family and biologic variables in the same etiologic studies of schizophrenia: a proposal

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The Classical Experiment

On March 24, 1882, Roch Koch reviewed a breathtaking series of experiments before the Physiological Society of Berlin, experiments that provided conclusive proof of the bacterial etiology of tuberculosis (Koch 1942). He described the fundamental steps by which he excluded competing etiological hypotheses, leaving the tubercle bacillus as the causative factor.

• First, he systematically identified methylene-blue-stained rod-shaped bacteria in tuberculous lesions from diseased organs of men and animals, ruling out the hypothesis that different forms of the disease might be caused by different agents.

• Second, he carefully prepared pure cultures of the bacillus, separating them from any other noxious agent that might have been present in the diseased tissue.

• Third, he inoculated these cultures into a variety of animals, producing unmistakable tuberculous lesions from which he could again extract the bacillus; comparable animals who were not inoculated remained healthy.

In the same year that Koch described his classic experiments, Emil Kraepelin gave up his neuroanatomical investigations to begin a career of psychological studies that was to yield a fundamental and enduring delineation of the syndrome of schizophrenia.

Kraepelin began these studies in the productive and vastly influential laboratory of Wilhelm Wundt, the founder of experimental psychology. Kraepelin's interest in the experimental analysis of psychopathology persisted throughout his career.

The work of Koch and Kraepelin fitted well with the zeitgeist of the scientific world of Germany in the last quarter of the 19th century—a world intensely preoccupied with the controlled, experimental analysis of complex natural phenomena. The singular contributions of both men and of the zeitgeist itself have profoundly affected the approach to all aspects of medical research. The study of schizophrenia proved no exception. Spurred by the successful experimental identification of the cause of general paresis, many investigators, Kraepelin included, tried unsuccessfully to develop experimental proof of the causes of the "exogenous intoxications" of schizophrenia.

Two major problems caused investigators to abandon the experimental approach to discovering the etiology of schizophrenia. Ironically, these problems were produced by the very variables that seemed to be the most likely causal agents of schizophrenia: the afflicted person's genotype, his family upbringing, and his position in the social structure.

The Problem of Marker Variables

The first problem, the problem of marker variables, concerned the selection of valid, reliable, and objective indices of the magnitude of these variables. (We use the
The term "marker" simply to refer to measurable surface variables that reflect deeper but not directly measurable variables.) As the science of sociology progressed, marker variables assessing an individual's position in the social structure became available. The most reliable were indices constructed from the individual's occupation and education. Greater problems existed for family variables: What were the putatively noxious variables, and how were they to be assessed? And still further problems were encountered with genetic variables: How can we know whether an individual has a schizogenic genotype? Schizophrenia itself is clearly not a marker. We know from concordance rates in identical twins, for example, that from 20 percent to 80 percent of co-twins, with genotypes identical to schizophrenic-index twins, may be free of schizophrenia. Thus we have to rely on probabilistic markers based on family history. If an individual has a co-twin who is schizophrenic, he definitely has a genotype that may be schizogenic; if he has a first-degree relative with schizophrenia, he may have a genotype that may be schizogenic.

The Problem of Control

The second problem for the classical experimenter was that he could never hope to gain direct control over the experimental variables most relevant to schizophrenia. This problem is, of course, a crucial one. Experimental control is an indispensable requirement in medical and psychiatric research for three major reasons:

- First, the causal variable must be permitted significant variation to give a potential cause a chance to produce its hypothesized effect (geneticists would describe this as a "heavy loading"). Thus, for example, Koch could give some of his experimental guinea pigs a good dollop of bacteria while others received none at all. Obviously, if his technique permitted him to give only a modest inoculation to some animals and, for comparison purposes, just a little less to others, the end results would have been inconclusive.

- Second, it is necessary to establish that the putative cause has preceded its hypothesized effect. This requirement is obvious in the Koch experiment; it is why he had to inoculate healthy animals and could not rely simply on identifying bacilli in already-established pathologic lesions.

- Third, it is necessary to ensure that the putative cause is not confounded with variables extraneous to the hypotheses. For this reason, Koch passed his bacillus through several cultures to make sure that no other noxious agent from the diseased organs that had yielded the initial bacteria was present in the inoculum.

Quasi-experimental Analysis

These elementary tenets of scientific logic were obvious to every serious scholar in the field of schizophrenia research, and the effort to work around them was indeed frustrating. Gradually, a new approach to the logical analysis of causation began to take shape. This approach has been designated as quasi-experimental analysis by Campbell and Stanley (1963) who provided a systematic description of its various techniques. The basic idea is simple: The researcher tests his hypotheses as an astronomer would rather than as an experimental bacteriologist would tend to do; taking advantage of natural variation of the putative causal agent, he observes the consequent variation in the hypothesized effect. By the use of clever devices the investigator can still approximate the three requirements of the true experiment: significant variation, prior causation, and freedom from confounding variables. The history of significant investigation into the cause of schizophrenia, particularly in the last 15 years, consists of moderately successful quasi-experiments. Briefly, let us examine some representative studies for their strengths and shortcomings. We shall focus specifically on the study of genetic and family variables; social (chiefly social class), biochemical, and physiologic variables will be excluded to simplify the discussion and because they are less relevant to the concerns of this issue of the Bulletin.

The design of quasi-experiments when there are two or more contending sets of causal variables may take one of two forms. In the single factor design, one variable is singled out and the rest are held constant. The important feature of this experiment is its ability to demonstrate the independent effect of the one causal variable selected for study. It can never, however, estimate the causal role of the other variables; nor can it ascertain whether the selected variable directly influences the
hypothesized effect or, rather, depends on the magnitude of one or more of the remaining variables. Koch's experiments with the tubercle bacillus were single factor experiments in which extraneous variables, such as tissue and laboratory contamination, were held constant (at a very low level). The results were impressive. All the inoculated guinea pigs, and none of the uninoculated ones, became tubercular. In more technical terms, the bacillus variable accounted for 100 percent of the variance of guinea pig disease. Did this mean that the bacillus was the only cause of tuberculosis? It did not. Later, a second type of design, the multifactor design, revealed significant host factors: Some individuals (including Koch himself) could be infected with substantial doses of bacilli and never contract the disease; they were protected by a host factor. In multifactor designs, at least two variables are permitted to vary independently.

