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Early Detection and Prevention
of Behaviour Disorders

Editors S. A. Mednick, F. Schulsinger, B. Bell, P. H. Venables and
K. O. Christiansen

# Genetics, Environment and Psychopathology

S. A. Mednick,
F. Schulsinger,
J. Higgins and
B. Bell
Editors

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Genetics, Environment and Psychopathology

NORTH-HOLLAND RESEARCH SERIES ON EARLY DETECTION AND PREVENTION OF BEHAVIOUR DISORDERS

VOLUME I

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P C

Genetics, Environment and Psychopathology

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1974

In 1962 the Psykologisk Institut began a program of research aimed at the early detection and prevention of mental illness. Theoretical and methodological considerations led us to initiate a series of studies using what has come to be called the "high-risk" method. This work with high-risk samples grew from our dissatisfaction with the concentration of research on individuals already schizophrenic, most often chronic. In 1962, we defined a population of 207 children of schizophrenic women (high-risk sample) and 104 controls (low-risk sample). These 311 subjects were intensively examined and preparations were made in the Danish registers to follow them. In 1965, a social worker was sent to interview the subjects in their homes. As a function of the results of this interview and reports from registers on hospitalization and treatment for mental illness, in 1967, we defined an initial population of 20 psychiatric breakdowns all stemming from the high-risk group.

Among the important variables which differentiated these breakdown subjects from controls were perinatal, early maternal separation, psychophysiological, and verbal associative factors. The perinatal factors were unexpected and were related empirically to the psychophysiological abnormalities found in the breakdown group. We determined to establish a new high-risk group with more systematically gathered perinatal data. We were invited by a group led by Professor Preben Plum of Copenhagen's University Hospital (Rigshospitalet) to take part in their large perinatal project encompassing 9006 consecutive deliveries between September 1, 1959 and December 1, 1961. For each delivery were coded the social circumstances, pregnancy, delivery, neonatal condition and results of a medical, developmental and neurological examination at one year of age.

In view of the central importance which psychophysiological factors had now assumed in this high-risk work, Professor Peter H. Venables joined as an active coinvestigator. (Professor Venables had been the Institut's consultant on psychophysiology since 1962.) A new assessment battery was constructed which took into account the results of the 1962 assessment, technological advances in the field since 1962, and recent research findings with schizophrenics. Samples of children with schizo-

phrenic, mixed psychiatric and normal parents were chosen from the cohort of 9006 whose perinatal data were available from the Plum group.

In 1972, we began an extensive reassessment of the original 1962 high-risk project subjects. At that point they ranged between 20–30 years of age. An important goal of this reassessment was the establishment of a reliable diagnosis (where appropriate) and an evaluation of their current life status. This assessment included psychophysiological and cognitive tests, a social interview, and a battery of diagnostic devices. The diagnostic devices included a 31/4 hour clinical interview by an experienced diagnostician, an MMPI, which provided an independent objective diagnosis, and the psychiatric hospitalization diagnoses and records. The diagnostician completed the Spitzer and Endicott Current and Past Psychopathology Scale (CAPPS) and Wing's Present Status Examination, 9th Edition (PSE), both computer-scored interview schedules, and also made clinical diagnoses.

We are currently working on the assessment of the reliability of the interview results and the relating of life history and personal characteristics to the current diagnoses. Preliminary analyses already reveal that certain psychophysiological measures could form a part of a battery which might be used in the early detection of schizophrenia-prone individuals.

Research on primary prevention
In 1968, the Institut was invited by the World Health Organization to undertake high-risk research in Mauritius. We seized this opportunity to investigate three questions:

(1) What possibilities and difficulties does large scale screening for psychophysiological deviance hold for early detection of high-risk individuals?

(2) What are the developmental and behavioral correlates of psychophysiological deviance?

(3) Having identified high-risk populations (psychophysiologically), what possibilities exist for reducing the probability of their later suffering breakdown (so-called primary prevention)?

In Mauritius, Mednick, Abdool Raman, Schulsinger, Brian Sutton-Smith and Peter H. Venables completed an intensive half-day exam-

ination of 1800 Mauritian 3 year-old children. The psychophysiological aspects of the assessment were directed by Venables; Dr. Brian Bell directed the laboratory in Mauritius. We have established two whole-day nursery schools in Mauritius and have selected 200 psychophysiologically deviant children and controls (from the 1800) to take part in the nursery schools and to be community controls. Arrangements have been made with the Mauritian government to follow these 1800 children through the school system and beyond.

The Institut is cooperating with the Schizophrenia Research Center of the Alcohol, Drug Abuse and Mental Health Administration, United States Public Health Service, and the European Regional Office of the World Health Organization in organizing an international conference in Copenhagen in the coming year to consider scientific and ethical problems in primary intervention with high-risk groups. We plan to seek the advice of the conference-participants for guidance in our intervention work in Mauritius.

