Furthermore, as a result of the CT scan studies of the Northwick Park group, Crow's own views on what forms the most useful clinical basis for a Type I/Type II separation are evolving and changing (Crow 1985).

There is, however, some evidence which has a bearing on a related concept, that of a separation of schizophrenia into two groups on the basis of whether negative or positive symptoms predominate. Dworkin and Lenzenweger (1984) have examined the available published extracts from systematic twin studies including our own. Using their own unpublished system, which they find to be reliable in rating the presence of negative symptoms, they were able to divide up probands from MZ pairs into "high negative" and "low negative" categories. The results are summarized in table 3, where a fairly consistent picture emerges. In all twin studies, except for that of Kringlen (1967), higher concordance is found where the proband exhibits a high rate of negative symptoms. This approach is rather different from and considerably simpler than the Crow subtypology. Nevertheless, there is clearly a resemblance between these results and those of our own efforts to apply the operationalized Crow criteria to the Maudsley schizophrenic twin series.

It is tempting to speculate that in cleaving off a group of patients with Type II/mixed, or predominantly negative symptoms, we are simply selecting a more severely affected group which, as with nonparanoid, hebephrenic, or "H-type" cases, tends to occupy a more extreme position on a continuum of liability. It might be argued, therefore, that all of these findings are reminiscent of the earlier work of Gottesman and Shields (1972) who took a more straightforward approach to the question of severity. The probands from identical twin pairs were divided according to time spent in hospital. Where the proband had spent less than 2 years in the hospital, there was a concordance of only 27 percent as against a rate of 77 percent where a proband had spent more than 2 years in the hospital since the onset of his/her illness. Similarly, where probands had shown an inability to stay out of the hospital for at least 6 months since the onset of their disorder, the rate of schizophrenia in the cotwins was 75 percent.

The evidence considered so far would seem to favor the existence of "more genetic" and "less genetic" varieties of schizophrenia lying on the same continuum, with cutoff points dependent on chosen clinical criteria. A more radical suggestion has recently been put forward by Murray, Lewis, and Reveley (1985), that "sporadic" or nongenetic forms of schizophrenia may be quite common and that presence or absence of a family history of the disorder provides a useful starting point for such a classification scheme. There are undoubtedly many organic conditions that can present with a schizophrenic-like disorder (Davison and Bagley 1969; Propping 1983), but well-established cases of "symptomatic" schizophrenia which, from a genetic viewpoint, might be considered as "phenocopies" were uncommon in clinical practice before the epidemic of amphetamine and cocaine abuse. Murray, Lewis, and Reveley (1985) suggest that sporadic cases of schizophrenia may be commoner than is generally supposed

Table 3. Concordance for schizophrenia in monozygotic twins as function of degree of negative symptoms in probands[1]

	Concordance (%)	
Study	**High negative**	**Low negative**
Fischer	64	14
Gottesman & Shields	50	33
Kringlen	32	48
Slater	75	46
Tienari	50	0
Weighted mean	52	36

[1]After Dworkin and Lenzenweger (1984).

and that the environmental causes often go undetected. They point out that identical twins discordant for schizophrenia show marked differences in cerebral ventricular size on CT brain scans. Although the numbers involved were small, Reveley et al. (1982) found a significant tendency for the affected proband to have larger ventricles than the nonschizophrenic cotwin. It was postulated that this might reflect early trauma such as birth injury, and a subsequent study (Reveley, Reveley, and Murray 1984) found a relationship between enlarged cerebral ventricles, negative family history of psychiatric illness, and positive history of early cerebral insults in schizophrenic twins. However, it should be noted that "family history negative" here meant absence of illness in relatives other than the cotwin so that the sample of "family history negative" probands appears to have included some individuals with affected cotwins. Thus, the apparent elegance and simplicity of a family history positive/family history negative division may be dangerously deceptive.

There are a number of general and specific objections to a family history positive/family history negative split (Eaves, Kendler, and Schulz, in press). First, any plausible model of transmission (McGue, Gottesman, and Rao 1985) would predict that those patients without a family history of schizophrenia would include a high proportion of genetic cases who are "chance isolates" as well as those who are true nongenetic cases. However, there would be no straightforward way of differentiating between the two without waiting a generation. Second, the chances of obtaining a positive family history of psychiatric disorder are closely related to the quality of information available. Thorough family interview studies inevitably uncover more secondary cases among relatives than do studies based on history alone. Third, the proportion of family history positive cases must also depend on family size and on the proportion of relatives who have passed through the age of risk. Most authors agree that there is an increased rate of schizophrenia and of spectrum disorders among the relatives of persons with schizophrenia rather than an increase in psychopathology generally. Nevertheless, Reveley, Reveley, and Murray (1984) have taken a broad perspective on what constitutes a "family history positive" case and include a family history of *any* major psychiatric disorder. If we suppose that the population risk in adults for major psychiatric disorder is (conservatively) about 10 percent, then we would obtain a distribution of family history positive cases by chance alone like that shown in table 4. Obviously this is not entirely realistic since it does not take into account the tendency of most psychiatric disorders to aggregate in families. However, the table serves to illustrate that family size cannot be ignored as a potential confounding variable in studies of this type. Eaves, Kendler, and Schulz (in press) give strong additional reasons to abandon the strategy as it has been used thus far.

Table 4. Proportion of a population expected to be "family history positive"[1]

Proportion (%)[2]	No. of relatives
10	1
19	2
27	3
34	4
41	5
47	6
52	7

[1]For a 10% base rate trait by chance (McGuffin, Farmer, and Gottesman, in press).
[2]Proportion p, calculated as $p = 1 - (1 - \pi)^n$ where π = population frequency and n = number of relatives.

A more direct criticism of the hypothesis of Murray, Lewis, and Reveley (1985) is that we might expect to see a consistent relationship between presence or absence of family history and cerebral ventricular size in other studies of schizophrenics. However, as table 5 shows, there is a disappointing lack of agreement between studies carried out in different centers. Some (e.g., Turner, Toone, and Brett-Jones, in press) support Murray's hypothesis, one (Nasrallah et al. 1982) produced findings in the opposite direction of that predicted, while most others actually find no significant differences between the family history positive and family history negative groups.

Do earlier twin or family studies provide any clarification? Only a minority of even the most thoroughly investigated schizophrenics have secondary cases in their first or second degree relatives and over 60 percent must be classified as "family history negative" (Bleuler 1978) or 81 percent if restricted to parents and siblings (Gottesman, Shields, and Hanson 1982). Given that this is so, it could be asked whether discordance in identical twins might be due to an admixture of genetic and nongenetic cases. The question was first investigated by Luxenburger (1928). He found that discordant pairs had other affected family members as often as did concordant pairs—results that were subsequently replicated by other investigators. Furthermore, a study of the adult offspring of MZ twins discordant for schizophrenia revealed a similar risk for the disorder in both

Table 5. Computed tomographic brain studies: Ventricle-brain ratio (VBR) in family history positive (FHP) vs. family history negative (FHN) schizophrenics[1]

Authors	Summary of findings
Reveley, Reveley & Murray (1984)	Mean VBR in FHN twins significantly *greater* than in FHP twins.
Nasrallah et al. (1982)	Mean VBR in FHN patients significantly *less* than in FHP patients.
Owens et al. (1985)	More FHP than FHN patients with VBR > control mean.
Farmer et al. (in press) Kolakowska et al. (1985) Reveley & Chitkara (1985)[2]	No significant difference between FHP and FHN patients.
Turner, Toone & Brett-Jones (1986)	Mean VBR in FHN patients significantly *greater* than in FHP patients.