In studies of the role of family and biologic variables in the etiology of schizophrenia, the problem of significant variation has never been serious. There are wide variations in genotypes as well as in family types, and investigators have had no difficulty in capitalizing on this natural variation in their studies. The problem of prior causation has been much more difficult. For genetic variables, of course, this is not a true obstacle. If we can establish or estimate the subject's genotype at the age at which he enters our study, we can assume that this genotype has been invariant since the moment of his conception (although recent genetic evidence throws some doubt on this assumption). Whatever the relationship between genotype and schizophrenia may be, it can be said—at a minimum—that the former precedes the latter. The same cannot be said for family variables. If we assess any family variable after an individual has become schizophrenic, we have no way of knowing what its magnitude was before the onset of illness. Historical reconstruction of family life in infancy and childhood from the reports of adolescents or adults is notoriously inaccurate (Yarrow, Campbell, and Burton 1970). Further, we have little or no data on the stability over time of directly observable family variables. Thus, we cannot extrapolate backward to the phase of family life before the onset of schizophrenia if our data are collected after onset. To meet this problem head on, several investigators have begun longitudinal investigations to determine the priority of family variables (Goldstein and Rodnick 1975). In these studies, variables are measured in families of children who are at risk for schizophrenia but who do not, at the time of measurement, show obvious signs of the disorder. The third problem, confounding of causal variables, has presented extreme difficulties and is considered in some detail in the next section.

Biologic and Family Studies

Investigators throughout this century have recognized that some kind of family variable must be "included in" their studies. Until recently, those with a biologic interest conducted single factor experiments in which the biologic variable was permitted to vary. Of these, only genetic investigators have recognized that family variables must be held constant to avoid confounding. Unfortunately, to our knowledge no other biologic investigations have attempted to include family variables in their studies of schizophrenia, either as controlled, constant variables in single factor designs or as independent variables in multifactor designs. Genetic investigators introduced the identical twin study method in an effort to control the entire set of family variables (by keeping a constant but unknown level). In their studies, the research case was the co-twin, and the genetic loading was permitted to vary by comparing co-twins identical to a schizophrenic index twin with co-twins fraternal to a schizophrenic index twin. Based on the belief that any twin pair—whether fraternal or identical—would be exposed to the same family variables, twin studies attempted to control family variables by assuming their consistency—in a special sense—across twin pairs. Evidence soon began to show, however, that this assumption was unfounded; identical twins were treated more similarly by their families than fraternal twins (Jackson 1960). Thus the higher concordance rates of identical twins could be explained by either family variables (different parental rearing techniques for identical twins as compared to fraternal twins) or genetic variables—a classic case of confounding.

The first twin studies made an effort, albeit unsuccessful, to include family variables in investigations that were otherwise biologic. The more recent genetic studies have maintained this tradition. Let us see how they have fared.

In the last decade there have been several notable single factor designs. Pollin and Stabenau (1968) attempted to control the genetic variable by comparing
the differences in family variables of identical twins discordant for schizophrenia (only one twin afflicted). All twins were studied in late adolescence or adulthood after the index twin had become schizophrenic. It was difficult to reconstruct family variables that might have preceded the onset of schizophrenia, and the most striking findings pertained to indicators of environmental factors that were more easily reconstructed, such as birth weight, which was usually less in the index twin.

As in any single factor design, generalizations are limited. Here, of course, we cannot study the influence of genetic variables. Moreover, since the genetic loading of all subjects is uniformly high, any environmental factors—family or otherwise—that are significantly related to schizophrenic outcome may operate only in the presence of high genetic loading. The influence of those variables when the loading is low cannot be ascertained from this design.

Two other sets of single factor studies involved adopted offspring: the Oregon Adoption Study (Heston and Denney 1968) and the Danish Adoption Studies (Rosenthal et al. 1968 and Kety et al. 1968). Here, natural variation in genetic loading is permitted by comparing offspring whose biologic parents were schizophrenic with offspring of normal parents. In these studies, family variables are held at a constant (although unknown) level by the use of adoptions; it is assumed that the rearing techniques of adopting parents for both groups of children are relatively normal or at least comparable across groups. Findings to date indicate a preponderance of schizophrenic outcome in the group with schizophrenic biologic parents and thus suggest the independent influence of genetic factors on schizophrenic outcome. In the Oregon Adoption Study, a series of secondary analyses attempted a single factor design by holding genetic loading constant and examining the effect of locus of care of adopted child (family vs. foundling home) and social class. These analyses showed no influence of gross environmental factors.

The most specific multifactor design yet attempted in this area is the recent study of Wender et al. (1974); it is, however, an incomplete multifactor experiment. The genetic factor was permitted to vary by comparing adoptees with normal biologic parents with adoptees whose biologic parents were schizophrenic. The unique feature of this design was that the first group was subdivided into individuals reared by presumptively normal adopting parents, the index group, and those reared by frankly schizophrenic parents. This last subgroup is called the cross-fostering group and the study can be designated the Cross-fostering Study. A potential fourth group, adopted offspring whose adopting and biologic parents were both schizophrenic, would have been theoretically interesting to study but was too rare to be included in the overall design. The major finding of the Cross-fostering Study was a preponderance of schizophrenic outcome in the index group (schizophrenic biologic parents, normal adoptive parents). The investigators concluded, with reservations, that their data provided no evidence of a role for family factors in the etiology of schizophrenia but did reconfirm the genetic hypotheses.

The Pollin and Stabenau, Oregon, and Cross-fostering Studies all included family variables in their designs. The first two were essentially single factor designs in which the genetic variable was held constant. In the third, the genetic and family variables were both permitted to vary. Pollin and Stabenau developed some very interesting leads concerning family variables, despite the Herculean task of reconstructing early childhood family environment from whatever data were available two to three decades later. Let us concentrate here, however, on the Oregon and Cross-fostering Studies because they better illustrate the problems of including family variables in biologic studies and because the investigators, particularly in the Cross-fostering Study, have concluded that family variables are unlikely to have a substantial etiologic role.

The Oregon Study’s single factor design permitted the family variable to vary by comparing adoptees reared in families from the time of adoption with those raised in foundling homes for an average of 2 years before final adoption by a family. In effect, the family variable (if it is fair to so designate it) is represented by a contrast between groups reared by a family—any kind of a family—and those who were reared in an institution.