The adoptee register
A large section of this volume is devoted to work on the role of genetic factors in the etiology of psychopathology. All of this work using adoptee samples was initiated by Seymour S. Kety, David Rosenthal and Paul Wender who encountered difficulty in carrying out their research designs in the U.S. They came to the Institut to work with Fini Schulsinger on the genetics of schizophrenia because of the favorable research climate which Denmark offers. With the support of NIMH grants to these four researchers, a register of over 14,500 non-familial adoptions has been assembled. Through the positive cooperation of Kety, Rosenthal, Wender and Schulsinger, studies have also been completed with this register on the role of genetic factors in psychopathy, alcoholism and criminality.

Transgressive behavior
In addition to mental illness, a considerable number of the 1962 high-risk subjects evidenced asocial behavior. Since 1972 the Institut has developed an increasing interest in such transgressive behavior and has completed projects investigating the interaction of psychophysiological and familial-milieu factors relating to recidivistic asocial behavior.

The Institut is now planning a second volume of research papers: this volume will include detailed reports of the Mauritius project together with a consideration of our current research into transgressive behavior.

Copenhagen,   S.A.M.
28 April 1974   F.S.
                                                                    J.H.
                                                                    B.B.

ACKNOWLEDGEMENTS

This book brings together a number of studies conducted at the Psykologisk Institut in Copenhagen over the past decade. A large number of people have, over the years, generously contributed not only their knowledge and skills but also their enthusiasm.

A number of the papers in this volume are reprinted by kind permission of the original publishers.

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Part I. Some Methods of Behavior Genetic Research in Psychopathology

Part II. A High-Risk Project

Some methods of behavior genetic research in psychopathology

This section is devoted to the description of and rationale for two approaches to research into the etiology and prophylaxis of psychopathology. The first of these, discussed by Mednick and McNeil, is the longitudinal study of groups with a known genetic high-risk of psychopathology in order to determine relevant antecedent factors in morbidity. The second, presented by Rosenthal, is the study of adopted subjects together with their biological and adoptive families as a means of unconfounding genetic and environmental contributions to psychopathology.

CURRENT METHODOLOGY IN RESEARCH ON THE ETIOLOGY OF SCHIZOPHRENIA: SERIOUS DIFFICULTIES WHICH SUGGEST THE USE OF THE HIGH-RISK-GROUP METHOD*

SARNOFF A. MEDNICK and THOMAS F. McNEIL

Mednick and McNeil critically review research utilizing patients, patients' families and patients' chilhood records. They recommend the longitudinal study of high-risk samples as a superior alternative.

Schizophrenics excite a good deal of behavioral research. The goal of much of this research is to produce information concerning the etiology of schizophrenia. It may be difficult, however, to isolate etiological factors through studies carried out with individuals who have lived through the process of becoming and being schizophrenic. The behavior of these individuals may be markedly altered in response to correlates of the illness, such as educational, economic, and social failure, prehospital, hospital, and posthospital drug regimens, bachelorhood, long-term institutionalization, chronic illness, and sheer misery. In research with nonschizophrenics, these same factors have been shown to measurably affect behavioral research results. If researchers used control groups which were equated with their schizophrenic groups for all of these correlates of schizophrenia, then any observed differences could be reasonably ascribed to the variable of schizophrenia. But such control groups are apparently not readily available. Consequently, in comparisons of normals and schizophrenics, it is often difficult to judge what portion of the reported differences have unique relevance to schizophrenia. If, for example, comparisons of nonpsychiatric prisoners

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and normals produced differences identical to those found for schizophrenics and normals, we might tend to attribute the schizophrenic-normal differences to the effects of institutionalization rather than some intrinsic quality of the schizophrenic.

Variables such as institutionalization and drug effects may be termed epiphenomenal. When these epiphenomenal correlates of schizophrenia are studied for their own sake, we find that they have important effects on perception (Silverman et al., 1966), psychological adjustment (Knupfer et al., 1966), family harmony (Crain et al., 1966a, 1966b), personality tests (Braginsky et al., 1966), and interview data (Pokorny, 1962). Yet, almost no research on the schizophrenic takes these consequents into account when planning for a control group. Because of this, most research on schizophrenics runs a great risk of ascribing results to the variable of schizophrenia when actually some part of the differences observed may be due to one or more of this myriad of consequents.

For example, in discussing a study in stimulus generalization, Mednick and Freedman (1960) stated, "Using the dimension of space [he] found that schizophrenics generalized more than normals." Mednick, implying that generalization is important in etiology, neglected to consider the fact that his schizophrenics had been hospitalized 119.05 months while his normal control group had been hospitalized only 2.18 months. In this manner, while attempting to study some aspects of schizophrenia, Mednick could have been, unwittingly, chiefly investigating the effects of long-term institutionalization.

Three research methods

Most psychological and psychiatric research on the etiology of schizophrenia takes one of three forms: (a) observation of already schizophrenic individuals, (b) observation of the families of schizophrenics, or (c) inspection of earlier records reporting on childhood behavior of adult schizophrenics. We shall discuss the methodological problems of each of these approaches.

Observation of already schizophrenic individuals

This method is the most common one. Typically, the subjects are patients in mental hospitals, as in the Mednick example above. Since institutionalization is the most common and easily defined offender, let us begin by examining evidence that differences ascribed to diagnosis might at least in part be attributable to institutionalization.