[1]*After McGuffin, Farmer, and Gottesman (in press).*
[2]However, one-way analysis of variance showed significant differences, with VBR in FHN patients > VBR in FHP patients > VBR in controls.

the children of the schizophrenic probands and the children of their nonschizophrenic cotwins (Fischer 1971). (The latter finding has been confirmed and extended in the offspring of her MZ and DZ twins by Gottesman and Bertelsen, in preparation.) Both findings strongly suggest that a genetic/sporadic admixture hypothesis to explain discordance for schizophrenia in identical twins is incorrect but support the idea that "sporadic" or nongenetic forms of schizophrenia are uncommon. This being so, planned studies of discordant twins should provide an ideal means of pinpointing specific environmental stressors which may precipitate the disorder in the genetically susceptible as well as indicating possible protective factors.

One further strategy for exploring the diagnostic ingredients in the compound, schizophrenia, has been introduced by Fischer, Gottesman, and Bertelsen (1985) using a unique sample of all Danish psychiatric inpatients who mated with other inpatients and produced "super high-risk children." Within a larger data set of 139 dual-mating couples who had produced 378 offspring surviving beyond age 15, they chose first to explore the concept popular in Scandinavia of reactive psychosis and its relationship to schizophrenia and manic-depressive disorder. Matings between schizophrenic and reactive psychotics did not lead to an increased risk for schizophrenia over the risk for children with one parent affected; similarly the matings between bipolars or unipolars and reactives did not increase the expected risk for manic-depressive disorder. Although the samples were too small for firm conclusions, it would appear that reactive psychosis contributes neither genetic nor environmental risk-increasing factors for the liability to either of these major disorders. Analyses of the 120 offspring born to 49 schizophrenic parents in the sample are in progress.

Models and Modeling

Once the existence of an important genetic predisposition to develop schizophrenia has been established, it becomes important to provide a theory (or theories) to account for its mode (modes) of transmission, allowing for simultaneous genetic and cultural transmission. Psychiatric geneticists have not yet solved the problem, in part because of the difficulty of specifying the appropriate phenotype to analyze and also because of the unknown degree of etiological heterogeneity. Consider the difficulty of specifying the mode of transmission of blindness, deafness, or mental retardation. Faraone and Tsuang (1985) should be the starting point for those who would try to master the complexities of genetic modeling for schizophrenia.

We can only illustrate some of the issues and partial solutions in this brief exploration. After their comprehensive review of modeling efforts, Faraone and Tsuang (1985) conclude there is little support for the idea of a single major locus accounting for the transmission of the disorder. Multifactorial polygenic models, as we shall show below, have the most "votes" from the field with the added advantage of incorporating cultural transmission into the models. A genetic model, called the "mixed model," proposed a single major locus together with a multifactorial and polygenic component; it remains a possibility but is exceedingly difficult to test with available data (Lalouel et al. 1983).

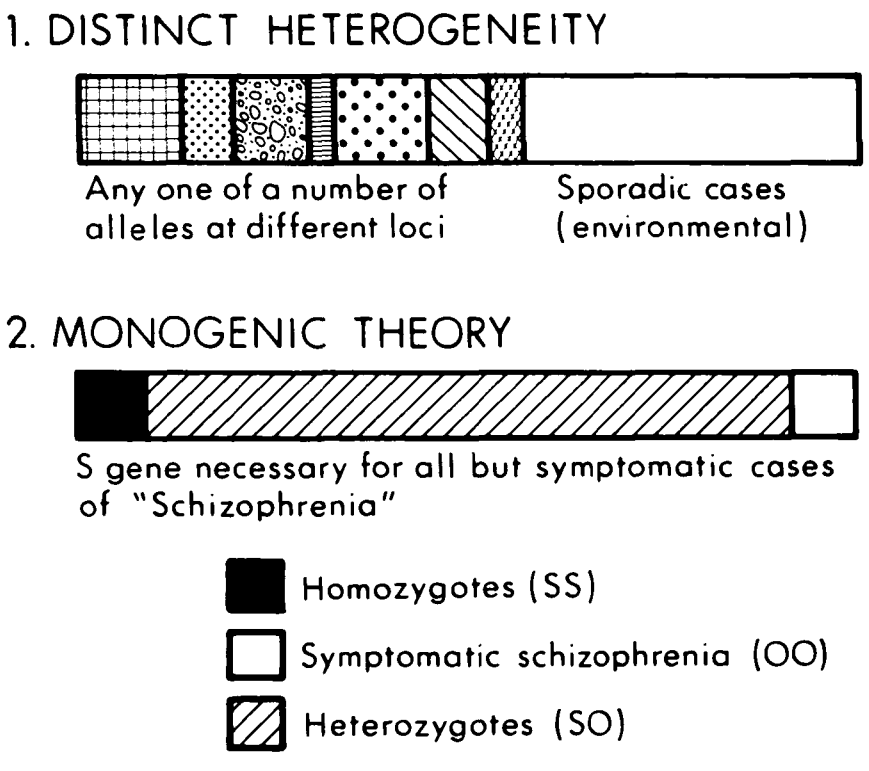
Overview of Genetic Transmission Theories. Four major classes of models have been invoked to account for the patterns of transmission observed in the pedigrees of schizophrenics and pooled risks to their relatives. The distinct hetero-

geneity model specifies that schizophrenia is composed of a large number of qualitatively separate diseases, many genetic in origin and others environmentally caused. Such a view fits the data on severe mental retardation and blindness. With this model we might expect catatonic schizophrenia to be a single major locus (SML) disease on one chromosome and phenothiazine-resistant schizophrenia to be an SML disease on another chromosome as well as recognizing symptomatic schizophrenias associated with amphetamine and cocaine abuse. The model requires each of the SML varieties to have pedigrees consistent with either dominant or recessive inheritance.

The second model is the monogenic or SML model with all schizophrenics having the same gene at the same locus as with the rare mendelian disorder Huntington's disease. The third model is known as multifactorial-polygenic (MFP) and usually incorporates a threshold effect. It generates the hypothesis that schizophrenia is caused by a combination of a number of specific genes in combination with a number of prenatal and postnatal environmental factors, biological as well as psychosocial. The fourth model can be called a mixed model as described above. An overriding model can be called a combined model because it incorporates all of the elements of the four models named. Figures 1 and 2 illustrate simple versions of each class of model.

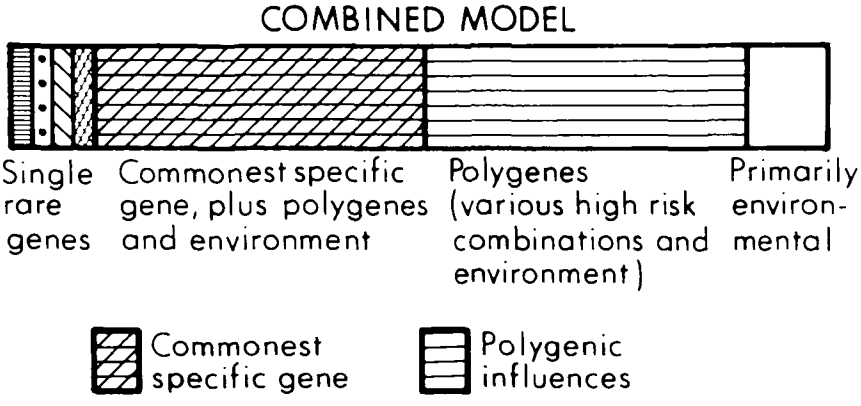
As the simpler versions have been modified by their proponents, they overlap in their borrowed assumptions and do not run the risk of being refuted in any final fashion. All the modified theories make implicit or explicit use of a threshold concept because they deal with affected and unaffected dichotomies.

Figure 1. Illustrations of hypothetical genotypes and kinds of heterogeneity according to 3 genetic models.[1]



[1]After Gottesman, Shields & Hanson (1982).

Figure 2. Schematic overview of possible proportions of schizophrenic genotypes under assumption of a combined model.[1]



[1]After Gottesman, Shields & Hanson (1982).

The distinct heterogeneity model in figure 1 would have the posited genotypes, dominant, recessive, and even sex-linked, as well as the genocopies (Propping 1983) on the left and the phenocopies (Davison and Bagley 1969) on the right.