In the Cross-fostering Study the family variables were permitted to vary by comparing children reared by a schizophrenic mother or father with children whose adopting parents had no major psychiatric disorder. The assumption is that the rearing by the schizophrenic is worse than the rearing of the adopting parents in the index group who had no major psychopathology. Can we say that these studies have succeeded in including family variables where the earlier twin investigators failed?
Critical Family Variables: Two Criteria

To answer this question, we need to introduce some minimal criteria as to what constitutes an adequate marker of variation in critical family variables. In other words, how do we know if the variables included in a study actually represent critical family variables? Two simple criteria will suffice:

- We must be reasonably sure that the variables selected are among the most likely to be toxic to the point of being schizogenic.
- We must be reasonably sure that the variables act in a prolonged and relatively undiluted way on the offspring being studied.

Kallmann (1938) and similar twin investigators met the first criterion: Whatever the toxic influences present in the family, both members of a twin pair might be influenced by them in some way. But Kallmann failed to meet the second criterion. He knew that different children in the same family received different exposure to both noxious and beneficial variables, but he assumed that twins—whether fraternal or identical—received the same exposure. He was wrong. Identical twins tend to receive similar exposure, but fraternal twins do not—indeed, the Pollin studies suggest that even identical twins have substantially different exposure to family variables.

The Oregon Study failed to meet the first criterion. In this study, family rearing was mostly by relatives of the biologic schizophrenic mother. We simply do not know if this social environment was more or less toxic than the foundling home environment. It is true that the Oregon Study presents evidence of serious social deprivation in the foundling home environment. No current theory, however, on the family or immediate social environment discusses social deprivation as a specifically toxic variable, specific in the sense of producing schizophrenia rather than a more general or varied set of developmental disturbances. In fact, most theories assume the presence of some kind of intact family, usually a family that to the outside appears to be cohesive and tightly structured. Thus, the simple fact of growing up in a relatively intact and stable family is by no means a guarantee that major toxic variables are not present as is assumed in the Oregon Study. With regard to the second criterion, the necessity for prolonged and undiluted exposure, it is by no means certain that the Oregon Study meets this criterion either. We can assume that if there were a toxic variable present in foundling homes (social deprivation of some kind) every child would have received prolonged and heavy exposure to it. Since the children enter the homes as neonates and spend an average of 2 years there, it is hard to imagine any toxic variables in the home being mitigated by outside influences (older children, of course, would be exposed, for example, to schools and peers). Nonetheless, selective exposure to toxic variables within a social setting is a major problem, one to which we shall return.

The Cross-fostering Study would appear to have trouble meeting both criteria. The presence of schizophrenia in a single parent is an unreliable indicator of toxicity. There is no simple correlation between severity of schizophrenia in a parent and the exposure of an offspring to toxic family variables. In the first place, schizophrenia—even among chronic patients—is a fluctuating process. In many nonchronic cases there are lengthy periods of relative remission. We would want to know during what phase of the parent's illness the offspring were in their younger developing years. More important, there is no simple known correlation between the competence of parenting and the presence or absence of schizophrenia. Obviously, the gross disruptions of family life occasioned by hospitalizations and bizarre behavior cannot be construed as supportive of healthy child development. But although such disruptions are clearly disturbing, they have not been seriously considered as specifically schizogenic by major workers in the family field for over two decades. Rather, more specific deficits of parenting have been related to schizophrenia in cross-sectional studies in which the offspring and parents are studied at the same time after the onset of the illness. A case in point is the well-known family variable of mutuality developed by Wynne et al. (1958). This is the capacity of a parent to maintain a mutually shared focus of attention with a significant other on an external stimulus source or internal thought or idea. A deficit in this capacity is referred to as a transactional thought disturbance. In a more recent study, Wynne (1968) has shown this variable to be only weakly correlated with diagnosed schizophrenia in the parent but highly correlated with schizophrenia in the offspring. With respect to the second criterion, prolonged
and undiluted exposure to the noxious variable, a number of investigators have described properties of the family group that may mitigate the impact of the schizophrenic parent. For example, Anthony (1970) has described regenerative processes in family groups that permit them to seal off the major impact of the ill parent and to renew an orderly and gratifying family life.

In the last two decades, family researchers have approached the separate problems of toxicity and exposure with a single general solution. Contemporary family researchers are no longer studying the typical attitudes or child-rearing practices of single parents. Rather, they have concentrated on the family as a unitary group. The potentially noxious properties of family life, as well as the intensity of exposure to these variables for individual members, can be studied simultaneously with reference to assessment of the family group as a whole. Two very different examples illustrate this point:

1) The first concerns studies of a family property that has come to be known as the family boundary. Wynne was the first to recognize the utility of this concept in the study of the possible role of the family in the etiology of schizophrenia (Wynne et al. 1958). Based on clinical studies alone, Wynne and his colleagues posited a set of family rules that compelled all members in families of schizophrenics to perceive their relationships with one another as mutually satisfying and without flaw. These rules required that any information from outside the family that might contradict such a view was to be disregarded. In other words, social process within the family established a boundary through which all information about the family must be filtered. Information indicating flaws in the perceived, satisfying mutuality of relationships (“pseudomutuality,” from the perspective of the observer) had to be edited out. The theory made it very clear that many or most individuals in the family might, in the conduct of their individual lives, pay scrupulous attention to information input of every variety. When the family came together as a unitary social group, however, everyone acted to maintain the boundary, or the rubber fence, as Wynne called it. Many years later, using sophisticated computer-automated experimental techniques, Reiss and his colleagues were able to demonstrate clearly the presence of a socially dependent information barrier in families of schizophrenics (Reiss 1971 and Reiss and Sheriff 1970). The presence of a boundary of this sort constitutes both a toxic family influence and a guarantee that all members of the family will have a sustained and undiluted exposure to this influence. This last is true because the boundary guarantees the profound social isolation of the family from a wider social context that might dilute the toxic family variable.