Almost all schizophrenics whose behavior is summarized in our journals are originally found in hospitals. A survey of five recent volumes of the *Journal of Nervous and Mental Disease*, the *Journal of Abnormal Psychology*, and the *American Journal of Psychiatry* showed that 63% of some 115 empirical studies which compared schizophrenic with schizophrenic or schizophrenic with normal, did *not* provide information on the length of hospitalization of their subjects. The other 37% noted that their chronic or process schizophrenics had been hospitalized for an average of 7.1 years and the acute or reactive subjects had been hospitalized for an average of 2.3 years. In almost all cases the normals were not hospitalized, so that this factor was not controlled at all.

Despite the existence of great differences in length of hospitalization, the authors of these studies typically attributed their results exclusively to diagnostic group. In many cases, at least some part of the results could as easily have been ascribed to hospitalization. Let us consider two cases which demonstrate this point.

Silverman (1964), using the Titchener and Pettigrew apparatuses, demonstrated that normals, acute schizophrenics, and chronic schizophrenics (in that order) tend to evidence increasing severely restricted perceptual scanning and narrow concept width. As might be expected, his three groups differed substantially in duration of hospital stay. Concerned, and wishing to evaluate the effects of institutionalization, Silverman et al. (1966) took the unique step of repeating the same two tests used on the schizophrenic subjects on 50 long-term and 50 short-term nonpsychiatric prisoners, all felons. (They roughly equated the prisoners and schizophrenics for length of institutionalization.) They found that the differences observed on these conceptual and perceptual measures among the normals and "acute" and "chronic" San Quentin inmates were almost precisely the same as those among the normals and acute and chronic schizophrenics. The mean scores for the im-

prisoned and the hospitalized were highly similar.

> The failure to observe noteworthy differences between them (referring to the schizophrenic vs. the prisoner groups) on the Titchener Illusion and on the Pettigrew Category Width Test indicated that exaggerated performances on these procedures are not pathognomic of particular subtypes of schizophrenia ... comparable response patterns may be found among nonschizophrenics who live in a similar environment (p. 656).

Thus, the results of the first Silverman study, originally ascribed to the effects of schizophrenia, could conceivably be completely attributed to the fact that the groups had resided in hospitals for different numbers of years.

In addition to the *effects* of being hospitalized, there seems to be some selection among those who frequent particular hospitals, in this case, Veterans Administration hospitals. Gladis and Wishner (1962), noting a series of studies "suggesting that schizophrenics are peculiarly sensitive to aversive content," conducted a verbal learning study employing aversive and neutral learning materials. As they had hypothesized, the VA hospitalized schizophrenics showed much more relative sensitivity to aversive material than did the control subjects (evening college students). However, Gladis and Wishner also took the precaution of including a control group of VA surgical and medical patients. The results for the schizophrenic and surgical and medical (nonpsychotic) VA groups were virtually identical.

> It is worth emphasizing that if only schizophrenic (hospitalized) subjects had been employed one might have been willing to conclude that the results obtained support a hypothesis previously mentioned, namely, that schizophrenics are uniquely sensitive to aversive stimulus characteristics in the environment. The markedly similar performance of the nonpsychotic subjects strongly suggests that Veterans Administration hospital status and not diagnostic label was the relevant factor in this study (Gladis and Wishner, 1962, p. 254).

The Silverman et al. and Gladis and Wishner studies suggest that testing hospitalized patients can bias learning, perception, and thinking measures independently of diagnostic group. In their studies, hospitalization seemed to be the basis for differences they observed between schizophrenics and nonschizophrenics. The effectiveness of mental hospital life in influencing the behavior of inmates has been documented by Goffman (1961) and Belknap (1956). There are at least two ways that hospitalization might affect research results. It might (a) alter the patient's attitude and personality and, in turn, produce changes in

our test measures, or (b) the patient may simply bias his responses to our tests in terms of some personal motive related to his hospital career.

With respect to personality alteration effects, Sommer and Hall (1958) have given evidence relating to the personality changes engendered by an institutional setting. A scale of alienation was administered to admission ward, active treatment, and continued treatment (chronic) patients as well as to hospital physicians. The chronic patients were significantly more alienated than either the admission ward or active treatment patients. Most surprising was the finding that the hospital physicians were significantly more alienated than were the admission ward patients. One possible interpretation of these data is that institutionalization influences scores on this psychological research instrument more than does schizophrenia.

The hospital patient facing an investigator may slant his responses in a direction favoring a specific goal, such as discharge. This would be an example of the second way hospitalization can affect research results. Dunham and Weinberg (1960) have observed that:

> Since discharge is the highest value among patients, especially in the hopeful wards, certain general practices emerge. These behavioral acquisitions, as peculiar hospital products, take the form not only of external conformity, but of concealment of delusions and even hallucinations, provided the patients can control them. Many patients even consider improvement as subsidiary to discharge from the hospital (pp. 89–90).

