

Summary

Photochemical reactions in the troposphere, stratosphere, and mesosphere are, to a large extent, reactions among minor constituents of the atmosphere. The chemistry is markedly limited by the minimum wavelength of the solar radiation which penetrates to a given atmospheric level. It is useful to differentiate between the chemistry of city smog and that of the ambient atmosphere, but the entire atmosphere is being polluted and the difference is one of degree.

Both laboratory and field studies are contributing to our knowledge of atmospheric photochemistry, and the most convincing conclusions have been obtained by combining the results of the two methods of investigation.

References and Notes

1. T. M. Donahue, *Science* **159**, 489 (1968).
2. R. D. Cadle, W. H. Fischer, E. R. Frank, J. P. Lodge, Jr., *J. Atmos. Sci.* **25**, 100 (1968); R. W. Fenn, H. E. Gerber, D. Wasshausen, *ibid.* **20**, 466 (1963).
3. C. E. Junge, *Air Chemistry and Radioactivity* (Academic Press, New York, 1963).
4. R. D. Cadle and M. Ledford, *Int. J. Air Water Pollut.* **10**, 25 (1966); J. M. Hales, thesis, University of Michigan (1968).
5. G. Liuti, S. Dondes, P. Harteck, *J. Amer. Chem. Soc.* **88**, 3212 (1966).
6. Many rate constants are temperature dependent. However, for purposes of comparison,

only values for $\sim 300^\circ\text{K}$ are given in this article. The rate constants presented were in many cases selected from among several given in the literature. Although considerable judgment was used in the selection, there was often little basis for choice among several values. If we use the product of the rate constant and reactant concentrations, the rate of disappearance of reactants or formation of products may be estimated as above. The rates obtained in this way are used as a guide to the relative importance of simultaneous reactions occurring in the atmosphere.

7. R. D. Cadle, in *Air Pollution Handbook*, P. L. Magill, F. R. Holden, C. Ackley, Eds. (McGraw-Hill, New York, 1956), pp. 3-1 to 3-27.
8. E. R. Gerhard and H. F. Johnstone, *Ind. Eng. Chem.* **47**, 972 (1955); T. C. Hall, Jr., thesis, University of California, Los Angeles (1963); N. A. Renzetti and G. T. Doyle, *J. Air Pollut. Control Ass.* **8**, 293 (1959); *Int. J. Air Pollut.* **2**, 327 (1960).
9. P. Urone, H. Lutsep, C. M. Noyes, J. F. Parcher, *Environ. Sci. Technol.* **2**, 611 (1968).
10. H. F. Johnstone and D. R. Coughanowr, *Ind. Eng. Chem.* **50**, 1169 (1958).
11. R. D. Cadle and J. W. Powers, *Tellus* **18**, 176 (1966).
12. R. D. Cadle and R. C. Robbins, *Discuss. Faraday Soc.* **30**, 155 (1960).
13. E. L. Wong and A. E. Potter, Jr., *J. Chem. Phys.* **39**, 2211 (1963).
14. R. D. Cadle, *Discuss. Faraday Soc.* **37**, 66 (1964).
15. H. W. Ford, G. J. Doyle, N. Endow, *J. Chem. Phys.* **26**, 1337 (1957).
16. J. P. Lodge, Jr., and J. B. Pate, *Science* **153**, 408 (1966).
17. H. W. Ford and N. Endow, *J. Chem. Phys.* **27**, 1156 (1957).
18. F. Kaufman and J. R. Kelso, *ibid.* **40**, 1162 (1964).
19. H. W. Ford, G. J. Doyle, N. Endow, *ibid.* **26**, 1336 (1957).
20. L. R. J. McHaney, thesis, University of Illinois (1953).
21. L. A. Cavanagh, C. F. Schadt, E. Robinson, *Environ. Sci. Technol.* **3**, 251 (1969).
22. Of course, CO_2 is involved in plant photosynthesis.
23. P. A. Leighton, *Photochemistry of Air Pollution* (Academic Press, New York, 1961).
24. R. D. Cadle and H. S. Johnston, in *Proceedings of the Second National Air Pollution Symposium* (Stanford Research Institute, Menlo Park, California, 1952), pp. 28-34.
25. R. D. Cadle and J. W. Powers, *J. Phys. Chem.* **71**, 1702 (1967).
26. W. E. Wilson, Jr., and J. T. O'Donovan, *J. Chem. Phys.* **47**, 5455 (1967).
27. M. A. A. Clyne and B. A. Thrush, *Proc. Roy. Soc. London Ser. A Math. Phys. Sci.* **275**, 559 (1963).
28. J. N. Pitts, Jr., A. U. Khan, E. B. Smith, R. P. Wayne, *Environ. Sci. Technol.* **3**, 241 (1969).
29. I. M. Campbell and B. A. Thrush, *Proc. Roy. Soc. London, Ser. A Math. Phys. Sci.* **296**, 222 (1967); F. Kaufman and J. R. Kelso, *Discuss. Faraday Soc.* **37**, 26 (1964); O. R. Lundell, R. D. Ketcheson, H. I. Schiff, paper presented at the 12th International Symposium on Combustion, Poitiers, France, 1968.
30. L. F. Phillips and H. I. Schiff, *J. Chem. Phys.* **37**, 1233 (1962).
31. F. Kaufman, *Ann. Geophys.* **20**, 106 (1964).
32. R. D. Cadle, R. Bleck, J. P. Shedlovsky, I. H. Blifford, J. Rosinski, A. L. Lazrus, *J. Appl. Meteorol.* **8**, 348 (1969).
33. T. G. Scholz, L. E. Heidt, E. A. Martell, D. H. Ehalt, *Trans. Amer. Geophys. Union* **50**, 176 (1969).
34. A. E. Bainbridge and L. E. Heidt, *Tellus* **18**, 221 (1966).
35. T. G. Kyle, D. G. Murcray, F. H. Murcray, W. J. Williams, *J. Geophys. Res.* **74**, 3421 (1969).
36. Based on *U.S. Standard Atmosphere 1962* (U.S. Government Printing Office, Washington, D.C., 1962).
37. P. M. Furukawa, P. L. Haagenson, M. J. Scharberg, *Nat. Center Atmos. Res. Tech. Note* **26** (1967), pp. 0-55.
38. B. G. Hunt, *J. Geophys. Res.* **71**, 1385 (1966).
39. J. B. Pearce, *ibid.* **74**, 853 (1969).
40. The National Center for Atmospheric Research is sponsored by the National Science Foundation.