2) A second example of assessment of the family group as a whole can be drawn from a variety of studies of interaction between mothers and infants published during the last decade. These have presented evidence that the neonate and the mother both make a necessary and fundamental contribution to the quality of their overall relationship and specific interaction. For example, Bell and Ainsworth (1972) showed that infants who cry a great deal tend to frustrate their mother’s efforts to care for them and to provoke their mother’s withdrawal from them. This sequence of alienation—between mother and infant—can be a product of either excessive fussiness in the neonate or insufficient frustration tolerance in the mother, or both. Fraiberg’s (1974) studies of interaction between mothers and blind neonates and infants is a dramatic example of the same processes. Blind infants failed to develop the differentiated facial expressiveness of sighted infants. Mothers ordinarily depend on these signals in the course of developing social bonds with their infants, and their absence leads to potentially dangerous estrangements between mother and child. Precise and sophisticated methods for studying the fit between mother and infant are now available so it becomes possible to derive a number of quantitative indices of the success or failure of fit and the evolution of the fit over time. These indices themselves can be used as independent variables, marking the variation of critical family variables in studies of normal and pathologic child development. It is not paradox, as some may argue, that the child’s behavior is used as part of the assessment of mother-child fit—the independent variable—and as the basis for measuring the dependent variable, adequacy of individual development. Figure 1, adapted from Lewis and Lee-Painter (1974), shows that it is entirely logical to assess the mother-child fit (the independent variable) at one time and then assess the adequacy of the child’s development at a subsequent time. The shift in level of analysis from dyadic (or social) to individual is a familiar
problem for social scientists, and a number of analytic techniques for dealing with it are readily available (e.g., Riley 1963). Variables reflecting mother-infant fit conform to our two basic criteria: they adequately assess the quality of toxicity and the magnitude of exposure of the offspring.

These considerations of exposure to toxic family variables render the Oregon and Cross-fostering Studies relatively mute on the issue of the family's role in the etiology of schizophrenia. Can we fault these investigations for the omission of pertinent data on family interactions? This is a difficult point. It must be underscored that most measures of properties of the family as a group require direct observation of the quality of family interaction itself. The nature of the family boundary, for example, or the quality of mother-child fit cannot easily be reconstructed from evidence collected years later, a fundamental method of both the Oregon Adoption and Cross-fostering Studies. It is debatable—and in the main irrelevant for our present analysis—whether these investigations made reasonable compensations in their secondary analyses or interpretations of data for the absence of direct evidence of critical family variables. It is a fundamental thesis of the present paper that, in many respects, the absence of adequate family variables in the Oregon and Cross-fostering Studies is an excellent, although indirect, index of the present state of family research per se. As we shall try to show, family research in the last two decades, wittingly or unwittingly, has surrendered to the problem of the etiology of schizophrenia. Several trends in family research have made it quite possible for otherwise exemplary projects, such as the Oregon and Cross-fostering Studies, to omit serious consideration of the basic findings in the family field.

Obstacles to the Inclusion of Family Variables in Biologic Studies

Insubstantiality of Family Variables: The Thinghood Problem

We have heard for many years of the importance of studying "gene-environment interaction" in the etiology of schizophrenia. This phrase produces an eerie feeling similar to that of waking from a vivid dream—the unsettling experience of the partial fusion of fantasy and reality. When we talk of an individual's "genes," we are referring to a very specific set of nucleic acids arranged in a highly ordered stereochemical configuration. The relationship between genes and the rest of the cell can be carefully mapped in terms of transfer nucleic acids,
enzymes, co-factors, and substrates. Many of these entities can now be directly visualized on the screens and film of electron microscopes. When we talk of an individual's "environment," however, we refer to a great, misty vagueness somewhere "out there" that has the property of somehow impinging on his life. This can include the quality of nourishment he received while still in his mother's womb, the smells from the chestnut vendor's stand on the corner, and the current price of gold on the London market. If we introduce the specification "family" into this mist, we have greatly reduced the vagueness. But the problems remain legion; the family environment can still properly include the individual's emotional nourishment from his mother while he was an infant, the smell of his sister's perfume, and the current price of his father's trout flies, the manufacture and sale of which constitute the sole support of the family. We need not belabor the point to emphasize that biologic variables are currently much more rigorously defined than the variables in family studies.

The Oregon and Cross-fostering Studies have as their biologic variable the schizophrenic genotype. The family variables are, by comparison, very vague—a notion of general family competence seems to underlie both studies. What would a biologist say if a family researcher attempted to study the biologic origins of schizophrenia through the use of some omnibus variable such as "biologic competence"? If family-biologic studies are designed to use biologic variables that are as substantial as genotype (or even more substantial, such as the variation of particular enzymes or specific indicators of neurologic function like the evoked response), they must include family variables whose substantiality is comparable.

The substantiality of any variable, whether family or biologic, usually depends on a fastidious process of definition. This definition has, at a minimum, three components:

- It must have an operational component so that the manner in which the variable is to be measured or inferred is precisely described;
- It must have a contrast component so that the variable is clearly distinguished from other, similar variables with which it might be confused; and
- It must have a theoretical component so that the functional relationship between the variable and others in the system or domain is spelled out, insofar as possible. A concept of a net of functional relationships between the specified variable and others gives added meaning and clarity to the variable itself. These definitional processes can endow a variable with a property described by Boring as thinghood. Such biologic variables as genotypes, enzymes, and substrates have the quality of objective "things" that are "out there" in nature.

Examining just how a biological variable takes on thinghood, using the enzyme platelet monoamine oxidase as an example, is helpful. One current biologic theory posits a deficiency of this enzyme as a correlate of schizophrenia (Wyatt, Belsleaker, and Murphy 1975). Monoamine oxidase itself, which is probably more than one enzyme, serves to oxidatively deaminate the large number of monoamines (e.g., dopamine, norepinephrine, epinephrine, phenylethylamine, tryptamine, and serotonin) as well as diamines (e.g., histamine), many of which are believed to be neurotransmitters.

Platelet monoamine oxidase activity was initially studied because it was thought to provide an easily accessible analog to the enzyme in the brain. Recently a deficiency in monoamine oxidase activity was found in the blood platelets of some schizophrenics and was demonstrated to be a biologic trait that is under genetic control. The deficiency does not seem to be present in the brain. A result of the platelet monoamine oxidase activity deficiency can be postulated: Schizophrenia may be like phenylketonuria which has its biological origin not in the brain but in the periphery. Phenylketonuria is produced by a deficiency in a liver enzyme, not a brain enzyme.