Furthermore, Dunham and Weinberg indicated that patients seeking discharge see all of their behavior as being related to this goal. As one patient stated, "I try to do my best around here. I run errands and do anything to help the hospital. I figure that it may help me get back to the doctor and it may help me to get out of here" (p. 104). Braginsky et al. (1966) have empirically demonstrated the decided effect which hope or fear of discharge can have on questionnaire and paper-and-pencil research. Chronic and acute patients (mostly schizophrenic) shifted their scores on a group of MMPI test items in accordance with whether they thought their performance would help them get out of the hospital or remain in it. The chronic patients slanted their responses so as to appear sick, while the acute patients "faked" in the direction of greater health. Had the experiment not been studying response biases but rather differences between the chronic and acute groups on the MMPI items, the differences which were found would have typically been attributed to some less superficial cause. Gordon and

Groth (1961) have shown the influence of this same variable on the semantic differential. They found differences on semantic differential ratings between patients who wanted to remain in the hospital and those who wished for an early discharge. Again we must ask, to what extent does response slanting produce differences reported between acute and chronic schizophrenics and normals? On the other hand, how often have such pervasive attitudes produced response biases that have contributed only extreme variance to research results?

Zarlock (1966) observed a related phenomenon with patients in recreational, occupational, social, and medical situations. Each of these situations was set up with the same research personnel except that in the medical situation, the personnel wore white coats and nurses wore uniforms. He tape-recorded conversations and observed physical behavior. Instances of pathological verbal behavior were judged from typescript of the tapes; bizarre physical behavior was rated in the actual situations. The bizarre and pathological behavior was at least 10 times more frequent in the medical situation than in the other three situations and ranged up to 100 times more frequent. Zarlock (whose study would have been improved by the inclusion of normal control groups) suggested that the white coats *demanded* deviant behavior in the schizophrenic patient. In any case, this study raises serious questions regarding the reliability and the interexperimenter generality of the behavior we observe and report. To what degree do differences between schizophrenics and normal controls depend on whether the investigator wears a white coat?

Shakow (1946) and his Worcester co-workers have long recognized the need to understand the response of the patient to the experimental situation. Indeed, a member of this group, Rickers-Ovsiankina (1937), carefully chose as controls

> institutionalized individuals such as inmates of state infirmaries, who in general, live according to a routine similar to that of our patients. Twenty-five of them were destitute and the rest were suffering from some form of chronic illness, such as arthritis, cardiac conditions, neuritis, etc. (p. 157).

Differences she reported between her control and experimental samples are less likely to be ascribable to hospitalization effects.

Observations of families of schizophrenics

Let us consider another research area, the family. Fontana (1966) has carefully evaluated the methodology of research dealing with the "familial etiology of schizophrenia". He divided the studies into three groups: (a) clinical observations from treatment situations, (b) retrospective accounts from interviews, and (c) current family interaction recorded directly by the investigator. He dismissed the clinical approach – while of value for insights and hypotheses, "intrinsic difficulties make it unsuitable as a firm basis for a scientific methodology." With respect to retrospective studies, it seems clear that parental recollection data are too unreliable to serve as scientific evidence. The evidence (cited by Fontana) for distrusting the validity of historical parental reportage is decisive. Further confirming evidence can be found in Mednick and Schaffer (1963), Hefner (1962), and Hefner and Mednick (1969).

Fontana raised the problem of the "etiological assumption" which forms the basis of family studies of schizophrenia. This assumption states that disturbed family processes had a role in the development of schizophrenia. It is just as reasonable to assert the obverse of this assumption: The serious illness of the schizophrenic as a child or adolescent had a role in the development of family disturbance. Fontana did not present evidence which might help us choose between the alternative assumptions. There is some indirect evidence. In general, it suggests that

> patterns of parent-child relations similar to those we find in schizophrenia have been described for several other types of illnesses, manic-depressive psychosis, ulcers, and anorexia nervosa as well as for juvenile delinquency and drug addiction (Kohn and Clausen, 1956, p. 312).

Indeed, maternal overprotection and elevated family conflict have also been reported for the parents of diabetics (Crain et al., 1966a, 1966b), hemophiliacs (Mattson and Gross, 1966), infantile paralytics (Rosenbaum, 1943), and children with scoliosis and osteomyelitis (Kammerer, 1940). In these cases it seems likely that the overprotection and marital conflict were results rather than a cause of the disease. This suggests the use of control groups consisting of families with a chronically ill child. Illustrating the importance of this, Pokorny (1962) studied the family background of schizophrenics but used the families of

tubercular patients as controls. He found no evidence of differences between these groups in "completeness of family life" or "security of childhood." (He did note some differences in other areas.) Klebanoff (1957) compared the mothers of childhood schizophrenics with the mothers of normal children on the Parent Attitude Research Instrument and found the usual tendency for the mothers of schizophrenics to have more pathological attitudes than mothers of normal children. There was no difference, however, between the mothers of the schizophrenic children and a control group consisting of mothers of hospitalized brain-injured and retarded children. Klebanoff stated that his results support the hypothesis that "pathological attitudes observed in the mother arise as a result of the stress of trying to deal with the disordered child." Nameche (see Ricks, 1967) has presented evidence that the family with a to-be-schizophrenic child suffers progressive deterioration before the onset of the illness. Studying families of individuals already schizophrenic may generate new methodology and hypotheses; however, because of the apparent heavy influence of the illness on the families' responses, extreme caution must be employed in asserting cause and effect relationships. As stated by Fontana (1966), "The greatest value of current studies of family interaction seems to lie in the guidelines the findings might provide for longitudinal research."