The Genetics of Schizophrenic and Schizoid Disease

Leonard L. Heston

The contribution of genetic factors to the etiology of schizophrenia has been confirmed decisively. Because the investigations that have led to this result have uncovered questions cutting across several fields of inquiry, a fresh look at some central aspects of the schizophrenia problem is warranted. These questions and the factual background underlying them are the main concerns of this article. Because emphasis is placed on formulating testable hypotheses, the evidence is organized in support of a particular genetic theory.

The Basic Evidence

During the first half of this century, systematic family studies demonstrated that the distribution of schizophrenia is that of a genetic disease. Relatives of schizophrenics were found to be afflicted with the illness much more frequently than members of the general population. The child of a schizophrenic parent, for example, was found to have a risk of schizophrenia about 15 times that of a member of the population at large. It was found that, among all classes of relatives, the closer the ge-

netic relationship to a schizophrenic proband (or index case) is, the greater is the likelihood of schizophrenia in the relative. Finally, and most telling of all, monozygotic twins were found to be concordant with respect to schizophrenia about four times as often as dizygotic twins. Several authorities have critically reviewed these basic data (1, 2). But, despite the supporting evidence, a genetic etiology for schizophrenia was not widely accepted, especially in this country. It was pointed out that the investigators did not pay enough attention to important procedural matters, such as providing sampling safeguards and insuring against bias on the part of the investigator. But the paramount objection to a genetic interpretation of the evidence was the objection that the whole research strategy was faulty. The results of these studies, it was held, were just as compatible with transmission of schizophrenia through the social environment as with transmission through genes. The closer the

The author is assistant professor of psychiatry at the University of Iowa Medical School, Iowa City.

genetic relationship, the closer the social relationship. Were genes or was noxious social learning responsible for the familial clustering of schizophrenia?

Recently, several studies have been aimed at closing those methodological and conceptual gaps. In these newer studies diagnoses either were made by raters who did not know the genetic background of the subjects or were taken unchanged from medical records. Care was taken to remove sampling biases, and, most importantly, control groups were used. The strategy permitted separation of the effects of genes from the effects of social environment through the use, as subjects, of children reared in adoptive or foster homes.

The results of one such study are shown in Table 1 (3). The experimental subjects were individuals born to schizophrenic mothers, and the controls were individuals born to parents who had no record of psychiatric disturbance. The members of both groups had been permanently separated from their biological mothers in the first month of life and reared mainly in foster or adoptive homes. The subjects, as adults, were assessed through psychiatric interviews and review of every available record—for example, school, police, Veterans Administration, and medical—and then evaluated by a team of clinicians. The significant excess of schizophrenia found among those subjects whose biological mothers were schizophrenic seems impossible to explain except on a genetic basis. Moreover, among those same experimental subjects, and thus also linked to schizophrenia by the evidence, was an even greater excess of various apparently nonschizophrenic disorders. The latter finding, which is reflected in nearly every entry in Table 1, is a central concern throughout this article.

The preliminary results from a very similar study which stressed exemplary investigative safeguards were much the same. Rosenthal *et al.* (4) reported that biological children of schizophrenics reared in adoptive homes exhibited “schizophrenic spectrum” disorders in significant excess over similarly reared controls. The “schizophrenic spectrum”—an expression coined in a quite reasonable attempt to find a term that would encompass the various disorders seen among biological relatives of schizophrenics—including schizophrenia, possible schizophrenia, borderline states, certain paranoid disorders, schizoid disorders, and the condition known as inadequate personality.

Karlsson (5), as one result of his study of schizophrenia in Icelandic families, found that 6 of 29 persons, some of them siblings, born to a schizophrenic parent but reared in foster homes developed schizophrenia. None of their 28 foster sibs who were reared in the same homes developed schizophrenia. This difference, too, is significant. Karlsson did not ascertain any disorders other than typical schizophrenia among his subjects.

In two ingeniously designed research projects, adopted individuals served as the starting point. Wender *et al.* (6) studied the biological and adoptive parents of ten adopted schizophrenics and the adoptive parents of ten normal persons. The biological parents of the schizophrenics were found to exhibit significantly more psychopathology than either group of adoptive parents. In a similar but wider-ranging study conducted by Kety *et al.* (7), psychopathology, again reported as “schizophrenic spectrum” disorders, was found to be concentrated in significant excess among the biological relatives of adopted schizophrenics. The adoptive families of schizophrenics were indistinguishable from the adoptive and biological families of adopted controls. Since the psychopathology found in these studies was significantly greater among the group of biological relatives of the schizophrenic probands than among the adoptive relatives who actually lived with them, this evidence too strongly favors genetic over social transmission of schizophrenia.

The results of the studies of adopted and foster children—results which are strikingly consistent from study to study, considering the vagaries of research in this area—present seemingly insurmountable difficulties for adherents of environmental theories of schizophrenia. The evidence must surely compel acknowledgment of a genetic contribution to schizophrenia, and probably to related disorders as well. To go further, however, requires information on other types of genetic relationships and larger numbers of subjects. Happily, the older family studies can now meet these needs. For perhaps the most important contribution of the recent studies of adopted and foster children is the fact that they have confirmed the results of the older studies in all material respects. The familial clustering of psychopathology that had been documented in such detail has been linked to one critical variable, a genetic relationship to schizophrenia.

The Schizoid

The presence of so much psychopathology other than typical schizophrenia among relatives of schizophrenics was first noticed by physicians on visiting days in the earliest asylums. Isaac Ray, writing in 1863, gave a good description (8). Because the relatives' disabilities resembled schizophrenia, investigators associated with the Munich school called these disabilities “schizoid” (schizophrenic-like). Describing the schizoid individual, delimiting schizoid from psychiatric and general populations, and placing the schizoid in relation to the schizophrenic were central concerns of the psychiatry of that day. After perhaps the longest detour in the modern history of science, we have come full circle in returning to the same concerns. Meanwhile, problems of nomenclature have developed.