The hypotheses surrounding low monoamine oxidase activity are particularly attractive because they are consistent with several biochemical theories of schizophrenia—those claiming a role for excessive dopamine or for excessive methylation of the indolylalkylamines, tryptamine and serotonin. Excess functional dopamine is tied to the amphetamine model of psychosis which parallels many aspects of schizophrenia. Excess tryptamine and serotonin may be methylated to form the short-acting hallucinogens, dimethyltryptamine (DMT) and 5-methoxy-diethyl tryptamine.

The deficit of monoamine oxidase in the platelets of some schizophrenics is consistent with a theoretical biochemical network that continues to generate numerous experiments, but there are additional reasons for the...
enzyme's "thinghood" status as a biologic variable. One of these is the great variety of methods available for assessing its activity levels.

The way that monoamine oxidase and most other enzymes are measured is by their activity—the rate at which they convert one substance (substrate) to another (metabolite). The actual quantity or weight is not usually measured. The reliability of the measure is assessed in many ways. The simplest test is to split the sample and carry the assay separately all the way through, comparing final values. Samples taken from the same person at different times during the same day, the same week, and at longer intervals also provide an estimation of reliability. Furthermore, assays can be run at different times and by different personnel. It is important to carry out these and other such painstaking studies, since even established clinical laboratories in the best of hospitals have considerable problems producing high reliability. The enzyme itself can be studied by many techniques. It can be purified—broken away from other proteins and lipids—its exact structure can be examined, and its amino acid sequence can be determined. Its movement can be studied in a gel to which an electric current is applied (electrophoresis). It can be assessed by making an antibody specific to the enzyme and measuring the antibody under different conditions such as heat, alternate substrates, inhibitors, and pH. All of these establish the enzyme's "thinghood" and may help to determine how it might be different in normals and schizophrenics, if in fact it is.

Compared to the tangibility of biologic variables such as enzyme activity levels, many family variables seem like the ephemeral concoctions of an imprudent, overimaginative social scientist. The difference, of course, is illusory. Without being backed into a completely solipsistic corner, we can firmly assert that biologic variables—such as "enzyme activity level"—and family variables—such as "maternal dominance"—are slowly built up by the same reciprocal process of observation and interpretation. They are both "constructs" useful for explaining direct observations. Their epistemologic status is identical. Many family researchers despair of achieving for their own variables the degree of specificity and thinghood acquired by biologic variables. We believe this pessimism is unfounded. More optimistically, we argue that specificity and thinghood may be acquired by guarding against four current tendencies in the derivation of variables for family research.

**Derivation of Variables:**

**Undesirable Tendencies**

**Deriving Variables from Common Sense**

The first undesirable tendency is the too-easy derivation of variables from common sense. Most notions of "dominance," "submission," and "communication clarity" are good examples. These concepts are appealing because they seem so intuitively self-evident. Thus, an investigator will seek to establish that families of schizophrenics have more "conflict" or that there is an aberrant power relationship between parents in "mother-dominant" families. In effect, the definition of these variables depends on the assumption that we are all, in effect, sociologists or social psychologists. Each of us, that is, has made observations about others and has integrated these observations into some schema or theory that we use to guide our own actions and predict the responses of others. These naive psychologies and sociologies have themselves become the explicit object of study in recent years. They can vary quite radically, and this is why an intuitive use of them is so risky. We do not all share a common sense of the meaning, for instance, of "maternal dominance," and the use of concepts of this kind is bound to lead to disagreement and ambiguity.

**Relying on Single Methods**

A second undesirable trend is the construction of variables that are too closely tied to specific methods of measurement. An excellent example is Ferreira and Winter's *spontaneous agreement*, which is measured by giving each individual in the family a questionnaire on his preferences, such as food, activities, and famous individuals. Subjects fill out the questionnaire without being able to talk with one another. The score is the total number of preferences all members share. Ferreira and Winter (1974) state that this variable reflects "the communality of views" (p. 366) between two or more individuals in the same family which is, presumably, the
product of effective "communication." The variable has been important in family research because it is one of the few with adequate psychometric properties. Split-half reliabilities (Ferreira and Winter 1965) and test-retest reliabilities (Ferreira and Winter 1966) are high, and concurrent validity is high in that spontaneous agreement repeatedly distinguishes between families with and without psychiatric illness (Ferreira and Winter 1968) and, more recently, between newly married couples—where it is low—and "old marrieds"—where it is high (Ferreira and Winter 1974). However, its utility is sharply limited because it has never been measured by any method other than Ferreira and Winter's questionnaire. The questionnaire itself has items pertaining to only the most routine and mundane aspects of everyday living. We do not know if spontaneous agreement reflects a "communality of views" on more emotionally loaded issues like sexual practices or on issues that are not likely to be conscious, such as a shared view of a particular offspring (e.g., "He shows the gifts of his dead Uncle Max and will redeem this family from its poverty and oblivion"). The use of other methods to measure spontaneous agreement would give the underlying variable more specificity and thinghood.

**Depending on Content Analysis**

A third undesirable trend, related to reliance on a single method, is the substantial dependence on content analysis of speech for the derivation of variables. Although content analysis has a major role to play in family research, it has clearly been overused. It is a method of analyzing family discussions that are tape or video recorded. The overall discussion is divided into units (e.g., sentences, statements), and each unit is then coded by its meaning as defined in a coding manual, according to the judgment of a coder. The most frequently used approach has been Bales' (1951) system. Here, each statement is placed in one of 12 mutually exclusive categories according to whether its primary meaning seems to be to give or get information or to express positive or negative affect. Many of the problems of rater reliability and validity have been solved in other approaches, but fundamental problems remain with the content analysis approach. In the first place, though few family researchers now realize it, content analysis received its original impetus from analysis of written texts. (An interesting early example is described by Dovring (1954) in which content analysis was used by religious authorities in 18th century Sweden to determine the possible impact of some seditious religious texts. The authorities counted references to various religious symbols and themes as part of their estimate.) Subsequently, content analysis of newspapers, political tracts, folk tales, and many other printed materials became a major research tool. To be sure, sociologists and social psychologists applied the method to actual speech rather than texts, and many—including Bales, who used his system for groups of nonrelated individuals—had considerable luck with this approach.