The rectangle depicting the monogenic theory saves some space for symptomatic, schizophrenia-like psychoses with no expectation that they will be transmitted in the next generation. The three possible genotypes at the "schizophrenia locus" are SS, SO, and OO. Unlike the Huntington's disease model, only a small proportion of the SO genotypes develop the disease whereas all HO become affected with HD. The penetrance of the S gene is allowed to be different in each genotype in the generalized SML theory (Matthysse and Kidd 1976; O'Rourke et al. 1982). This is the same as saying that different proportions of each genotype are to the right of one threshold and therefore affected. No major effect of any hypothesized SML gene has been detected yet in obligate genotypes in the expected mendelian ratios. O'Rourke et al. (1982) concluded that the general SML two-gene model can be rejected. It did not explain the patterns of affectation in the familial distributions of 21 family and twin studies in the worldwide literature, even allowing for complete flexibility in the degree of penetrance. They found that the risks in MZ twins and the offspring of dual-mating schizophrenics were too high compared to other classes of relatives. Using a broad and a narrow concept of schizophrenia inferred from the individual studies resulted in 33 percent and 45 percent of them, respectively, being inconsistent with the model. O'Rourke et al. did not test other models in figure 1 or 2.

Fitting a model on statistical grounds is not the same as proving the truth of the model; it is necessary but not sufficient evidence in a broader research program. Not fitting or refuting a particular model still can be challenged on the grounds of the assumptions required to test the model. Karlsson (1982) and Matthysse, Holzman, and Lange (1986) speculate about the continued viability of an SML model for different reasons; neither of their models has been tested against comprehensive data sets or pooled LTMRs in different classes of relatives. Let many flowers bloom.

To illustrate the MFP model in figure 1, we selected a relatively simple five-locus version with two possible alleles at each locus. On this model schizophrenia is expressed once an accumulation of genetic (specific and general) and environmental (general) factors, after allowance for compensatory assets, exceeds a threshold value in the combined liability distribution. Figure 1 illustrates only the specific genetic factors in the MFP model.

A capital-letter allele increases liability while lower-case alleles decrease liability. Our 5-locus model generates 11 genotypic classes with 0 to 10 liability-increasing genes; 243 different genotypes are generated, but most are functionally equivalent to others. The three 5-locus genotypes illustrated are a subset of 51 such possibilities. The genotypes shown as high risk and very high risk are beyond the threshold because of additional liability factors and a shortage of assets. The model allows even very high risk genotypes to stay compensated and clinically unaffected. The fact that the vast majority of schizophrenics are "family history negative" is easily managed by this MFP model.

McGue, Gottesman, and Rao (1983, 1985), building on the invention of qualitative path analysis (Rao et al. 1981), used the data points from pooled LTMR in the Western European family and twin studies in table 1 to test one- and two-threshold MFP models. As part of the program, they tested the same data set for a fit to a generalized SML model for the first time in a "showdown" for the two models. Goodness-of-fit tests led to the rejection of the SML and to the acceptance of MFP for

different reasons from those used by O'Rourke et al. (1982). The best-fitting MFP path model was one that makes provision for cultural "heritability" or transmissibility (c^2), genetic heritability (h^2), family environment unique to twins (t^2), and effect of assortative mating. For the wider concept of definite plus probable schizophrenia, all values were significant with h^2 of .63, c^2 of .29, and t^2 of .09.

As a precaution against the effect of heterogeneity among the studies contributing noise to any one data point, McGue et al. deleted such points when there was significant heterogeneity and found no major effect on the conclusions. Deleting all twin data from the analyses resulted in a lower genetic heritability (.42) and a larger cultural heritability (.53) than was obtained in the full model for all data. As a precaution against the modeling procedure itself giving misleading results, they also fitted family data on tuberculosis to the MFP threshold model; their analyses revealed that cultural heritability, as logically expected, was overwhelming with a value of .62 and genetic heritability was only .06 for an infectious disease with some demonstration of genetic resistance to the bacillus. Relying on twin data only would have been completely misleading for tuberculosis! Pooling studies, pooling classes of relatives, and avoiding the weakening of data heterogeneity have provided enough statistical power to permit resolving SML vs. MFP models for the same data set. The model fits, but we cannot yet conclude that it represents truth.

It may well be that all four classes of models are partially correct. Figure 2 embodies that kind of ecumenicism. The combined model does not immediately lead to refutable hypotheses, but it is compatible with the discussion about etiological heterogeneity above. The different proportions of the phenotype allocated in the rectangle to the different models cannot be taken literally, but they do reflect our own reading of the literature. In this respect we are casting our lot with those who try to account for the etiology of a number of the common genetically loaded diseases such as diabetes, coronary heart disease, and the entire range of mental retardation. Anderson, Chern, and Schwanebeck (1981), simulating combined models to account for heterogeneity in epilepsy, have given us in the schizophrenia field food for thought.

The LTMR for epilepsy was set at 1 percent. Of many possible model sets for a combined model, they chose the following (cf. figure 2): 20 autosomal recessive traits each with 50 percent penetrance and a phenotypic frequency of 1 in 80,000 *plus* 10 autosomal dominant traits each with 50 percent penetrance and a frequency of 1 in 40,000 *plus* two common autosomal dominants with 50 percent penetrance and a frequency of 1 in 2,000 *plus* two multifactorial polygenic systems each with h^2 of .50 and a frequency of 3 in 1,000 *plus*, finally, a sporadic component with a frequency of 2.5 in 1,000. The simulation generated predictions about mating types in parents and risks to their offspring as well as projections relevant to the frequency of multiplex families (those with two or more affected). Such simulations have heuristic value; in light of figure 2, we would suggest a different "mix" for schizophrenia model simulations. If you find yourself gasping for parsimony at this point, ask yourself where parsimony has taken us in the search for the causes of schizophrenia. The explanation of brain function may well require a new level of complex genetic theories (Sutcliffe et al. 1983).

Genetic Markers

Genetic markers are a special category of biological markers. Although still too often used in a loose sense in the psychiatric literature, the term genetic marker is probably best restricted to cover traits that have a simple, known mendelian mode of inheritance and that are demonstrably polymorphic (i.e., where there are two or more alleles with a gene frequency of at least 1 percent) (Giblett 1969). Erlenmeyer-Kimling (submitted for publication) has reviewed possible biological markers. The better known genetic markers include red cell antigens such as ABO, rhesus, and MN, as well as major histocompatability (HLA) antigens, various blood protein polymorphisms, and red cell enzymes. In addition to these "conventional" markers, the advent of "the new genetics" of recombinant DNA (Emery 1984) has meant that many more genetic markers (probes) are now available and that the day is not far off when the human genome (i.e., the set of 22 pairs of autosomes and 2 sex chromosomes) will be extensively mapped. So far, over 900 genes have been assigned to chromosomal locations (De la Chapelle 1985), but only about a quarter of genes so far mapped are detectably polymorphic (*American Journal of Human Genetics* 1983) and only a proportion of these have been investigated in relation to schizophrenia (McGuffin and Sturt 1986).

Possible associations discovered by recent population studies involving blood complement factors (Rudduck 1985) merit further investigation, but most genetic marker findings in schizophrenia to date

have been disappointingly inconsistent, and convincing replications of positive findings have been rare. A notable exception is the evidence concerning the HLA system and clinical subtypes of schizophrenia. Recall our doubts about such subtypes being other than proxies for a dimension of severity. Even so, we would be interested in susceptibility genes associated with resistance to severe illness.