To me, “schizoid” and “schizophrenic spectrum” seem to denote precisely the same disabilities, except that the latter term also includes schizophrenia. One consideration that may have led Kety (7), Rosenthal (4), Wender (6), and their co-workers to coin the new term is the obvious danger of confusing “schizoid” with “schizoid personality.” The latter term, a diagnosis in the American Psychiatric Association and World Health Organization nomenclature, although descended from descriptions of the abnormal relatives of schizophrenics, has evolved and changed in meaning so that it is no longer applicable to most of those relatives. For example, it was not often applied to relatives of schizophrenics by the rating clinicians in the studies of adopted and foster children. But other diagnoses currently considered applicable to such individuals also fit these relatives imperfectly, so no formal categorization is now available. Because of a central trait of the schizoid—his clinical resemblance to the schizophrenic—and because of the desirability of maintaining continuity with older studies, I use the term “schizoid” as a name for the schizophrenic-like disabilities seen in relatives of schizophrenics, or for the individual manifesting such disabilities.

Nearly all observers of the schizoid have noted his clinical resemblance to the schizophrenic, but clinical criteria adequate to reliably distinguish the schizoid from members of a general or a psychiatric population or even from other kinds of abnormal persons with a coincidental genealogical con-

nection to a schizophrenic are most imperfect (9). Though unsatisfactory, the only means of identifying many—perhaps most—schizoids remains genealogical, and a clinical understanding of the schizoid can best be gained by reading descriptions of abnormal relatives of schizophrenics (see 10–13 for good examples). The circularity thus introduced is regrettable but inescapable. The schizoid exists, and he sometimes shows as much impairment psychiatrically as a typical schizophrenic.

Several problematical behaviors have been associated with the schizoid. Among males, antisocial behavior has been found commonly enough to warrant the older subdesignation “schizoid psychopath.” Entries in the police records of the schizoid psychopaths in my study reflected impulsive, seemingly illogical crime such as arson, unreasoning assault, and poorly planned theft (3). Social isolation, heavy intake of alcohol, and sexual deviance have been noted frequently. Other schizoids, both male and female, have been described as eccentric, suspicion-ridden recluses. The main disability of still other schizoids, mostly females, has been found to be incapacitating attacks of panic or unreasoning fear in response to ordinary social challenges.

On a more technical level the resemblance to schizophrenia is more apparent. Rigidity of thinking, blunting of affect, anhedonia, exquisite sensitivity, suspiciousness, and a relative poverty of ideas—in variable combinations and intensities—characterize both the schizoid and the schizophrenic, through such characteristics are less prominent in the former. Though schizoids do not show a well-marked thought disorder, delusions, and hallucinations, descriptions of some of the behavioral lapses of schizoids, especially the schizoid psychopath, are bizarre enough to suggest micropsychotic episodes.

Slater took a different approach. He listed a series of explicatives, partially reproduced in Table 2, used by relatives of schizophrenics when describing their abnormal but nonschizophrenic relatives (13). Slater went on to say (13, p. 83) that “the same or similar words or phrases occur in descriptions of abnormal personalities from other kinds of families, but much less frequently, not in such concentrated form, and they are usually submerged by descriptions of a very different tone.”

Because Kallmann’s investigations of the families of schizophrenics were by far the most extensive that have been

Table 1. Results of a study of individuals born to schizophrenic mothers and reared in adoptive or foster homes, and of controls born to normal parents and similarly reared.

Item	Control	Experimental	Exact probability (Fisher’s test)
Number of subjects	50	47	
Number of males	33	30	
Age, mean (years)	36.3	35.8	
Number adopted	19	22	
MHSRS, means*	80.1	65.2	0.0006
Number with schizophrenia	0	5	.024
Number with mental deficiency (I.Q. < 70)†	0	4	.052
Number with antisocial personalities	2	9	.017
Number with neurotic personality disorder‡	7	13	.052
Persons spending more than 1 year in penal or psychiatric institution			
Number	2	11	.006
Total years incarcerated	15	112	
Number of felons	2	7	.054
Number serving in armed forces	17	21	
Number discharged from armed forces on psychiatric or behavioral grounds	1	8	.021
Social group, first home, mean§	4.2	4.5	
Social group, present, mean§	4.7	5.4	
I.Q., mean	103.7	94.0	
Years in school, mean	12.4	11.6	
Number of children, total	84	71	
Number of divorces, total	7	6	
Number never married, > 30 years of age	4	9	

* The MHSRS is a global rating of psychopathology moving from 0 to 100 with decreasing psychopathology. Total group mean, 72.8; S.D., 18.4. † One mental defective was also schizophrenic; another had antisocial personality. ‡ Considerable duplication occurs in the entries under “neurotic personality disorder”; this designation includes subjects diagnosed as having various types of personality disorder and neurosis whose psychiatric disability was judged to be a significant handicap. § Group 1, highest social class; group 7, lowest.

made, his concept of the schizoid is of critical importance (11). From his description (11, p. 102) it is clear that he relied heavily on the schizoid’s clinical resemblance to the schizophrenic. Kallmann regarded the distinguishing features of the schizoid to be the “fundamental symptoms of schizophrenia in the milder form of characterological abnormalities . . . dominating the personality of the individual in question.” Kallmann also looked analytically at traits other than those obviously associated with schizophrenia or schizoidia that seemed to occur in excess among relatives of schizophrenics, with the aim of including or excluding them from the group of schizoid traits. On various grounds he excluded all the traits that he considered.

One of the traits which Kallmann considered and rejected, mental deficiency, perhaps deserves another look. About 6 to 10 percent of schizophrenics (see 14) and their first-degree relatives (see 3, 11) are mentally subnormal, as

compared with 3 percent of the general population. The expected reciprocal relationship, an excess of schizophrenics among mental defectives or their relatives, was found by Penrose (15) and Böök (16) among mental defectives but not by Reed and Reed (17) in their monumental survey of the relatives of mental defectives. Also, Kallmann found a much higher rate of mental deficiency (10.8 percent) among relatives of simple schizophrenics, where there is a clinical commonality of sorts, than among relatives of other subtypes in the Kraepelinian classification. The evidence for or against an association between schizophrenia and mental deficiency is inconclusive, and more data are needed before the matter can be decided.

Obviously there is much yet to be learned before we can describe and delimit schizoidia. However, the same thing can be said of schizophrenia itself, and in this regard study of the schizoid may lighten some dark corners.

Table 2. Explicatives used by relatives of schizophrenics in describing their schizoid relatives. [After Slater (13)].