The fundamental problem with content analysis is that speech between individuals who know each other well becomes idiosyncratic, elliptical, and full of special and unique expressive symbols; meaning is conveyed on many levels. Speech departs radically from written reports which must communicate to unknown readers by use of conventional symbols and meanings. To keep a content analysis approach objective and reliable, the coder cannot exercise subtle, clinical judgment as to the idiosyncracies and particularisms of any speech unit. Any objective coding system must refer back to the conventional meanings and functions of particular words in order to code them. Although several landmark studies have used this approach (for example, Mishler and Waxler 1968), there is a growing recognition of the relative opacity of content analysis methods.

The weaknesses of content analysis are clearest when the variables it produces are considered for inclusion in mixed family-biologic designs. In these designs, a sharp contrast can be seen in the fundamental logic by which content analysis variables and biologic variables are derived. Content analysis depends on the coder's inference on the conventional *meaning* of an event (a verbal statement) observed in a family study. As we have seen in the discussion of studies involving monoamine oxidase, biologic measurement emphasizes the *function* of a particular event. We often estimate the activity level of an enzyme by measuring its functional effect on a substrate. By contrast, content analysis measures the impact of a family event on the coder himself.

Recently, techniques have been developed that may well replace content analysis. These procedures assess
events in family interaction by their impact on other aspects of family behavior. In this respect, they are precisely analogous to biologic measures. One very promising procedure is the referential communication task (Krauss and Glucksberg 1969). In this experiment, two family members serving as subjects are separated by a screen. Each has an identical set of complex designs in front of him. The experimenter indicates to one member a particular design in his set and asks him to describe it with sufficient clarity so that the other subject, based on this description, can pick it out of his set. The clarity of communication is not measured by analysis of content or the meaning of the speaker's words but by whether the listener can select the proper design. The referential communications task is one of a new set of procedures that permits the measurement of family variables by their impact on other family variables.

Using Variables Based on Special Training

A fourth undesirable trend is the reliance on variables whose importance can only be understood by very specially trained investigators. Usually this training is in the form of a special type of clinical experience. The concept of pseudomutualty in families of schizophrenics (Wynne et al. 1958) is a good example. The main outlines of the concept can be understood by any reasonably well-educated psychiatric researcher; but only a well-trained family therapist who has worked with families of schizophrenics will recognize, from its impact on him, the grinding and disorienting impact of the reality distortions required to support pseudomutuality. The same is true for concepts such as projective identification (Zinner and Shapiro 1972). Only a psychoanalytically trained therapist, one who has regularly been forced to experience the projections of patients in the midst of intense transference neuroses, may be able to appreciate fully the devastating force of this process in family life. General concepts, such as these, are useful organizers within the family field. But they need to be broken up into simpler, more understandable components before they can be used in truly interdisciplinary studies in cooperation with biologic investigators.

Absence of Distinctions between Groups and Individuals

A great deal of clinical family research has been fueled by the provocative experience of family therapists. Family therapists have observed that it is effective to concentrate all therapeutic efforts on the family as a unit. The power of the technique is often enhanced if all behaviors, particularly deviant ones, are seen as serving a positive function for the entire family group. In this way, all members of the family come to understand their specific roles in the stimulation and maintenance of problem behavior in some of the members. Although this approach has had remarkable benefits (see two recent and well-controlled outcome studies: Langsley and Kaplan 1968 and Parsons and Alexander 1973), it has presented major difficulties for systematic research on the family and schizophrenia. In many research projects the individual qualities of family members have been obscured. In fact, the de jure and even de facto recognition of the individual has been withdrawn. This trend has made it almost impossible to coordinate a great deal of family research with biologic investigations of schizophrenia. For this coordination, family variables must be conceptualized as exogenous toxins acting on the individual in the same sense that genotypes or enzymes are conceptualized as endogenous toxins. In other words, the individual must remain the basic research case.

Research Orientation: The Individual

Reviving this orientation will require some concrete efforts including, at a minimum, the ones that follow.

Precise diagnoses of schizophrenia. A precise diagnosis of schizophrenia must be made in all family studies. A very large number of family studies merely distinguish between "normal" and "abnormal" families. The latter are defined as families in which any member suffers from any manifest psychiatric disturbance. In fact, research has shown replicable differences between interaction patterns of schizophrenics in families of patients of differing types, such as the impulse-control disorders (Hassan 1974, Reiss 1971, and Stabenau et al.)
1965), and between various subtypes of the disorder, such as process and reactive schizophrenia (Baxter and Arthur 1963, Farina, Holzberg, and Dies 1968, and Mishler and Waxler 1968). Diagnostic precision facilitates the comparison of family interaction variables and specific pathologic outcomes.

Specific variables. More specific variables linking family variables to individual outcome must be conceptualized and studied. It is not enough to explore statistical relationships between family variables and individual outcomes even if the problems of prior causation and confounding of variables can be solved. It is necessary to specify the precise mechanisms by which certain family variables can influence individual development. Nascent concepts of special relevance to schizophrenia have focused on the family as a regulator of information flow and interpretation (Jones and Gerard 1967 and Reiss 1971). The child's capacity to deal with the information properties of external and internal stimuli may be linked to the patterns of information processing in his family. The details of these proposals and the significant amount of data already available to support them cannot be described here. However, since increased attention is being paid to disturbances in attentional, cognitive, and symbolic functions as the core disturbance in schizophrenia, these family theories have special pertinence.

Vulnerability and invulnerability concepts. Concepts defining the vulnerability and invulnerability of the child to specific family influences must be developed. The influence of the family therapy movement has emphasized the enormous impact of family process on all family members—its capacity to induce a remarkable series of disturbances from ulcerative colitis to severe depression to delusions in adults and children. Even family therapists, who are presumably otherwise healthy, experience profound, though transitory, psychic disturbances when working with families. Thus, it has been assumed that any member of the family—at any age—can be radically changed through participation with his family or by joining another. However, a shift to a joint focus on the family and the individual must reveal that an individual's development is subject to many influences other than that of his family, and it remains reasonable to assume that the major impact of his family on permanent characteristics of the child's personality may be restricted to certain particularly vulnerable periods of his development.