These arguments are not presented to discredit the hypothesis that family structure and interactional patterns may be etiologically important in schizophrenia. They instead suggest that in studying the family of an individual already schizophrenic, we may be hard-pressed to separate etiological factors from family reactions to the illness.

But institutionalization and families' reaction to their children's severe illnesses are not the only factors that influence research in an uncontrolled manner. We must face the fact that we are studying individuals who, in comparison to their controls, have had less sexual experience and less marriage, lack occupational success, have been exposed to prehospital, hospital, and posthospital drug regimens, are educationally disadvantaged, and often have suffered lives of chronic illness and sheer misery and loneliness. While some of these factors could be considered contributory causes, they are certainly also *consequents* of the schizophrenic condition. These consequents of the schizophrenic condition heavily shade and quite often completely overshadow our attempts to examine the origins of schizophrenia.

If we are to continue to study the etiology of schizophrenia through individuals already schizophrenic, there are only two choices: (a) We must obtain adequate controls. These controls must match our schizophrenic subjects for the usual factors plus extent of institutionalization, presence of severe and chronic illness, educational level and achievement, sexual and marriage history, occupational success, past and present drug regimens and misery and loneliness. (b) The second would eliminate the contaminating variables from consideration by establishing the effects of these variables on the specific measures to be used in a given investigation. After the Silverman et al. (1966) findings, anyone who would study some aspect of the perceptual behavior of hospitalized schizophrenics who did not first evaluate the effects of institutionalization on his measures would be laying himself wide open to the danger of spending his time unproductively. Research measures that survive this kind of evaluation can be said to have a much higher likelihood of being related to the etiology of schizophrenia. Either of these alternatives may prove difficult to effect. A way of overcoming the difficulties inherent in studying individuals already schizophrenic may be to study them *before* they become schizophrenic. Two methods may be found in the literature, the childhood records method and the high-risk-sample method.

Childhood records method

The childhood records method studies school, child guidance clinic, or birth records of individuals now schizophrenic. This method has been used quite successfully by many investigators (Albee et al., 1964; Birren, 1944; Nameche et al., 1964; O'Neal and Robins, 1958; and many others). This method has the great advantage of evaluating records produced by individuals ignorant of the eventual schizophrenic condition of their charges. The information, at the time it was inscribed, was relatively current, not retrospective. The subjects on which the study focuses are all schizophrenic. (For a more complete discussion of this method see Ricks, 1967; Roff, 1967). Along with these advantages come some problems. The records are produced by different individuals with differing vocabularies. If one therapist calls a patient "nervous" is this equivalent to what another terms "tense"? The information is not complete and systematic. If a child is not explicitly called "nervous"

does this mean he was not nervous or that the therapist saw no gain in mentioning this factor in his case report? When working with 20–30 year-old case records, one must take what one finds. One must be very lucky to find, in these data, information which tests hypotheses of interst to the researcher.

Perhaps the most serious shortcoming of the childhood records method is the danger of disabling sampling biases. Since this problem is difficult to explain in the abstract, it will be discussed in relation to a study by Albee et al. (1964). This study is part of a series of studies; this example was chosen because of the methodological sophistication of the authors. This study selected schizophrenics hospitalized "in the Cleveland area" who had attended second grade in Cleveland. The elementary school IQ scores for the schizophrenics were then compared with the IQ scores of their elementary school classmates and found to be lower. It is important to note that the schizophrenics were apparently lifelong residents of Cleveland; the only direct information on the mobility history of the control group is that they resided in Cleveland when they attended elementary school. Approximately 4% of the Cleveland population migrates out of that area each year. From figures available, it could be conservatively estimated that over the period of time covered by the study, 50% of the original control group had already moved from the Cleveland area (Lansing and Mueller, 1967). None of the schizophrenics had moved out of the area; thus, the two groups differ markedly not only in diagnosis but also in mobility. Mobility has been shown to be directly related to IQ (Gist and Clark, 1938; Maxwell, 1954) and educational and social class level (Lansing and Mueller, 1967). In view of the finding that disturbed individuals evidence greater mobility than nondisturbed individuals (Robins and O'Neal, 1958), it seems clear that the Albee et al. study selected a very special subgroup of nonmobile schizophrenics. The more mobile schizophrenics who had left the Cleveland area (and were consequently included in the "control" group) were very likely to have scored higher on IQ tests in second grade. This sampling bias might explain at least part of the reported 11-point IQ score differences between the controls and hospitalized schizophrenics. It seems possible that any selection from the third grade population of a subgroup which was nonmigrant (i.e., still living in the metropolitan statistical area of Cleveland) would have been biased toward a lower IQ test score. In