<i>Paranoid eccentricities:</i> suspicious, sensitive, sullen, touchy, grouchy, morose, resentful, unforgiving, difficult, quarrelsome, self-conscious, jealous, litigious, critical, and others.
<i>Eccentricities:</i> giggly, opinionated, pedantic, narrow-minded, meticulous, obstinate, humorless, rigid, little-minded, spiritualists, and many others.
<i>Lack of feeling:</i> passive, cruel, calculating, placid, hard and stingy, unsympathetic, cold, withdrawn, little-feeling, and others.
<i>Reserve:</i> shy, serious, haughty, snobbish, studious, unforthcoming, taciturn, unsociable, seeks solitude, and so on.
<i>Anergic:</i> dependent, tired, slack, unreliable, subservient, and so on.

Table 3. Data on monozygotic twins of schizophrenics.

Investigator	Pairs (No.)	Schizophrenia (No.)	Other significant abnormality* (No.)	Normal, or mild abnormality (No.)
Essen-Möller (19)	9	0	8	1
Slater (13)	37	18	11	8
Tienari (41)	16	1	12	3
Kringlen (12)	45	14	17	14
Inouye (42)	53	20	29	4
Gottesman and Shields (23)	24	10	8	6
Kallmann† (43)	174	103	62	9
Totals	358	166 (46.4%)	147 (41.1%)	45 (12.6%)

* Investigators' diagnoses: ? schizophrenia, schizophreniform, transient schizophrenia, reactive psychosis, borderline state, schizoid, suicide, psychopathic, neurosis, and variations of these diagnoses. † From Shields, Gottesman, and Slater (44).

Schizophrenia is defined operationally, not etiologically. It is the clinician who determines whether schizophrenia is present. But of course the limits of the clinical entity may not correspond to those of the etiological entity. In fact the linking of schizoidia to schizophrenia by genetic evidence raises serious questions about the etiological reality of the clinical definition of schizophrenia. There has always been a fuzzy border about schizophrenia along which several named entities, including abortive, ambulatory, borderline, latent, pseudoneurotic, pseudopsychopathic, and reactive schizophrenia and the "schizotype" of Meehl (18) have seemed to lie. These terms may best be viewed as attempts to cope with an operationally defined border between schizoidia and schizophrenia that is clinically imprecise because it is biologically unreal.

Quantitative Aspects

Given a schizophrenic who has a monozygotic twin, the empirical probability that his twin will also be schizophrenic has been found to be about 0.46 (Table 3). Most of the remaining 54 percent of monozygotic twins of schizophrenics have also been found to be abnormal. From clinical descriptions included in five studies (12, 13, 19-21) it appears that nearly all of the abnormal though nonschizophrenic co-twins were schizoid. Overall, only about 13 percent of the monozygotic twins of schizophrenics have been regarded as normal or nearly normal, and, because most of the errors inherent in this sort of research tend to increase the proportion of apparent normals, this is surely an overestimate. But, while a critic could easily quibble about any of the proportions in Table 3, a crude but critical conclusion is inescapable: monozygotic twins of schiz-

ophrenics are about as likely to be schizoid as schizophrenic. What then is inherited? These considerations led Essen-Möller (19) to regard schizoidia as the basic inherited trait, and Kringlen, in a careful and sensitive analysis of twin research, including his own major study, seems to have reached a similar conclusion, although he regarded the predisposition as less specific (12). At the very least a *prima facie* case has been made for considering the whole group of schizoid and schizophrenic disorders as alternative expressions of a single genotype. Moreover, because monozygotic twins are identical genetically, there is presumptive evidence that the range of variability within pairs can in principle be accounted for by environmental factors. The genes allow a range of outcomes.

A critical point to be established is the proportion of schizoids or schizophrenics among the first-degree relatives (parents, sibs, children) of schizophrenics. Table 4 gives Kallmann's results. No one else has investigated so many relatives of schizophrenics, and few others have conducted field studies intensive enough to identify schizoids. The more intensive modern studies have tended to show somewhat larger proportions of afflicted relatives (3, 10, 22). So did Slater among dizygotic twins of schizophrenics (13). The proportions found by Gottesman and Shields (23) and by Ödegard (24) were somewhat smaller. Kallmann's values may be taken as fair average estimates of the proportion of schizoids or schizophrenics among first-degree relatives of schizophrenics.

Table 4 also shows the results of four studies of the children of two schizophrenics. An estimated 66 percent of the children of these matings were schizoid or schizophrenic, again, this is surely an underestimate because the subjects were still quite young. The

results of one such study, that of Lewis (25), was not included. Lewis did not give ages, and he stated that his follow-up was incomplete. Rosenthal has recently reviewed these studies (26).

An important unknown must now be considered. There is no adequate estimate of the proportion of schizoids in the general population. Then, is the clustering of schizoids among relatives of schizophrenics greater than might occur by chance? Although the proportion of schizoids found in families of schizophrenics is surely greater than that expected by even the most pessimistic observer of the general population, a better answer is that neither the relatives of other kinds of psychiatric patients nor the controls used in psychiatric studies have been found to be afflicted in significant numbers with disorders of a schizoid character or with any kind of behavioral disorder to the extent seen in relatives of schizophrenics. Further evidence—the small proportion of schizoids found among descendants of normal relatives of schizophrenics—is discussed below.

While the lack of data for the general population and the related lack of data for the families of schizoid probands preclude estimates of gene frequency, it should be noted that schizoid disorders surely afflict a large proportion of the population. With only isolated exceptions, schizophrenia afflicts about 1 percent of any population. If each schizophrenic has five living first-degree relatives (about the number in Kallmann's study), a simple extrapolation yields an estimate of 4 percent for the proportion of schizoids plus schizophrenics in the general population. This crude estimate can only make the point that any population, and especially any psychiatric population (persons identified because they came to psychiatric clinics or hospitals), is likely to contain large numbers of schizoids. One of the most neutral implications of this conclusion has an obvious application to the choosing of control groups for research in schizophrenia.

Genetic Hypothesis

The most parsimonious explanation of the data is given by the hypothesis that a defect in a single autosomal gene accounts for the genetic contribution to both schizoid and schizophrenic disease (the "dominance hypothesis"). By including schizoid dis-

ease (schizoidia), this hypothesis extends that of Slater (27). The view that schizoidia and schizophrenia are a single disease genetically is supported by their clinical similarity and is virtually required by the finding that the disorders occur with equal probability in monozygotic twins of schizophrenics. Further support for the hypothesis is presented in Fig. 1. The proportions of affected first-degree relatives fit reasonably well with the theoretical proportions expected under the dominance hypothesis.