Associations between certain specificities of the HLA system and a number of common diseases are now well established (Thomson 1981). Such disorders include juvenile diabetes, multiple sclerosis, and ankylosing spondylitis. Most HLA-associated diseases are not rare, have a tendency to run in families, and show complex patterns of inheritance that are not classically mendelian. Not surprisingly, therefore, schizophrenia came under scrutiny not long after the first HLA-disease reports (Cazzulo, Smeraldi and Penati 1974; Eberhard, Franzen, and Low 1975). Studies of schizophrenia as a whole, however, provided no clear pattern of association across different centers (McGuffin 1979). It was only when schizophrenia was broken down into possible subtypes that a more consistent set of results emerged. In particular, there was evidence of an association between paranoid schizophrenia and HLA A9, while the hebephrenic subtype showed a less consistent association with HLA A1. Table 6 shows the total of nine published studies that provide data on an A9-paranoid schizophrenia association (McGuffin and Sturt 1986).

Seven of these are consistent with the presence of an association and, when the data are pooled, it seems highly unlikely that the association has arisen by chance ($\chi^2 = 19.378$, p corrected for number of comparisons = 0.0003). There are a number of difficulties with such a pooling. First, it is not clear whether the diagnosis of a paranoid subtype is comparable in the different centers. Second, A9 is a composite antigen consisting of two subspecificities, AW23 and AW24 (Festenstein and Demant 1978), and it is not clear which of these is more important in the paranoid schizophrenia association. Third, and perhaps most important, despite its high statistical significance, the strength of association is low. The estimated relative risk of developing paranoid schizophrenia for an A9 positive individual compared to an A9 negative individual is 1.6. If we assume, as we have done earlier, a liability/threshold model for the transmission of schizophrenia, then we can use the method given by Edwards (1965) to calculate that the contribution of the HLA locus to variation in liability to paranoid schizophrenia is only about 1.1 percent. It therefore appears that the HLA studies may indicate a minor susceptibility locus rather than an important major gene effect in paranoid schizophrenia. The results would require only slight modification of our earlier speculations that the separation between paranoid and other types of schizophrenia is entirely quantitative and based purely on different thresholds on a liability continuum. Instead, we would have to allow

Table 6. Frequency of HLA A9 in paranoid schizophrenics compared with controls (after McGuffin & Sturt 1986)

Study	% Controls	*n*	% Patients	*n*	X "relative risk"	X^2
Leeds (McGuffin, Farmer & Yonace 1981)	17.90	458	32.14	28	2.17	3.37
Marseilles (Julien et al. 1978)	21.10	250	47.37	38	3.35	11.26
Milan (Smeraldi, Bellodi & Cazullo 1976)	26.94	386	42.86	42	2.03	4.56
Prague (Ivanyi, Zemek & Ivanyi 1978)	22.83	1,200	29.50	200	1.41	4.17
Mannheim (Gattaz & Beckmann 1980)	20.97	472	31.15	61	1.70	3.19
Iowa (Crowe et al. 1979)	9.98	1,263	21.43	14	2.46	1.87
Gunma (Miyanaga, Machiymaya & Juji 1984)	59.58	1,252	35.00	20	0.37	4.55
Lund/Umeå (Rudduck et al. 1984)	16.10	919	10.00	30	0.58	0.79
Amsterdam (Ivanyi et al. 1983)	19.25	1,018	30.65	62	1.85	4.63

Note.—Combined X = 1.591, SD = 105. $X^2 = 19.378$ ($p = 1.1 \times 10^{-5}$, p corrected = .00032). Heterogeneity $\chi^2 = 19.020$, $df = 8$ ($p = .015$). X = cross-product ratio or relative risk.

that there may also be overlapping sets of polygenes, each of which modify the clinical picture in subtly different ways.

By contrast with the association studies, linkage studies which seek to detect a marker gene in close proximity to a major disease gene on the same chromosome have been predominantly negative with respect to HLA. Turner (1979) reported that there was suggestive, but inconclusive, evidence of linkage between HLA and "schizotaxia" in "typical" families multiply affected by schizophrenia but not in "atypical" families in which multiple family members were affected not just by schizophrenia but by other conditions such as affective disorder. McGuffin, Festenstein, and Murray (1983) failed to replicate this finding and subsequent investigators (Andrews et al., in press; Chadda et al. 1986; Goldin, DeLisi, and Gershon 1987) are also negative.

So far, there are no published positive results of studies of schizophrenia and new genetic markers of recombinant DNA technology, so-called restriction fragment length polymorphisms (Botstein et al. 1980). But there is considerable optimism about the future usefulness of such markers in detecting major gene effects and resolving problems of heterogeneity in schizophrenia and other common diseases (White et al. 1985). Unfortunately, the statistical analysis of linkage studies involving conditions with complex and nonmendelian patterns of inheritance presents formidable problems that will need to be solved before the "new genetics" can yield tangible benefits for schizophrenia research (Kidd 1981; Cloninger, Reich, and Yokoyama 1983; Kidd 1985; Sturt and McGuffin 1985).

References

Abrams, R., and Taylor, M.A. The genetics of schizophrenia: A reassessment using modern criteria. *American Journal of Psychiatry,* 140:171–175, 1983.

Alpert, M., ed. *Controversies in Schizophrenia: Changes* and *Constancies.* New York: The Guilford Press, 1985.

American Journal of Human Genetics. The human gene map. Volume 35:134–156, 1983.

Anderson, V.E.; Chern, M.M.; and Schwanebeck, E. Multiplex families and the problem of heterogeneity. In: Gershon, E.S.; Matthysse, S.; Breakefield, X.O.; and Ciaranello, R.D., eds. *Genetic Research Strategies in Psychobiology and Psychiatry.* Pacific Grove, CA: Boxwood Press, 1981. pp. 341–351.

Andreasen, N.C. Positive vs. negative schizophrenia: A critical evaluation. *Schizophrenia Bulletin,* 11:380–389, 1985.

Andrews, B.; Watt, D.C.; Gillespie, C.; and Chapel, H. A family study of genetic linkage in schizophrenia. *Psychological Medicine,* in press.

Astrachan, B.M.; Harrow, M.; Adler, D.; Brauer, L.; Schwartz, A.; Schwartz, C.; and Tucker, G. A checklist for the diagnosis of schizophrenia. *British Journal of Psychiatry,* 121:529–539, 1972.

Baron, M.; Gruen, R.; Kane, J.; and Asnis, L. Modern research criteria and the genetics of schizophrenia. *American Journal of Psychiatry,* 142:697–701, 1985*a*.

Baron, M.; Gruen, R.; Rainer, J.D.; Kane, J.; Asnis, L.; and Lord, S. A family study of schizophrenic and normal control probands: Implications for the spectrum concept of schizophrenia. *American Journal of Psychiatry,* 142:447–455, 1985*b*.

Bartko, J.J., and Carpenter, W.T., Jr. On the methods and theory of reliability. *Journal of Nervous and Mental Disease,* 163:307–317, 1976.

Blashfield, R.K. *The Classification of Psychopathology: Neo-Kraepelinian and Quantitative Approaches.* New York: Plenum Press, 1984.

Bleuler, E. *Dementia Praecox or the Group of Schizophrenias.* (1911) Translated by J. Zinkin. New York: International Universities Press, 1950.

Bleuler, M. *The Schizophrenic Disorders.* Translated by S. Clemens. New Haven: Yale University Press, 1978.

Botstein, D.; White, R.L.; Skolnick, M.; and Davis, R.W. Construction of a genetic linkage map in men using restriction fragment length polymorphisms. *American Journal of Human Genetics,* 32:312–331, 1980.

Brockington, I.F.; Kendell, R.E.; and Leff, J.P. Definitions of schizophrenia: Concordance and prediction of outcome. *Psychological Medicine,* 8:387–398, 1978.

Bruyn, G.W.; Bots, G.T.; and Do, R. Huntington's chorea: Current neuropathological status. In: Chase, T.N.; Wexler, N.S.; and Barbeau, A., eds. *Advances in Neurology: Huntington's Disease.* New York: Raven Press, 1979. pp. 83–93.