Some family researchers will argue against this shift of focus back to the individual and to the redefinition of family variables as those acting on him from without. They will say that the unique contribution of the family approach is to recognize that the individual's behavior is understandable only as a manifestation of the group's function. The paper by Waxler in this issue exemplifies this point of view. We would argue that the two points of view are not mutually exclusive by making a distinction between variables that maintain family interaction patterns and family variables that influence individual development.

Consider Waxler's argument in this issue: She presents evidence indicating that the family subtly encourages deviant behavior in one of its members because the deviant behavior helps the family develop a sense of identity by clarifying its norms. Deviance of the individual serves to maintain family behavior patterns, which in turn encourages continued deviance. This cycle is familiar to biologists who are used to thinking about feedback and homeostasis. In families, this homeostatic process is responsible for maintaining and sustaining the deviance-producing patterns of family interaction at a fairly consistent level. However, it is entirely logical to ask, What is the impact of this kind of family cycle on the development of its offspring? This problem can be represented by the diagram in figure 2, which is a specification of the more general analytic scheme illustrated in figure 1. Since the cycle operates to maintain deviance-producing family interaction patterns at a fairly stable level, this aspect of the function of the cycle can be represented by the magnitude of the deviance-producing behavior itself. This magnitude represents the level at which the feedback control mechanism is set. For example, consider a family system made up of a thermostat, a furnace, and a room whose temperature is registered by the thermostat. If we want to know the variables that maintain room temperature, we will study the feedback control functions of the three-member system. We may also wish to study the variables that influence the developmental history of the furnace, considered individually. A helpful approach is consideration of the mean ambient temperature of the room as an index of the level at which the feedback system operates and assessment of its impact on the furnace. A feedback system set at a high level will lead to impaired develop-
Figure 2. The family as a deviance-producing system and the effect on the deviant member.¹

![Diagram](image)

ASSESSMENT OF FAMILY AS DEVIANCE-PRODUCING SYSTEM

- **Early**: Requirement for norms of deviant behavior of "patient" → Assessment of family as deviance-producing system
- **Later**: "Normal" family behavior → Stable pathologic outcome

¹ An adaptation of the conceptual scheme illustrated in figure 1 to show how Waxler's homeostatic theory of deviance in families might influence long-term development of a relatively stable pathologic outcome in the child.

Unquestionably, a major impetus for biologic investigations of schizophrenia is now being spurred, and will continue to be in the immediate future, by the explosion of knowledge in two related fields: cell biology and neurobiology. In combining the basic findings from both these fields, one can imagine that the schizophrenia story may eventually be told entirely in biologic terms. Beginning with a precise specification of the schizophrenic genotype, it will be possible to give account of a specific sequence of events beginning in the cell, with specific nucleic acid sequences conveying certain information through transfer RNA to specific enzyme-cofactor-substrate systems in the nerve cell. At this point, neurobiology will take over to explain how such systems regulate synaptic functions. The specific defects along this train of reactions in schizophrenia will be mapped out and perhaps anatomically located in a specific brain system. Once the chain of events has been traced this far, it will be possible to estimate the impact of deficits in this neurobiologic system on the neurobiologic systems controlling perceptual, associative, and motor functions. The biologic characterization will surface only at the "last minute," at which point specific neurobiologic end states can be connected directly with the primary symptoms of schizophrenia. Where in this complex causal chain might family variables have an impact? Might the family boundary act as an additional controlling factor for enzyme synthesis? Does maternal-infant fit operate to influence these brain functions? The absurdity of these inapposite propositions raises a very real specter: an immense, creative surge of interest in cellular biology and neurobiology may lead to a series of models of schizophrenia where family variables are excluded a priori.

The old-fashioned concept of stress might be resurrected to accommodate observations that show that the family, after all, plays some role in the "evocation" of schizophrenia if not in its "fundamental etiology." Family strife of various kinds, like other social stressors, will—by well-known mechanisms—influence various endocrine systems that, in turn, modify the fundamental gene-enzyme-synapse chain. However, if after decades of conscientious research family researchers can't get into the schizophrenia model except through this hand-me-
down path of "stress," they might as well hang up their spikes right now. If the etiology model is constructed in this way—that is, by positing a chain of cellular events unbroken by nonbiologic elements until the "ultimate effects," the symptoms of schizophrenia—then family and other social variables will be excluded and true interdisciplinary research will be impossible.

We suggest a different approach to model building and experimental design. The aim of this approach is to conduct simultaneous and coordinated studies of the possible joint role of family and biologic variables as they may interact at various stages of the psychopathological chain of events underlying schizophrenia. We suggest this overall approach be followed until the time that one or both sets of variables clearly appear not to be etiologic. Our approach has two phases. In the first, a loosely defined population of schizophrenic patients is divided into more strictly defined subsets. In the second, specific quasi-experiments and true experiments are designed to assess the relative role of biologic and family variables in the etiology of the disorders in these subsets.

Defining Specific Subsets

The study of schizophrenia has been bedeviled by the problem of definition. Despite stringent attention to the problem of diagnosis it is, as yet, impossible to define a sharply demarcated set of individuals who can sensibly and universally be regarded as schizophrenic. Thus, when correlations between schizophrenia and possible etiologic variables are reported from two or more separate studies, it is always a matter of some dispute whether the findings are comparable. Even schizophrenic patients whose descriptive symptomatology is similar may have different courses and may have suffered from different etiologic conditions. The aim of the first step in our model-building strategy is to reduce the heterogeneity of schizophrenia by forming subsets of schizophrenic individuals; each subset would be similar not in descriptive symptomatology, but in the putative underlying psychopathologic process by which the illness was produced. The first step is to develop a set of variables that showed a high likelihood of being etiologic in previous studies. Such a list might include a family variable, such as impermeable family boundary, and a biologic variable, such as reduced platelet monoamine oxidase. These variables can then be used to segregate subsamples. (For example, a subgroup of schizophrenics that has abnormally low platelet monoamine oxidase would be defined.) No matter what variable is used to define the subgroup, the following criteria for definition should be met:

- The abnormal variable occurring in the subgroup must clearly distinguish that subgroup from the normal population, including nonhospitalized individuals without psychopathology and individuals ill and/or hospitalized for nonpsychiatric conditions.
- The abnormal variable should distinguish this subgroup from most, but not necessarily all, of the non-schizophrenic psychiatric population. A small segment of the latter might also show the abnormality. This nonschizophrenic segment should itself have some symptomatic coherence (e.g., it might consist entirely of severe depressives or severe obsessives); it would, at least provisionally, be regarded as having the same underlying psychopathologic process as the affected group of schizophrenics.
- Presence of the abnormal variable should be demonstrated repeatedly in the same subgroup, and a systematic effort must be completed to rule out the effects of obvious artifacts (e.g., dietary and pharmacologic factors).