Kallmann presented some data on second-degree relatives (11). Among 822 grandchildren of his schizophrenic probands he found 4.3 percent to be schizophrenic and 22.8 percent to be schizoid. The corresponding rates for nephews and nieces were considerably lower (3.9 and 6.2 percent). However, Kallmann pointed out that the normal sibs of his schizophrenic probands contributed many more nephews and nieces than the schizoid or schizophrenic sibs did. While the total of 27.1 percent for affected grandchildren is certainly close to the 25 percent expected under the dominance hypothesis, the proportions of affected nephews and nieces may or may not be compatible with that hypothesis.

The segregation of schizophrenia and schizoidia within families fits well with the dominance hypothesis. In Kallmann's study, which included three generations, the normal children of his schizophrenic probands produced few schizophrenic or schizoid children (1.8 and 2.6 percent, respectively), no more than might be expected in a general population. This is in contrast to the corresponding values of 13.7 and 33.4 percent for the children of the schizoid or schizophrenic children of Kallmann's schizophrenic probands (11).

The matter cannot be so simple, of course. The mechanisms involved in a disease like schizoidia-schizophrenia will surely be found to be extremely complex. Even phenylketonuria, which only a few years ago provided a prototype of rigorous simplicity for behavioral genetics, has turned out to be enormously complicated by secondary biochemical effects and by other, mostly unknown, factors (28). Heterogeneity is also likely. Probably the most completely known genetic disease in humans, glucose-6-phosphate dehydrogenase deficiency, occurs in at least 18 variants, each one presumably due to an amino acid substitution at a different place in the same enzyme (29).

Table 4. Percentages of first-degree relatives found to be schizophrenic or schizoid.

Relationship	Number of individuals	Schizophrenia* (%)	Schizoid (%)	Total: schizoid plus schizophrenic (%)
Children†	1000	16.4	32.6	49.0
Siblings‡	1191	14.3	31.5	45.8
Parents‡	2741	9.2	34.8	44.0
Children of two schizophrenics§	171	33.9	32.2	66.1

* Age-corrected rates. † From (11). ‡ From (43). § From Kallmann (11), Kahn (45), Schulz (46), and Elsässer (47).

But research must proceed from hypotheses based on present understanding. From that viewpoint, and for practical purposes, it is not at all unreasonable to proceed on the working assumption that most schizoidia-schizophrenia is associated with defects in a single basic biochemical or physiological pathway, transmitted by a single mode of inheritance. It matters little that new research will no doubt turn up complexities that cannot even be imagined today.

Apart from insights gained from analogies to other genetic diseases, there are factual reasons for expecting that many elements in addition to a single main gene go into the mix that results

in schizoidia-schizophrenia. First of all, there remain small deviations from the theoretical expectations under the dominance hypothesis, deviations which have been cited by Shields (2). These mainly take the form of a greater resemblance between relatives than can be explained by simple dominance. For example, the monozygotic twin of a severely afflicted individual is more likely to be schizophrenic than the twin of a mildly affected individual. If only a single gene were involved one would expect the risk of schizophrenia for a monozygotic twin of any schizophrenic to be equal to that of any other. Likewise, the larger the proportion of schizophrenic relatives is,

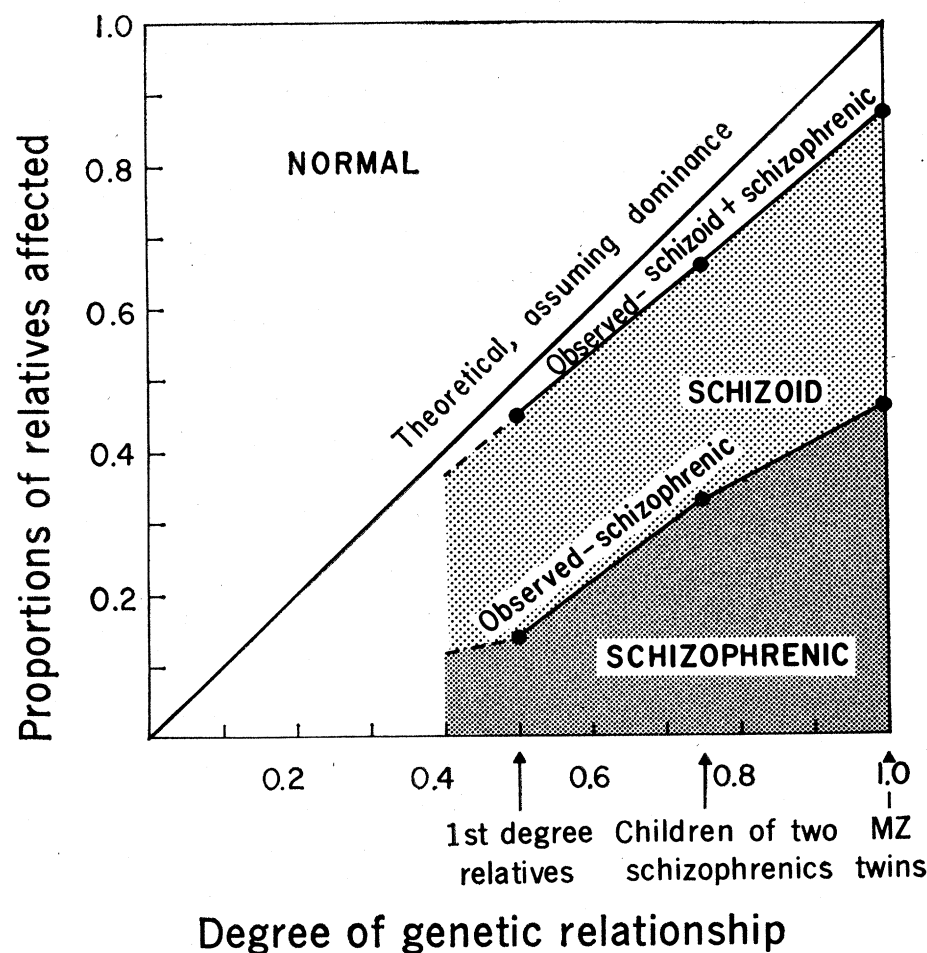


Fig. 1. Observed and expected proportion of schizoids and schizophrenics.

the greater is the risk of schizophrenia for any given individual. Another sort of problem is that of accounting for the variability seen among schizophrenics; this becomes more difficult when schizoids are included. Although there are no grounds for expecting any particular degree of resemblance between affected persons, it has often been argued that, if only one gene were involved, the range of observable phenotypes should be smaller than is the case. And the persistence of schizophrenia presents a problem. Before the introduction of antipsychotic drugs, schizophrenics reproduced at a rate 30 percent lower (16), and schizoids at a rate 22 percent lower (11), than the rate for the general population. Such reproductive deficits should have lowered the rates of occurrence of a disorder due to a main gene of large effect far below the presently observed rates for schizophrenia.