Buchsbaum, M.S.; Mirsky, A.F.; DeLisi, L.E.; Morihisa, J.; Karson, C.N.; Mendelson, W.B.; King, A.C.; Johnson, J.; and Kessler, R. The Genain quadruplets: Electrophysiological, positron emission, and x-ray tomographic studies. *Psychiatry Research,* 13:95–108, 1984.

Cantor, N., and Genero, N. Psychiatric diagnosis and natural categorization: A close analogy. In: Millon, T., and Klerman, G., eds. *Contemporary Directions in Psychopathology: Toward the DSM-IV.* New York: Guilford Press, 1986. pp. 233–256.

Carey, G., and Gottesman, I.I. Reliability and validity in binary rat-

ings: Areas of common misunderstanding in diagnoses and symptom rating. *Archives of General Psychiatry*, 35:1454–1459, 1978.

Carpenter, W.T., Jr.; Strauss, J.S.; and Bartko, J.J. Flexible system for the diagnosis of schizophrenia: Report from the WHO pilot study of schizophrenia. *Science*, 182:1275–1278, 1973.

Cazzullo, C.L.; Smeraldi, E.; and Penati, G. The leukocyte antigen system HLA as a possible genetic marker of schizophrenia. *British Journal of Psychiatry*, 25:25–27, 1974.

Chadda, R.; Kulhara, P.; Singh, I.; and Sehgal, S. HLA antigens in schizophrenia: A family study. *British Journal of Psychiatry*, 149:612–615, 1986.

Cloninger, C.R.; Reich, T.; Suarez, B.K.; Rice, J.P.; and Gottesman, I.I. The principles of genetics in relation to psychiatry. In: Shepherd, M., ed. *Handbook of Psychiatry*. Vol. 5. Cambridge: Cambridge University Press, 1985. pp. 34–66.

Cloninger, C.R.; Reich, T.; and Yokoyama, S. Genetic diversity, genome organization, and investigation of the etiology of psychiatric diseases. *Psychiatric Developments*, 3:225–246, 1983.

Cronbach, L.J., and Meehl, P.E. Construct validity in psychological tests. *Psychological Bulletin*, 52:281–302, 1955.

Crow, T.J. Is schizophrenia an infectious disease? *The Lancet*, I:173–175, 1983.

Crow, T.J. The two-syndrome concept: Origins and current status. *Schizophrenia Bulletin*, 11:471–486, 1985.

Crowe, R.R.; Thompson, I.S.; Flink, R.F.; and Weinberger, B. HLA antigens and schizophrenia. *Archives of General Psychiatry*, 36:231–233, 1979.

Cutting, J. *The Psychology of Schizophrenia*. Edinburgh: Churchill Livingstone, 1985.

Davison, K., and Bagley, C.R. Schizophrenic-like psychoses associated with organic disorders of the central nervous system: A review of the literature. In: Herrington, R.N., ed. *Current Problems in Neuropsychiatry*. Ashford, Kent: Headley Bros., 1969. pp. 113–184.

De la Chapelle, A. Mapping hereditary disorders. *Nature*, 317:472–473, 1985.

DeLisi, L.E.; Mirsky, A.F.; Buchsbaum, M.S.; van Kammen, D.P.; Berman, K.F.; Caton, C.; Kafka, M.S.; Ninan, P.T.; Phelps, B.H.; Karoum, F.; Ko, G.N.; Korpi, E.R.; Linnoila, M.; Scheinin, M.; and Wyatt, R.J. The Genain quadruplets 25 years later: A diagnostic and biochemical followup. *Psychiatry Research*, 13:59–76, 1984.

Dohrenwend, B.P. Clues to the role of socioenvironmental factors. *Schizophrenia Bulletin*, 2:440–444, 1976.

Dohrenwend, B.S.; Dohrenwend, B.P.; Gottesman, I.I.; Link, B.; and Neugebauer, R. Epidemiology and genetics of schizophrenia. *Social Biology*, 26:142–153, 1979.

Dworkin, R.H., and Lenzenweger, M.F. Symptoms and the genetics of schizophrenia: Implications for diagnosis. *American Journal of Psychiatry*, 141:1541–1546, 1984.

Early, T.S.; Reiman, E.M.; Raichle, M.E.; and Spitznagel, E.L. Left globus pallidus abnormality in never-medicated patients with schizophrenia. *Proceedings of the National Academy of Sciences*, in press.

Eaves, L.J.; Kendler, K.S.; and Schulz, S.C. The familial versus sporadic classification: Its power for the resolution of genetic and environmental etiologic factors. *Journal of Psychiatric Research*, in press.

Eberhard, G.; Franzen, G.; and Low, B. Schizophrenia susceptibility and HLA antigens. *Neuropsychobiology*, 1:211–217, 1975.

Edwards, J.H. Associations between blood groups and disease. *Annals of Human Genetics*, 29:77–83, 1965.

Emery, A.E.H. *An Introduction to Recombinant DNA*. Chichester: John Wiley & Sons, 1984.

Endicott, J.; Nee, J.; Fleiss, J.; Cohen, J.; Williams, J.B.W.; and Simon, R. Diagnostic criteria for schizophrenia. Reliabilities and agreement between systems. *Archives of General Psychiatry*, 39:884–889, 1982.

Erlenmeyer-Kimling, L. Biological markers for the liability to schizophrenia. In: Helmchen, H., and Henn, F.A., eds. *Biological Perspectives in Schizophrenia*. Submitted for publication.

Erlenmeyer-Kimling, L., and Miller, N.E., eds. *Research on the Prediction of Psychopathology*. Hillsdale, NJ: L. Erlbaum Associates, 1986.

Essen-Möller, E. The calculation of morbid risk in the parents of index cases as applied to a family sample of schizophrenics. *Acta Genetica et Statistica Medica*, 5:334–342, 1955.

Eysenck, H.J.; Wakefield, J.A.; and Friedman, A.F. Diagnosis and clinical assessment: The *DSM-III*. *Annual Review of Psychology*, 34:167–193, 1983.

Faraone, S.V., and Tsuang, M.T. Quantitative models of the genetic transmission of schizophrenia. *Psychological Bulletin*, 98:41–66, 1985.

Farmer, A.E.; Jackson, R.; McGuffin, P.; and Storey, P. Cerebral ventricular enlargement in chronic schizophrenia: Consistencies and contradictions. *British Journal of Psychiatry*, in press.

Farmer, A.E.; McGuffin, P.; and

Gottesman, I.I. Searching for the split in schizophrenia: A twin study perspective. *Psychiatry Research*, 13:109–118, 1984.

Farmer, A.E.; McGuffin, P.; and Gottesman, I.I. Twin concordance for *DSM-III* schizophrenia: Scrutinizing the validity of the definition. *Archives of General Psychiatry*, in press.

Feighner, J.P.; Robins, E.; Guze, S.B.; Woodruff, R.A.; Winokur, G.; Munoz, R. Diagnostic criteria for use in psychiatric research. *Archives of General Psychiatry*, 26:57–67, 1972.

Festenstein, H., and Demant, P. *HLA and H2: Current Topics in Immunology*. Vol. 9. London: Edward Arnold, 1978.

Finn, S.E. Base rates, utilities, and *DSM-III:* Shortcomings of fixed-rule systems of psychodiagnosis. *Journal of Abnormal Psychology*, 91: 294–302, 1982.

Fischer, M. Psychoses in the offspring of schizophrenic monozygotic twins and their normal co-twins. *British Journal of Psychiatry*, 115:981–990, 1971.

Fischer, M.; Gottesman, I.I.; and Bertelsen, A. Undersogelse af born hvis foraeldre begge har vaeret indlagt for psykiatrisk lidelse. [An examination of offspring both of whose parents have been admitted for psychiatric illness.] *Ugeskrift for Laeger*, 147:327–330, 1985.

Garrone, G.; Jablensky, A.; and Manzano, J. *Jeunes Parents Psychotiques et Leurs Enfants*. Villeurbanne: Simep S.A., 1986.