view of the large population turnover in the United States and the very special characteristics of this migratory group, the results of much of the childhood records research must be evaluated with caution. To avoid this sampling bias, one must begin with a large school population and trace *all* the pupils to find which had become schizophrenic. Without a national psychiatric register, this would be a difficult undertaking. Despite the difficulty, Robins (1966) has completed a surprisingly complete follow-up in the St. Louis area. Another approach might be to compare the nonmobile schizophrenics with a local control that was also nonmobile. Again, Robins (1967) has studied antecedents of character disorder in this manner. This would inform us regarding the preschizophrenic condition of the nonmobile schizophrenic. In view of the relatively high schizophrenic rate among migrants and the high migrant rate among the disturbed (Robins and O'Neal, 1958), generalization from such a nonmobile population could only be done with caution. Thus, while the childhood records method avoids the problems encountered in studying the schizophrenic, this method also has some potentially serious drawbacks.

We have made three points:

(1) Schizophrenics may be too "contaminated" by the consequents of their illness to be suitable subjects for research on the etiology of schizophrenia.

(2) The family with a child schizophrenic has been changed by the experience so that it is difficult to assess the original role of this family in the development of the illness.

(3) The childhood records method has many important advantages but often suffers from serious sampling problems as well as data insufficiencies at the source.

The high-risk-group method

These points emphasize the difficulty of developing etiological findings from studies based on individuals already schizophrenic.* In our

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* These criticisms are leveled specifically against research with schizophrenics. The applicability of this criticism to etiological research in other mental disorders may not be difficult to envision. We cannot, in fact, completely rule out the possible applicability of this line of argument to some correlative research in individual differences and personality development.

own reseach [...], we have turned almost completely from the study of the patient to the longitudinal study of young children at high risk for schizophrenia, children who have chronically and severely schizophrenic mothers. [...]

Advantages

There are certain methodological advantages in the longitudinal study of high-risk samples.

(1) The subjects are not yet schizophrenic; they have not experienced the epiphenomena of the illness. Thus, their reactions on our tests are not heavily colored by these epiphenomena.

(2) The researchers, relatives, and the subject himself do not know that he will become schizophrenic. This relieves the data of a certain part of the burden of bias. The bias is certainly not greater for the future schizophrenic than for other high-risk subjects who do not succumb to schizophrenia.

(3) The information gathered is current, not retrospective. That part of the investigation which is retrospective is less so than it would be if the subjects were adults.

(4) The data are uniformly and systematically obtained. This is in contrast to retrospective studies which make use of childhood and school records concerning adult schizophrenics.

(5) One advantage of the high-risk-group method which may not be immediately apparent is the fact that *the ideal controls for the high-risk subjects who become schizophrenic are the high-risk subjects who develop other deviancies and the high-risk subjects who do not become deviant.*

(6) There are other samples at high risk for schizophrenia but none of these fulfills the research requirements as well as the children of schizophrenics. Identical twins adult schizophrenics are too old as are siblings and parents of adult schizophrenics.

(7) Of the masses of research on the already schizophrenic there is doubtless much which does relate to etiology. Information on premorbid characteristics may be of value in culling these etiologically relevant findings. In this manner the two methods may be mutually supportive [...].

Problems

A long-term longitudinal study of a relatively large sample faces certain problems, the chief problem being successfully following the subjects. [...]

An additional problem of such a long-term study is the potential loss of key personnel. [...]

The fact that the high-risk children have at least one parent schizophrenic makes it difficult to consider their family rearing conditions as representative. However, since some portion of these children will have been raised by nonschizophrenic adoptive or foster parents or institutions, we can turn this situation to our advantage by comparison of psychiatric outcome as a function of differential family rearing conditions (Higgins, 1966).

An additional difficulty which plagues longitudinal research is the danger that 20 years later one is stuck with what could prove to be dated and trivial data. [...]

Cross-sectional high-risk-group research

We have stressed the longitudinal application of the high-risk-group method. It should also be pointed out that in situations in which longitudinal research is infeasible, the high-risk group may be studied cross-sectionally.

[...] We very carefully matched the high-risk group with a control group (no psychiatric admission in parents or grandparents) "individual" for individual on age, sex, father's occupational status, rural-urban residence, years of formal education, and institutional versus family rearing conditions. To the extent that the matching variables are relevant, differences between the high- and low-risk groups may relate to factors predisposing to mental illness, including schizophrenia. [...]

Why research on the etiology of schizophrenia is exceptionally difficult and how the high-risk-group method may be of use

We have severely criticized research into primary etiology based on

patient populations because the resulting observations are so heavily contaminated by nonprimary phenomena. The problems of research in schizophrenia actually run much deeper. Research on primary etiology is research into causes. But it is, at best, extremely difficult to securely construct unequivocal *causative* statements without *experimental* manipulation. Anything else is correlative. Experimental manipulation is the method of choice in research on the causes of disease. Thus, for example, we can inject a suspect virus into a laboratory animal and observe whether he develops poliomyelitis. That is, we can experimentally precipitate the condition and with appropriate controls unequivocally nail down at least one *cause*. This same experimental manipulation is possible for diseases such as ulcer, diabetes, and tuberculosis. For these diseases, organ systems sufficiently similar to humans may be found in laboratory animals which, within the bounds of our moral code, may be so used for research purposes.