Attempts to account for such findings have led to widespread espousal of polygenic theories of schizophrenia (12, 24, 30). As Gottesman and Shields have pointed out (31), the facts are explained adequately by polygenic theory. Most polygenic theorists have regarded schizophrenia as a threshold trait. But clinically schizoidia and schizophrenia seem to form a continuum of psychopathology, much as first described by Kretschmer (32). If there is a threshold it probably falls between the schizoid and the normal condition, but it seems that any such "threshold" is as likely to be a function of lack of diagnostic precision as a function of the disease. It is not necessary to consider other aspects of the polygenic argument here. Known modifiers of the phenotypic expression of the disease point toward plausible solutions of the problems encountered by the dominance hypothesis and toward resolution of the apparent differences between main-gene and polygenic theories.

Modifying Factors

One class of modifiers must be environmental events in the broadest sense—events occurring from conception onward that produce some change in the organism. The nature-nurture dilemma is unreal. It is change in the environment of the cell that induces change in the genetically mediated metabolic systems of the cell. The functional state of the cell is a result of the interplay

of these determinants. But realization that phenotypic traits depend on interaction between gene and environment imposes conditions on research aimed at assessing the environment contribution. Genes function within cells. They interact with chemical, thermal, or other physical events and not with the abstractions ("stress," for example) that too often have passed for environmental data. The ultimate questions implicit in the concept of gene-environment interaction are, for example: How does a noxious learning experience alter the environment of the cell? What response is elicited from the genetic program of the cell? How is the later operation of the cell modified? Of course, such questions cannot be approached directly today. But unless the environmental contribution is too variable from case to case to allow generalization, it should be possible to build up a series of associations between environment and behavior that would point toward the environmental events that enter into the gene-environment interaction. The critical requirement is that such associations be potentially translatable into events that occur at the level of the gene. Despite all the research that has been done on the effects of environment on the development of schizophrenia, and despite the scope for environmental factors demonstrated by the differences between members of monozygotic twin pairs, practically no associations that meet this requirement have been established. Clinicians have learned to predict the effects of environmental features on their patients, but it is difficult to see any etiological clues in this body of experience. On general clinical grounds it makes sense to continue to study the effects of environmentally stimulated autonomic and endocrine responses. An association between lower birth weight and the development of schizophrenia in one member of a monozygotic twin pair has been reported (21), but it must be quite imperfect in view of the failure of other investigators to confirm it (12, 23). Perhaps differences in autonomic responses among children of schizophrenics that were described in a preliminary report from a wide-ranging prospective study (33) are the most promising associations so far defined. Almost everything remains to be done.

A second class of modifiers consists of complex traits that have been linked to schizophrenia by decades of empirical research. Somatotype has been

found by several investigators to be associated with major modification of schizophrenia. Mesomorphs are underrepresented among schizophrenics, and especially underrepresented among schizophrenics younger than 25. Ectomorphs are correspondingly overrepresented. Schizophrenic mesomorphs are predominantly paranoid and have a shorter mean period of hospitalization than other schizophrenics. Parnell (34), who has reviewed the subject and contributed his own data, found all these associations to be statistically significant. A relation between intelligence and the prognosis in schizophrenia is well known: the higher the intelligence the better the prognosis. But higher intelligence may also affect the expression of schizophrenia. Lane and Albee (35) found that the I.Q. of children who later became schizophrenic was seven points lower than that of their siblings who remained nonschizophrenic. There are a host of other established associations between complex traits and schizophrenia—for example, patterns of autonomic nervous system reactivity, immunological phenomena, resistance to certain chronic diseases, and tolerance of wound shock. Some such traits appear to be only oddities, given our present knowledge; others are known to be linked to favorable or unfavorable prognosis in schizophrenia, and still others are known only to be more frequent or infrequent among schizophrenics. Several reviews of these findings are available (36).

The large number of such complex traits and the magnitude of the modification of schizophrenia associated with some of them must mean that they have a significant role in the ecology of the disease. For one thing, they suggest a plausible solution to the puzzle posed by the persistence of high rates of schizophrenia. Sir Julian Huxley *et al.* (37) postulated that the gene responsible for schizophrenia conferred sufficient physiological or reproductive advantages to maintain a balanced polymorphism. They listed several physiological traits found in schizophrenics that could be due to pleiotropism. Although the number of traits listed seems large, widespread pleiotropism might result from a mutation at a regulatory locus (38). But many modifying traits are clearly not due to pleiotropism, and some of those—particularly differences in somatotype and intelligence—which demonstrably affect the outcome in schizophrenia must have conferred general

biological advantages through much of man's history as well. In either event, schizophrenics possessing advantageous traits would be expected to reproduce at relatively higher rates than those not possessing such traits. Over time, the evolutionary process would, theoretically, act to establish sets of favorable traits that, on the average, would tend to accompany schizophrenia. Theory aside, the popular association between genius and insanity, thought to be erroneous by Kallmann, was given some substance by Karlsson's finding that creative achievements and schizophrenia occurred in the same family lines (39). I reported a similar impression; however, the evidence was not gathered systematically (40). Although the problem posed by the persistence of schizophrenia remains theoretical and unsolved, further exploration of modifying traits provides as likely a path as any other now in view toward solution of the puzzle.