Gattaz, W., and Beckmann, H. HLA antigens and schizophrenia. *Lancet*, I:98–99, 1980.

Gershon, E.S.; Matthysse, S.; Breakefield, X.O.; and Ciaranello, R.D., eds. *Genetic Research Strategies in Psychobiology and Psychiatry*. Pacific Grove, CA: Boxwood Press, 1981.

Giblett, E.R. *Genetic Markers in Human Blood*. Oxford: Blackwell, 1969.

Goldin, L.R.; DeLisi, L.E.; and Gershon, E.S. Relationship of HLA to schizophrenia in 10 nuclear families. *Psychiatry Research*, 20:69–77, 1987.

Goldin, L.R., and Gershon, E.S. Association and linkage studies of genetic marker loci in major psychiatric disorders. *Psychiatric Developments*, 4:387–418, 1983.

Gottesman, I.I., and Shields, J. *Schizophrenia and Genetics: A Twin Study Vangage Point*. New York: Academic Press, 1972.

Gottesman, I.I., and Shields, J. A critical review of recent adoption, twin, and family studies of schizophrenia: Behavioral genetics perspectives. *Schizophrenia Bulletin*, 2:360–401, 447–453, 1976.

Gottesman, I.I., and Shields, J. (with the assistance of D.R. Hanson). *Schizophrenia: The Epigenetic Puzzle*. Cambridge, MA: Cambridge University Press, 1982.

Grove, W.M. Comment on Lidz and associates' critique of the Danish-American studies of the offspring of schizophrenic parents. *American Journal of Psychiatry*, 140:998–1002, 1983.

Grove, W.M., and Andreasen, N.C. Multivariate statistical analysis in psychopathology. In: Millon, T., and Klerman, G., eds. *Contemporary Directions in Psychopathology: Toward the DSM-IV*. New York: Guilford Press, 1986. pp. 347–362.

Guze, S.B.; Cloninger, C.R.; Martin, R.L.; and Clayton, P.J. A follow-up and family study of schizophrenia. *Archives of General Psychiatry*, 40:1273–1276, 1983.

Henderson, N.D. Human behavior genetics. *Annual Review of Psychology*, 33:403–440, 1982.

Ivanyi, P.; Droes, J.; Schreuder, G.M.T.; D'Amaro, J.; and Van Rood, J.J. A search for association of HLA antigens with paranoid schizophrenia. *Tissue Antigens*, 22:186–193, 1983.

Ivanyi, P., Zemek, P.; and Ivanyi, P. HLA antigens as possible markers of heterogeneity in schizophrenia. *Journal of Immunogenetics*, 5:165–172, 1978.

Jablensky, A. Epidemiology of schizophrenia: A European perspective. *Schizophrenia Bulletin*, 12:52–73, 1986.

Johnston, C.; Pyke, D.A.; Cudworth, A.G.; and Wolf, E. HLA-DR typing in identical twins with insulin-dependent diabetes: Difference between concordant and discordant pairs. *British Medical Journal*, 286:253–255, 1983.

Julien, R.A.; Mercier, P.; Choaraqu, I.P.; and Sutter, T.M. Schizophrenes et antigenes d'histocompatibilite. *Encephale*, IV:99–113, 1978.

Karlsson, J.L. Family transmission of schizophrenia: A review and synthesis. *British Journal of Psychiatry*, 140:600–606, 1982.

Kendell, R.E. *The Role of Diagnosis in Psychiatry*. Oxford: Blackwell, 1975.

Kendler, K.S. Overview: A current perspective on twin studies of schizophrenia. *American Journal of Psychiatry*, 140:1413–1425, 1983.

Kendler, K.S., and Gruenberg, A.M. An independent analysis of the Copenhagen sample of the Danish Adoption Study of Schizophrenia: VI. The pattern of psychiatric illness, as defined by *DSM-III* in adoptees and relatives. *Archives of General Psychiatry*, 41:555–564, 1984.

Kendler, K.S.; Gruenberg, A.M.; and Tsuang, M.T. Psychiatric illness in the first degree relatives of schizophrenic and surgical control patients: A family study using *DSM-III* criteria. *Archives of General Psychiatry*, 42:770–779, 1985.

Kendler, K.S.; Gruenberg, A.M.; and Tsuang, M.T. A *DSM-III* family study of the non-schizophrenic psychotic disorders. *American Journal of Psychiatry*, 143:1098–1105, 1986.

Kendler, K.S., and Robinette, C.D. Schizophrenia in the National Academy of Sciences-National Research Council Twin Registry: A 16-year update. *American Journal of Psychiatry*, 140:1551–1563, 1983.

Kerr, A., and Snaith, P., eds. *Contemporary Issues in Schizophrenia*. London: Gaskell, 1986.

Kessler, S. Progress and regress in the research on the genetics of schizophrenia. *Schizophrenia Bulletin*, 2:434–439, 1976.

Kety, S.S. The syndrome of schizophrenia: Unresolved questions and opportunities for research. *British Journal of Psychiatry*, 136:421–436, 1980.

Kety, S.S.; Rosenthal, D.; Wender, P.H.; and Schulsinger, F. Studies based on a total sample of adopted individuals and their relatives: Why they were necessary, what they demonstrated and failed to demonstrate. *Schizophrenia Bulletin*, 2:413–428, 1976.

Kety, S.S.; Rosenthal, D.; Wender, P.H.; Schulsinger, F.; and Jacobsen, B. The biological and adoptive families of adopted individuals who become schizophrenic. In: Wynne, L.C.; Cromwell, R.L.; and Matthysse, S., eds. *The Nature of Schizophrenia*. New York: John Wiley & Sons, 1978. pp. 25–37.

Kidd, K.K. Genetic models for psychiatric disorders. In: Gershon, E.S.; Matthysse, S.; Breakefield, X.O.; and Ciaranello, R.D., eds. *Genetic Research Strategies in Psychobiology and Psychiatry*. Pacific Grove, CA: Boxwood Press, 1981. pp. 369–382.

Kidd, K.K. New genetic strategies for studying psychiatric disorders. In: Sakai, T., and Tsuboi, T., eds. *Genetic Aspects of Human Behavior*. Tokyo: Igaku-Shoin, 1985. pp. 235–246.

Koehler, K. First rank symptoms of schizophrenia: Questions concerning clinical boundaries. *British Journal of Psychiatry*, 134:236–248, 1979.

Kolakowska, T.; Williams, A.O.; Jambor, K.; and Ardern, M. Schizophrenia with good and poor outcome: III. Neurological "soft" signs, cognitive impairment and their clinical significances. *British Journal of Psychiatry*, 146:348–357, 1985.

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

Kringlen, E. Twins—Still our best method. *Schizophrenia Bulletin*, 2:429–433, 1976.

Lalouel, J.M.; Rao, D.C.; Morton, N.E.; and Elston, R.D. A unified model of complex segregation analysis. *American Journal of Human Genetics*, 35:816–826, 1983.

Langfeldt, G. Diagnosis and prognosis in schizophrenia. *Proceedings of the Royal Society of Medicine*, 53:1047–1052, 1960.

Leonhard, K. *The Classification of Endogenous Psychoses*. New York: John Wiley & Sons, 1979.

Leonhard, K. Different causative factors in different forms of schizophrenia. *British Journal of Psychiatry*, 149:1–6, 1986.

Lewontin, R.C.; Rose, S.; and Kamin, L. *Not in Our Genes*. New York: Pantheon, 1984.

Lidz, T. Commentary on "A critical review of recent adoption, twin, and family studies of schizophrenia: Behavioral genetics perspectives." *Schizophrenia Bulletin*, 2:402–412, 1976.

Lidz, T.; Blatt, S.; and Cook, B. Critique of the Danish-American studies of the adopted-away offspring of schizophrenic parents. *American Journal of Psychiatry*, 138:1063–1068, 1981.

Loehlin, J.; Willerman, L.; and Horn, J. Behavior genetics. *Annual Review of Psychology*, in press.