Conducting Multifactor Studies

A systematic approach is presented here for designing and interpreting multifactor studies used in testing the etiologic effects of combined biologic and family variables. Figure 3 illustrates this approach, which emphasizes the joint examination of at least two potential variables (x and y).

There are four steps involved in designing and interpreting multifactor studies.

Step 1

At some point in the study, both variable x and variable y must be shown to occur prior to the onset of
the schizophrenic illness. Longitudinal studies may be useful here, although more inferential data may also be used. For example, if we can show that it is very likely that the biologic variable is inherited and that there are no known environmental factors that raise or lower it, we may assume its occurrence prior to the onset of the illness.

**Step 2**

It is also important to show that neither the family nor the biologic variable is confounded with another variable equally likely to be etiologic. For example, the family variable must be independent of social class.

**Step 3**

If prior causation is substantiated and confounding is ruled out, then the following inferences are possible from multifactor studies:

- If abnormal variables x and y are present in a subset of psychiatric patients and absent in the normal population (figure 3b), then either or both are likely etiologic factors for that patient population; the difference between schizophrenia and nonschizophrenia remains unexplained and is presumably caused by a third variable, as yet unknown.
- If abnormal variable y is restricted to the subset of schizophrenics among the patient population defined by

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**Figure 3. Subsets of psychiatric patients based on abnormal family and biologic variables.**

a. A simple case in which abnormal variable x is held in common by a subset (subset x) of schizophrenic and nonschizophrenic patients.

b. A condition in which two abnormal variables, x and y, define a mixed subset of schizophrenic patients, suggesting that neither alone nor together can x and y explain the appearance of schizophrenia.

c. A condition in which variable y defines a subgroup of subset x; if other criteria are met, y may be assumed as critical for converting members of the subsample x into overt schizophrenic patients.

d. A situation in which variable x and y are both required to produce schizophrenia (as in 3c), but in which y alone—shared with a percentage of the normal population—would not produce any pathology.

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1 With x designated as a biologic variable and y as a family variable, or vice versa, this figure shows:
abnormal variable x (figure 3c), it is probably interacting with variable x to produce schizophrenia; variable x alone is not sufficient.

- If variables y and x intersect (figure 3d), then it is likely that variable y alone is insufficient to produce psychopathology. However, if y interacts with variable x it will produce schizophrenia. Variable x alone is also unable to produce schizophrenia but is sufficient by itself to produce psychopathology.

**Step 4**

As a fourth step, these multifactor designs should be enhanced by the strategic use of specific, elementary psychological defects. There is a long and rich history in schizophrenia research of attempts to define the psychological deficit from which all surface manifestations of the illness can be derived. For example, many investigators have explored a basic deficit in the process of set and attention (Buss and Lang 1965 and Shakow 1962); others have studied modes of psychological representation and stimulus control (London 1973a and 1973b and Silverman 1967); still others have investigated memory. In our strategy, we would suggest that a core psychological deficit be defined for patient population x (the subgroup of patients with abnormal variable x). In many studies, this will permit us to replace the presence or absence of schizophrenic symptoms as the dependent variable with more elementary psychologic functions. For example, suppose we found that patient population x could be differentiated from other patients and normals by a specific attentional deficit and that this attentional deficit could explain both the more complex and the surface symptoms observed in these patients (associational difficulties, confusion, withdrawal, and delusions). We could then design studies that examined the joint effects of variables x and y on this specific attentional deficit. Advantages of this particular strategy are:

- It permits the integration of specific studies on the etiology of schizophrenia with a complex and rich net of other psychologic and psychobiologic studies. For example, investigators are already acquiring information on many biologic correlates of attentional and memory processes (Callaway, Jones, and Layne 1965 and Warburton and Russell 1968). Psychic representational processes can be related to a wide variety of studies in cognitive psychology and psychoanalysis (London 1973a and 1973b).

- The use of elementary psychological variables in multifactor designs permits the reintroduction of animal models into the study of schizophrenia. Animal models have not been particularly useful as analogs of schizophrenia per se; what is the animal equivalent of an associational defect or a hallucination or an idea of reference? Satisfactory animal models do exist, however, for the study of attention and memory.

- The use of elementary psychological variables permits the reintroduction of true experiments into the set of studies on the etiology of schizophrenia. As we have already pointed out, an experimentalist cannot hope to produce schizophrenia in the laboratory, but he can, in carefully controlled experiments, observe the impact of a variety of variables on attentional and cognitive performance. Reiss (1971), for example, was able to experimentally control the exposure of individuals to the interaction of their families; in some families, this exposure produced a short-term deterioration of cognitive performance.

**Summary and Recommendations**

Our recommendations for combining biologic and family variables can be summed up as follows:

1) We favor multifactor designs wherever possible, with at least one biological and one family variable among the set of two or more independent variables.

2) We favor the more frequent use of elementary psychological variables as dependent variables in addition to the symptoms of schizophrenia per se. These may include attentional variables, stimulus representational variables, short-term memory variables, and cognitive variables.

3) Biologic variables need not be modified from present studies and can certainly include genotypes, enzyme levels, and peripheral indicators of neural functioning such as the evoked response.

4) We have formulated a number of requirements for the family variables:

- There should be evidence that they have a specific toxic effect likely to produce or to contribute, along with other variables, to a schizophrenic outcome or, even more desirably, to the elementary psychological variables whose deficit might constitute the core of schizophrenia.
There should be evidence that the individual has had *sustained exposure* to the specific, toxic variable during a vulnerable period in his development.

A variable must be adequately specified by a *clear operational definition*: it must be distinguished from similar variables and defined by its functional relationship with other family variables.

Wherever possible, variables should not be measured by content analysis; rather, they should be assessed through their *functional impact* on other family behavior (e.g., the referential communication task).

**References**


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