Modifying traits also suggest an approach to the problem of deviations from strict expectations under the dominance hypothesis. As pointed out above, polygenic theory can account for such deviations. But traits like somatotype and intelligence are themselves almost certainly polygenic. Polygenic modifiers of a single main gene explain the same facts, and indeed would yield the same mathematical results as simple additive polygenic theory per se. A multitude of genes summing to produce schizophrenia directly or a single main gene plus groups of genes summing to produce modifying traits account equally well for findings such as the tendency of monozygotic twins to be concordant with respect to severity of illness.

Conclusion

A main gene of large effect modified by multiple factors, including polygenic traits, suggests a number of testable hypotheses. Biochemical or other effects of a main gene should be present in schizoids as well as in schizophrenics. In family studies, the critical test of the place of the schizoid would be his reproductive performance in matings with normal individuals; 50 percent of the offspring of such matings should be schizoid or schizophrenic. However, polygenic modifiers should, on the average, maintain lesser degrees of disability in particular families. Thus, schizoid parents should have fewer

schizophrenic but more schizoid children than schizophrenic parents. There is incomplete support for this contention in Kallmann's study (11) of the grandchildren of his schizophrenic subjects: the schizoid children of his schizophrenic probands had more schizoid and fewer schizophrenic children than their schizophrenic siblings, but members of the third generation, the grandchildren of the probands, were too young to yield decisive evidence. Along the same lines, it would be expected that nearly all schizophrenics should have at least one schizoid or schizophrenic parent. Although the work of Kallmann and the intensive family studies of Alanen (10) and Lidz (22) support this expectation, more rigorous evidence is needed. The traits that favorably modify schizophrenia should be more apparent among schizoid than among schizophrenic relatives of schizophrenics. One would hypothesize, for example, that the more mesomorphic or more intelligent among the children of schizophrenics would tend to have less severe illnesses and to have more children than the less mesomorphic or less intelligent. These hypotheses, and many more that are implicit in the preceding discussion, constitute a significant refinement of the genetic hypotheses so far explored in schizophrenia.

Summary

The importance of genetic factors in the development of schizophrenia has by now been established beyond reasonable dispute, although it is clear that environment too plays its etiologic role. The results of recent research have refocused attention on schizoid disorders, a term applied to psychiatric disorders resembling schizophrenia which afflict relatives of schizophrenics. The many conceptual and research problems presented by the schizoid are considered.

Schizoids and schizophrenics occur with about the same frequency among monozygotic twins of schizophrenics. About 45 percent of the sibs, parents, and children of a schizophrenic are schizoid or schizophrenics, as are about 66 percent of the children of two schizophrenics. From the known risk of schizophrenia for the population as a whole, it is estimated that at least 4 percent of the general population will be afflicted with schizoid-schizophrenic disease.

Since monozygotic twins are identical genetically, it appears that the same genotype is compatible with either schizophrenic or schizoid disease. The proportions of affected first-degree relatives and the segregation of affected individuals within families closely approximate theoretical expectations based on the hypothesis of a defect in a single autosomal dominant gene. However, modifying traits play a significant role; this is discussed and integrated into the main genetic hypothesis. Emphasis is placed on hypotheses testable by future research.

References and Notes

1. E. Slater, in *The Transmission of Schizophrenia*, D. Rosenthal and S. Kety, Eds. (Pergamon, Oxford, 1968); D. Rosenthal, in *The Origins of Schizophrenia*, J. Romano, Ed. (Excerpta Medica Foundation, New York, 1967).
2. J. Shields, in *The Transmission of Schizophrenia*, D. Rosenthal and S. Kety, Eds. (Pergamon, Oxford, 1968).
3. L. L. Heston, *Brit. J. Psychiat.* **112**, 819 (1966).
4. D. Rosenthal, P. Wender, S. Kety, F. Schulsinger, L. Östergård, J. Welner, in *The Transmission of Schizophrenia*, D. Rosenthal and S. Kety, Eds. (Pergamon, Oxford, 1968).
5. J. Karlsson, *The Biological Basis of Schizophrenia* (Thomas, Springfield, Ill., 1966).
6. P. Wender, D. Rosenthal, S. Kety, in *The Transmission of Schizophrenia*, D. Rosenthal and S. Kety, Eds. (Pergamon, Oxford, 1968).
7. S. Kety, D. Rosenthal, F. Schulsinger, P. Wender, *ibid.*
8. I. Ray, *Mental Hygiene* (Hafner, New York, new ed., 1968).
9. K. Planansky, *J. Nerv. Ment. Dis.* **142**, 318 (1966); E. Essen-Möller, *Mscr. Psychiat. Neurol.* **112**, 258 (1946).
10. Y. O. Alanen, *Acta Psychiat. Scand.*, Suppl. No. 189 (1966).
11. F. J. Kallmann, *The Genetics of Schizophrenia* (Augustin, New York, 1938).
12. E. Kringle, "Heredity and Environment in the Functional Psychoses," *Norwegian Monogr. Med. Sci. Univ. Oslo* (1967).
13. E. Slater, with the assistance of J. Shields, "Psychotic and Neurotic Illness in Twins," *Med. Res. Council (Great Brit.) Spec. Rep. Ser. No. 278* (1953).
14. B. Hallgren and T. Sjögren, *Acta Psychiat. Neurol. Scand.*, Suppl. No. 140 (1959).
15. L. S. Penrose, *A Clinical and Genetic Study of 1280 Cases of Mental Defect* (Her Majesty's Stationery Office, London, 1938).
16. J. A. Böök, *Acta Genet.* **4**, 1 (1953).
17. E. W. Reed and S. C. Reed, *Mental Retardation: A Family Study* (Saunders, Philadelphia, 1965).
18. P. E. Meehl, *Amer. Psychol.* **17**, 827 (1962).
19. E. Essen-Möller, *Acta Psychiat.*, Suppl. No. 23 (1941).
20. P. Tienari, *Acta Psychiat.*, Suppl. No. 171 (1963).
21. W. Pollin, J. R. Stabenau, J. Tupin, *Psychiatry* **28**, 60 (1965).
22. T. Lidz, S. Fleck, A. Cornelison, *Schizophrenia and the Family* (International Universities Press, New York, 1966).
23. I. I. Gottesman and J. Shields, *Brit. J. Psychiat.* **112**, 809 (1966).
24. Ö. Ödegård, *Acta Psychiat.*, Suppl. No. 169 (1963), p. 94.
25. A. Lewis, *Acta Genet.* **7**, 349 (1957).
26. D. Rosenthal, *J. Psychiat. Res.* **4**, 169 (1966).
27. E. Slater, *Acta Genet.* **8**, 50 (1958).
28. C. Johnson, *J. Iowa Med. Soc.* **59**, 27 (1968).
29. H. Harris, *Brit. Med. J.* **2**, 135 (1968).
30. D. Rosenthal, *The Genain Quadruplets* (Basic Books, New York, 1963).
31. I. Gottesman and J. Shields, *Proc. Nat. Acad. Sci. U.S.* **58**, 199 (1967).
32. E. Kretschmer, *Physique and Character* (W. Sprott, Trans.) (Paul, Trench and Trubner, London, 1925).