Research in this spirit has succeeded in causing severe "behavior disorders" in lower animals, but these demonstrations have not been satisfying. For many investigators, the most important defining characteristic of the schizophrenic is his disorder of language and thought. The development of language and thought is an important defining characteristic of humans. It seems possible that schizophrenia is, at least in part, a peculiarly human disorder. If so, despite the advantage of experimental manipulation, animal research may not be the most productive avenue of study. The organ system under most serious question may not be sufficiently similar in man and lower animals.

Another line of research in this area which has used both experimental manipulation and human subjects precipitates "psychoses" by means of drugs or sensory restriction, distortion, or deprivation. While these methods offer obvious methodological advantages, their precise comparability with a naturally developing condition such as schizophrenia remains to be demonstrated. Hence an important method of choice, controlled experimental instigation of disorder, has not been freely available to investigators. This may help explain some of the frustration of research in this area.

How, then, are we to plan our strategy for research into the primary etiology of schizophrenia? The high-risk-group method, much-praised above, can be of great help but it is not sufficient; it does not involve *experimental manipulation*. We can point to maternal, physiological, and

associative variables that markedly distinguish the premorbid state of a group that later suffered breakdown, but we cannot be sure that any of these variables are, or are closely related to, primary causal agents. They certainly help define areas which should be further studied. *But correcting all or any of these deviances in our breakdown subjects [...] may not have circumvented their eventual breakdown if the breakdown sprang from inherited or acquired biochemical anomalies, early behavioral experiences, interim life experiences [...], or an interaction of all or some of these factors.* The maternal, physiological, and associative variables may only be epiphenomena of the primary etiological factors or epiphenomena of a very early undetected stage of schizophrenia. Again we must face the fact that research which does not involve experimental manipulation is correlative and has difficulty producing conclusions relating to causation.

The high-risk-group method does provide us with suggestion regarding areas worthy of exploration. A key to the exploitation of these suggestive leads lies in the italicized sentence above. The same moral code which bars scientists from attempting to experimentally manipulate the lives of humans so as to cause them to become schizophrenic would only encourage and support reasonable attempts at experimental manipulations which were aimed at reducing the incidence of breakdown. Positive results in such research would certainly warrant the construction of conclusions concerning the causes of *reduction of incidence* of schizophrenia. These results, however, would not by themselves warrant conclusions concerning the etiology of schizophrenia. (We may be able to pinpoint the administration of penicillin as a cure for an illness without detailed and specific knowledge of the cause of the illness.) However, if preventive research tells us that administration of a given drug or a given mothering experience (or combination of the two) will materially reduce the incidence of schizophrenia, we can begin to deduce causes of schizophrenia with more precision and undertake more focused and discriminating preventive research eventually leading to firmly based etiological conclusions.

The great conceptual problem facing the prospective research worker in the area of prevention is, "What justification can be found for choice of mode of intervention?" It is in this area that the high-risk-group method can make its contribution. Premorbid and experiential or personal deviancies detected in high-risk samples which have suffered

breakdown can point clearly to highly specific techniques of remedial preventive intervention (Mednick, 1965). [...]

A PROGRAM OF RESEARCH
ON HEREDITY IN SCHIZOPHRENIA*

DAVID ROSENTHAL

Rosenthal presents a number of straightforward but ingenious experimental designs, relying mainly upon adoptions, to unravel hereditary and environmental factors.

For good and various reasons, though not compelling ones, American behavioral scientists have long shown a remarkable indifference to the possible role of heredity in the etiology of behavioral disorders. The reasons included: a healthy skepticism regarding the validity and reliability of assessing traditionally defined diagnostic categories, such as schizophrenia, manic-depressive psychosis, psychoneurosis, psychopathy, and others; the association of fallacious, hereditary theories with the political ideology of the Nazis; the fact that genetic research has sometimes been linked to the suppression of black people; the repugnance to Americans of any theory that implied a genetic determination of behavior, even in part, in that it threatened to delimit our concept of personal freedom as well as our subjective or collective consciousness of such freedom; the fact that so-called genetic research has often been cavalier in its disregard of basic, accepted methodological practices, such as the use of a control group, or making assessments while blind with respect to the relationship between a subject and the index case in a given study; the popular but mistaken belief that if a disorder had a genetic basis, it was ipso facto untreat-

able; the absorption of psychologists in psychodynamic explanations of psychopathology and in principles of learning left little room for an ego-alien notion such as genetics in their conceptualization of behavioral disorder; and the fact that none of the behavioral disorders followed any clear Mendelian distribution.