Lowing, P.A.; Mirsky, A.F.; and Pereira, R. The inheritance of schizophrenic spectrum disorders: A reanalysis of the Danish adoptee study data. *American Journal of Psychiatry*, 140:1167–1171, 1983.

Luxenburger, H. Vorlaufiger Bericht uber psychiatrische Serienuntersuchunger an Zwillinger. *Zeitschrift für die gesamte Neurologie und Psychiatrie*, 116:297–326, 1928.

Matthysse, S. Theoretical commentary on Gottesman and Shields' review. *Schizophrenia Bulletin*, 2:445–446, 1976.

Matthysse, S., ed. *Psychiatry and the Biology of the Human Brain: A Symposium Dedicated to Seymour S. Kety*. Amsterdam: Elsevier/North-Holland, 1981.

Matthysse, S.; Holzman, P.S.; and Lange, K. The genetic transmission of schizophrenia: Application of mendelian latent structure analysis to eye tracking dysfunctions in schizophrenia and affective disorders. *Journal of Psychiatric Research*, 20:57–76, 1986.

Matthysse, S., and Kidd, K.K. Estimating the genetic contribution to schizophrenia. *American Journal of Psychiatry*, 133:185–191, 1976.

McGue, M.; Gottesman, I.I.; and Rao, D.C. The transmission of schizophrenia under a multifactorial threshold model. *American Journal of Human Genetics*, 35:1161–1178, 1983.

McGue, M.; Gottesman, I.I.; and Rao, D.C. Resolving genetic models for the transmission of schizophrenia. *Genetic Epidemiology*, 2:99–110, 1985.

McGue, M.; Gottesman, I.I.; and

Rao, D.C. The analysis of schizophrenia family data. *Behavior Genetics*, 16:75–87, 1986.

McGuffin, P. Is schizophrenia an HLA associated disease? *Psychological Medicine*, 9:721-728, 1979.

McGuffin, P.; Farmer, A.E.; and Gottesman, I.I. Is there really a split in schizophrenia? The genetic evidence. *British Journal of Psychiatry*, in press.

McGuffin, P.; Farmer, A.E.; Gottesman, I.I.; Murray, R.M.; and Reveley, A.M. Twin concordance for operationally defined schizophrenia. *Archives of General Psychiatry*, 41:541–545, 1984.

McGuffin, P.; Farmer, A.E.; and Yonace, A.H. HLA antigens and subtypes of schizophrenia. *Psychiatry Research*, 5:115–122, 1981.

McGuffin, P.; Festenstein, W.; and Murray, R.M. A family study of HLA antigens and other genetic markers in schizophrenia. *Psychological Medicine*, 13:31–43, 1983.

McGuffin, P., and Sturt, E. Genetic markers in schizophrenia. *Human Heredity*, 36:65–88, 1986.

McKusick, V.A. On lumpers and splitters, or the nosology of genetic disease. *Perspectives on Biology and Medicine*, 12:298–310, 1969.

McKusick, V.A. *Mendelian Inheritance in Man*. 7th ed. Baltimore: Johns Hopkins Press, 1986.

Meehl, P.E. Diagnostic taxa as open concepts: Metatheoretical and statistical questions about reliability and construct validity in the grand strategy of nosological revision. In: Millon, T., and Klerman, G., eds. *Contemporary Directions in Psychopathology: Toward the DSM-IV*. New York: Guilford Press, 1986. pp. 215–231.

Millon, T., and Klerman, G., eds. *Contemporary Directions in Psychopathology: Toward the DSM-IV*. New York: Guilford Press, 1986.

Mirsky, A.F.; DeLisi, L.E.; Buchsbaum, M.S.; Quinn, O.W.; Schwerdt, P.; Siever, L.J.; Mann, L.; Weingartner, H.; Zec, R.; Sostek, A.; Alterman, I.; Revere, V.; Dawson, S.D.; and Zahn, T.P. The Genain quadruplets: Psychological studies. *Psychiatry Research*, 13:77–94, 1984.

Mirsky, A.F.; Silberman, E.K.; Latz, A.; and Nagler, S. Adult outcomes of high-risk children: Differential effects of town and kibbutz rearing. *Schizophrenia Bulletin*, 11:150–154, 1985.

Miyanaga, K.; Machiymaya, Y.; Juji, T. Schizophrenic disorders and HLA-DR antigens. *Biological Psychiatry*, 19:121–129, 1984.

Murray, R.M.; Lewis, S.; and Reveley, A.M. Towards an aetiological classification of schizophrenia. *Lancet*, I:1023–1026, 1985.

Murray, R.M., and Reveley, A.M. Schizophrenia as an infection. *The Lancet*, I:583, 1983.

Nasrallah, H.A.; Charles, G.T.; McCalley-Whitters, M.; and Kuperman, S. Cerebral ventricular enlargement in subtypes of chronic schizophrenia. *Archives of General Psychiatry*, 39:774–777, 1982.

Nasrallah, H.A., and Henn, F., eds. *Schizophrenia as a Brain Disease*. New York: Oxford University Press, 1982.

Neale, J.M., and Oltmanns, T.F. *Schizophrenia*. New York: John Wiley & Sons, 1980.

Nicol, S.E., and Gottesman, I.I. Clues to the genetics and neurobiology of schizophrenia. *American Scientist*, 71:398–404, 1983.

Nuechterlein, K. Childhood precursors of adult schizophrenia. *Journal of Child Psychology and Psychiatry*, 27:133–144, 1986.

Ødegaard, Ø, Comments on the genetics issue. *Schizophrenia Bulletin*, 3:345–347, 1977.

O'Rourke, D.H.; Gottesman, I.I.; Suarez, B.K.; Rice, J.; and Reich, T. Refutation of the general single locus model in the aetiology of schizophrenia. *American Journal of Human Genetics*, 34:630–649, 1982.

Owens, D.G.C.; Johnstone, E.C.; Crow, T.J.; Frith, C.D.; Jagoe, J.R.; and Kreel, L. Lateral ventricular size in schizophrenia: Relationship to the disease process and its clinical manifestation. *Psychological Medicine*, 15:27–41, 1985.

Pap, A. *Semantics and Necessary Truth*. New Haven: Yale University Press, 1958.

Pearson, J.S., and Kley, I.B. On the application of genetic expectancies as age specific base rates in the study of human behavior disorders. *Psychological Bulletin*, 54:406–420, 1957.

Pogue-Geile, M.F., and Harrow, M. Negative symptoms in schizophrenia: Their longitudinal course and prognostic importance. *Schizophrenia Bulletin*, 11:427–439, 1985.

Pollin, W.; Allen, M.; Hoffer, A.; Stabenau, J.R.; and Hrubec, Z. Psychopathology in 15,909 pairs of veteran twins: Evidence for a genetic factor in the pathogenesis of schizophrenia and its relative absence in psychoneurosis. *American Journal of Psychiatry*, 126:597–609, 1969.

Pope, H.G.; Jonas, J.M.; Cohen, B.M.; and Lipinski, J.F. Failure to find evidence of schizophrenia in first-degree relatives of schizophrenic probands. *American Journal of Psychiatry*, 139:826–828, 1982.

Pope, H.G.; Jonas, J.M.; Cohen, B.M.; and Lipinski, J.F. Heritability of schizophrenia. *American Journal of Psychiatry*, 140:132–133, 1983.

Propping, P. Genetic disorders presenting as "schizophrenia." *Human Genetics*, 65:1–19, 1983.

Rao, D.C.; Morton, N.E.; Gottesman, I.I.; and Lew, R. Path analysis of qualitative data on pairs of relatives: Application to schizophrenia. *Human Heredity*, 31:325–333, 1981.

Reich, T.; Cloninger, C.R.; and Guze, S.B. The multifactorial model of disease transmission: I. Description of the model and its use in psychiatry. *British Journal of Psychiatry*, 127:1–10, 1975.