33. S. Mednick and F. Schulsinger, in *The Transmission of Schizophrenia*, D. Rosenthal and S. Kety, Eds. (Pergamon, Oxford, 1968).
34. R. Parnell, *Behavior and Physique* (Arnold, London, 1958).
35. E. A. Lane and G. W. Albee, *Amer. J. Orthopsychiat.* **35**, 747 (1965).
36. E. Gellhorn and G. Loofbourrow, *Emotions and Emotional Disorders: A Neurophysiological Study* (Harper & Row, New York, 1963); W. Ross, J. Hay, M. McDowal, *Psychosom. Med.* **12**, 170 (1950); P. Huston and M. Pepernik, in *Schizophrenia, A Review of the Syndrome*, L. Bellak, Ed. (Logos, New York, 1958); C. Rosenbaum, *J. Nerv. Ment. Dis.* **146**, 103 (1968); H. Freeman, in *Schizophrenia, A Review of the Syndrome*, L. Bellak, Ed. (Logos, New York, 1958); L. Rees, in *Schizophrenia: Somatic Aspects*, D. Rich-ter, Ed. (Macmillan, New York, 1957).
37. J. Huxley, E. Mayr, H. Osmond, A. Hoffer, *Nature* **204**, 220 (1964).
38. R. J. Britten and E. H. Davidson, *Science* **165**, 349 (1969).
39. J. Karlsson, in *The Transmission of Schizophrenia*, D. Rosenthal and S. Kety, Eds. (Pergamon, Oxford, 1968).
40. L. Heston and D. Denney, *ibid.*
41. P. Tienari, *ibid.*
42. E. Inouye, in *Proceedings, Third World Con- gress of Psychiatry* (Univ. of Toronto Press, Montreal, 1961), vol. 1, p. 524.
43. F. J. Kallmann, *Amer. J. Psychiat.* **103**, 309 (1946).
44. J. Shields, I. Gottesman, E. Slater, *Acta Psychiat. Scand.* **43**, 385 (1967).
45. E. Kahn, *Monogr. Gesamtegeb. Neurol. Psychiat.* **36**, 1 (1923).
46. B. Schulz, *Z. Gesamte Neurol. Psychiat.* **168**, 322 (1940).
47. G. Elsässer, *Die Nachkommen geisteskranker Elternpaare* (Thieme, Stuttgart, 1952).
48. I thank James Shields, John Price, Irving Gottesman, and Russell Noyes, who com- mented on various phases of this manuscript.

Casualties of Our Time

Social and technological changes produce new sources of death and disability which raise public issues.

Amasa B. Ford

"It is changes that are chiefly respon- sible for diseases, especially the greatest changes, the violent alterations both in the seasons and in other things."

—HIPPOCRATES

Violent alterations in the human environment have occurred at an in- creasing rate since the beginning of the Industrial Revolution. From the late 18th century, dislocation from the land, turbulent crowding in grow- ing cities, and the economic depriva- tions of factory life affected the health of the people. Old diseases like tuberculosis flared up, and new sources of death and disability devel- oped, such as the industrial injuries which were incurred by inexperi- enced hands attempting to master new machinery. Great changes, vis- ible in a man's lifetime, gave motives for new laws and institutions. Social hygiene, with tardy assistance from therapeutic medicine, brought effec- tive measures to bear on the new health problems, while hospitals, asy- lums, and other institutions were es- tablished to take the place of the now obsolete welfare systems of farm and village. Economic and technological changes thus produced specific new kinds of casualties, along with new resources for coping with them.

In the present century, the rate of

change has accelerated. Many old problems have been mastered, but new ones have arisen. "Poor laws" and workhouses have gone the way of phthisis and chlorosis. Now we must ask whether general hospitals can cope with increasing drug addiction among alienated youth or how health departments can protect the public against cigarettes and overeating. But before we can restructure our health services we must assess what we know about the particular health needs of today. Because established social in- stitutions have great inertia, change is slow and tends to lag behind need. New problems, therefore, call for spe- cial attention, since they foreshadow future needs.

The purpose of this report is to identify sources of death and major disability which are new or are of new importance in developed coun- tries in the two decades since World War II. Using examples from Great Britain and the United States, we make some estimates of how people are being affected.

Certain casualties result from im- mediate causes, such as the toxic ef- fects of a new drug or the increased use of motor vehicles. Many, possibly more, take the form of major disabil- ity resulting from conditions that have

complex origins. Examples are the extended survival of old people with chronic disease and the social aliena- tion of young people. A rough classi- fication by cause will serve as an out- line, since an understanding of how disease originates is the most reason- able basis for control and prevention. Effects on health may be produced by changes in population, by technologi- cal developments, by new factors in medicine, or by shifting social and cultural patterns. These categories, however, should not obscure the fact that specific casualties may result from multiple causes.

Signs of Change

Prosperity and life expectancy have reached unprecedented levels in de- veloped countries during the past 20 years, but there are indications that we may be approaching the limit of effectiveness of current methods of disease control and prevention.

In the early 1950's infant mortality rates ceased to improve at the rate which had prevailed for many years. In the decade 1946-56, rates had de- creased 46 percent in the United States and 45 percent in England and Wales. In the subsequent 10 years, they decreased only 16 and 22 per- cent, respectively. The estimated aver- age length of life, which in effect is inversely related to infant mortality, has increased to 70.1 years in the United States and 68.4 years in Eng- land and Wales, but the rates of in- crease since 1956 have been less than a fifth of what they were in the pre- vious 10 years. The progressive reduc- tion of deaths in the first year of life, which has been one of the finest fruits of social and medical development

Dr. Ford is assistant professor of medicine and preventive medicine at Case Western Reserve School of Medicine, Cleveland, Ohio 44106.