Reveley, A.M.; Reveley, M.A.; Clifford, C.A.; and Murray, R.M. Cerebral ventricular size in twins discordant for schizophrenia. *Lancet*, I:540–541, 1982.

Reveley, A.M.; Reveley, M.A.; and Murray, R.M. Cerebral ventricular enlargement in nongenetic schizophrenia: A controlled twin study. *British Journal of Psychiatry*, 144:89–93, 1984.

Reveley, M.A., and Chitkara, B. Subtypes in schizophrenia. (Letter) *Lancet*, I:1503, 1985.

Risch, N. Estimating morbidity risks in relatives: The effect of reduced fertility. *Behavior Genetics*, 13:441–451, 1983.

Rosenthal, D., ed. *The Genain Quadruplets*. New York: Basic Books, 1963.

Rosenthal, D. Three adoption studies of heredity in the schizophrenic disorders. *International Journal of Mental Health*, 1:63–75, 1972.

Rothblum, E.D.; Solomon, L.J.; and Albee, G.W. A sociopolitical perspective of *DSM-III*. In: Millon, T., and Klerman, G., eds. *Contemporary Directions in Psychopathology: Toward the DSM-IV*. New York: Guilford Press, 1986. pp. 167–189.

Rudduck, C. "Genetic Markers and Schizophrenia." Unpublished doctoral dissertation, Department of Genetics, University of Lund, Sweden, 1985.

Rudduck, C.; Franzen, G.; Low, B.; and Rosman, B. HLA antigens in patients with and without a family history of schizophrenia. *Human Heredity*, 34:291–296, 1984.

Sakai, T., and Tsuboi, T., eds. *Genetic Aspects of Human Behavior*. Tokyo: Igaku-Shoin, 1985.

Sartorius, N.; Jablensky, A.; Korton, A.; Ernberg, G.; Anker, M.; Cooper, J.E.; and Day, R. Early manifestations and first-contact incidence of schizophrenia in different cultures. *Psychological Medicine*, in press.

Scharfetter, C., and Nüsperli, M. The group of schizophrenias, schizoaffective psychoses, and affective disorders. *Schizophrenia Bulletin*, 6:586–591, 1980.

Schizophrenia Bulletin. (Issue theme: Israeli High-Risk Study) Vol. 11, No. 1, 1985.

Schizophrenia Bulletin. (Issue theme: European Psychiatry II) Vol. 12, No. 1, 1986.

Seltzer, C.C., and Jablon, S. Effects of selection on mortality. *American Journal of Epidemiology*, 100:367–372, 1974.

Smeraldi, E.; Bellodi, L.; and Cazullo, C.L. Further studies on the histocompatibility complex as a genetic marker for schizophrenia. *Biological Psychiatry*, 11:655–661, 1976.

Spitzer, R.L.; Endicott, J.; and Robins, E. Research Diagnostic Criteria: Rationale and reliability. *Archives of General Psychiatry*, 35:773–782, 1978.

Stephens, J.H.; Astrup, C.; Carpenter, W.T., Jr.; Shaffer, J.W.; and Goldberg, J. A comparison of nine systems to diagnose schizophrenia. *Psychiatry Research*, 6:127–143, 1982.

Strömgren, E. Statistical and genetical population studies within psychiatry. *Congress International de Psychiatrie, Paris, 1950*. Part VI. Paris: Hermann & Cie, 1950. pp. 155–188.

Sturt, E., and McGuffin, P. Can linkage and marker association resolve the genetic aetiology of psychiatric disorders? Review and argument. *Psychological Medicine*, 15:455–462, 1985.

Sutcliffe, J.G.; Milner, R.J.; Shinnick, T.M.; and Bloom, F.E. Identifying the protein products of brain-specific genes with antibodies to chemically synthesized peptides. *Cell*, 33:671–682, 1983.

Taylor, M.A.; Abrams, R.; and Gaztanaga, P. Manic depressive illness and schizophrenia: A partial validation of research diagnostic criteria utilizing neuropsychological testing. *Comprehensive Psychiatry*, 16:91–96, 1975.

Thomson, G. A review of the theoretical aspects of HLA and disease association. *Theoretical Population Biology*, 20:168–208, 1981.

Tienari, P.; Sorri, A.; Lahti, I.; Naarla, M.; Wahlberg, K.E.; Moring, J.; Pahjola, J.; and Wynne, L.C. Interaction of genetic and psychosocial factors in schizophrenia. *Schizophrenia Bulletin*, in press.

Torrey, E.F. Birth weights, perinatal insults, and HLA types: Return to "original din." *Schizophrenia Bulletin*, 3:347–351, 1977.

Torrey, E.F. *Schizophrenia and Civilization*. New York: Jason Aronson, 1980.

Turner, S.; Toone, B.; and Brett-Jones, A. Computerized tomography scan changes in early schizophrenia — Preliminary findings. *Psychological Medicine*, in press.

Turner, W.D. Genetic markers for schizotaxia. *Biological Psychiatry*, 14:177–205, 1979.

Ungvari, G. Validity of the ICD-9 schizophrenia classification: A blind family history study. *Acta Psychiatrica Scandinavica*, 68:287–296, 1983.

Ungvari, G. Comparative genetical analysis: A new tool for validating the schizophrenia subtypes. *Acta Medica Hungarica*, 41:229–238, 1984.

Ungvari, G. A contribution to the validity of Leonhard's classification of endogenous psychoses. *Acta Psychiatrica Scandinavica*, 72:144–149, 1985.

Watt, N.; Anthony, E.J.; Wynne, L.C.; and Rolf, J. *Children at Risk for Schizophrenia*. New York: Cambridge University Press, 1984.

White, R.; Leppert, M.; Bishop, T.; Barker, D.; Berkowitz, J.; Brown, C.; Callahan, P.; Holm, T.; and Jerominski, L. Construction of linkage maps with DNA markers for human chromosomes. *Nature*, 313:101–105, 1985.

Wing, J.K.; Cooper, J.E.; and Sartorius, N. *The Measurement and Classification of Psychiatric Symptoms*. London: Cambridge University Press, 1974.

World Health Organization. *Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death*. Vol. I. 8th ed. Geneva: WHO, 1967.

World Health Organization. *Report of the International Pilot Study of Schizophrenia*. Geneva: WHO, 1973.

World Health Organization. *Schizophrenia: An International Follow-up Study*. New York: John Wiley & Sons, 1979.

Wynne, L.C.; Cromwell, R.L.; and Matthysse, S., eds. *The Nature of Schizophrenia: New Approaches to Research and Treatment*. New York: John Wiley & Sons, 1978.

Zerbin-Rüdin, E. Endogene Psychosen. In: Becker, P.E., ed. *Humangenetik*. Vol. 2. Stuttgart: Thieme, 1967. pp. 446–577.

Zerbin-Rüdin, E. Psychiatrische Genetik. In: Kisker, K.P.; Meyer, K.P.; Meyer, J.E.; Müller, C.; and Strömgren, E., eds. *Psychiatrie der Gegenwart*. Vol. 1. 2nd ed. Berlin: Springer-Verlag, 1980. pp. 545–618.

Zubin, J. Implications of the vulnerability model for *DSM-IV* with special reference to schizophrenia. In: Millon, T., and Klerman, G., eds. *Contemporary Directions in Psychopathology: Toward the DSM-IV*. New York: Guilford Press, 1986. pp. 473–494.

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The Authors

Irving I. Gottesman, Ph.D., is Commonwealth Professor of Psychology, Department of Psychology, University of Virginia, Charlottesville, VA. Peter McGuffin, M.B., Ph.D., M.R.C.P., M.R.C. Psych., is Professor of Psychological Medicine, University of Wales, College of Medicine, Cardiff, Wales. Anne E. Farmer, M.B., M.R.C. Psych., is Lecturer in Psychiatry, Institute of Psychiatry, London, England.