Nevertheless, during the past fifty years, evidence for an hereditary contribution to the psychopathologies had been gathering steadily in Europe, and to a lesser extent in the United States. The evidence might have been fallible because of methodological insufficiencies, but its accumulating weight began to demand attention here. The evidence was based essentially on two kinds of studies:

(1) Consanguinity Studies. Here the assumption was that if a disorder occurred more frequently in the relatives of an affected individual than in the population at large, this finding provided evidence for an hereditary contribution to that disorder. Moreover, if the frequency of the disorder was greater in first degree relatives as compared to second or third degree relatives, this finding reinforced the evidence for an hereditary contribution. However, investigators who made these assumptions were ignoring the possibility that nongenetic factors could also have accounted for such distributions of the disorder. Such nongenetic factors could be psychological, such as parental behavior that has been described as attention-fragmenting, chaotic, or double-binding, to name a few of the terms used by psychodynamic environmentalists, or these factors could be sociocultural, so that a trait such as poverty might show the same patterns of correlation between degree of consanguinity and degree of poverty that one might find with various forms of psychopathology.

(2) Twin Studies. The classical twin study design is based on the fact that monozygotic twins have exactly the same heredity whereas dizygotic twins have only about half their genes in common. Therefore, it has been assumed that if pairs of monozygotic twins are concordant – i.e., have the same psychopathology – more often than pairs of dizygotic twins, then such a finding constitutes evidence of a genetic contribution to the disorder. This inference is based on the assumption that intrapair environmental factors are the same for both monozygotic and dizygotic twins. Usually the environmental factors that have been considered most relevant involved a common rearing in the same home. Since both members of the monozygotic and the dizygotic pairs

were reared together, then the assumption of equal intrapair environmental variance across groups was considered to have been met.

However, psychological factors unique to monozygotic twins, especially that of shared identity, have been described vividly by several investigators who maintain therefore that the equal environment assumption is ill-founded, that solely on psychological grounds one would predict a higher concordance rate for monozygotic twins, and that the inference of a genetic contribution to the disorder is not warranted based on such findings alone. We should note too that the classical twin study design invokes a unidirectional hypothesis; the prediction is always that there will be greater intrapair similarity for monozygotic twins. But there is almost never any reason to predict greater intrapair similarity for dizygotic twins, whether for genetic or for environmental reasons. Therefore, the traditional twin studies of psychopathology have been suggestive but not conclusive. Studies of twins reared apart could be helpful in that the problems associated with shared identity cannot arise in separated twins. However, it is difficult to obtain representative samples of separated twins, and the happenstance case by case reporting of such twins might involve selective bias.

For these reasons, Dr. Seymour Kety and I began a series of conversations about ten years ago in which we decided to embark on a different research strategy in attempting to resolve the old controversies. We planned to use naturally occurring adoptions to tease apart the hereditary and environmental factors that were thought to be implicated in most forms of psychopathology. Not long afterward we were joined by Dr. Paul Wender who had had the same idea. The psychopathology that we chose for our investigations was the one called schizophrenia. Most of the previous genetic research by far had been devoted to this disorder, and it was the one of greatest concern to the mental health professions and to the population at large. The environmental variable we chose to work on involved type of rearing, which many psychiatrists, psychologists, and laymen felt was the primary etiologic agent in the schizophrenic disorders. Since rearing involves a huge subset of variables, we chose to focus more specifically on rearing by or with a schizophrenic relative.

Of course, the idea of using adoption to separate the genetic and rearing variables is not new. Psychologists have employed this research strategy liberally in the study of intelligence (Burks, 1928; Honzik,

1937; Skeels, 1936; Skodak, 1939; Skodak and Skeels, 1949). One adoption study has been carried out with respect to alcoholism (Roe, 1945) and one with respect to antisocial behavior (zur Nieden, 1951). However, considering the potential value of such research, the adoption strategy has been used very sparsely. There were good reasons for this apparent neglect. Adoption agencies and the courts have been zealous in their desire to protect all parties to the adoption, the biological parents, the adopting parents, and the child, and the agencies have usually been unwilling to divulge any information about them to outsiders. Without the agencies' cooperation, it becomes extremely difficult to mount any adoption study at all, although we have generated one research strategy that circumvents this problem. Nevertheless, to carry out our studies in the way we wanted, we eventually felt obliged to go abroad, where cooperation was possible. Perhaps in the future there will be some liberalization of American agencies' rules with respect to information released to researchers. The researchers, in turn, will have to commit themselves to prescribed practices and constraints that must be acceptable to the agencies.

Although the adoption strategy is not new, Dr. Kety, Dr. Wender and I have developed research designs that build upon and amplify the potential usefulness of this strategy. We did not have all these designs in mind when we started, but as happens often in research, once we were enmeshed in the work itself, new findings and problems that arose suggested new methodological approaches. In this presentation, I will focus on these research designs rather than on the details of our research findings. However, I will touch briefly upon the findings, where they are available, using them primarily to indicate the power of the designs and the nature of the information they yield. Through all these designs, we treat heredity as though it were an independent variable, just like any other independent variable in a well carried out laboratory experiment.

Experimental designs

The first group of studies that I will discuss was carried out in Denmark under the excellent supervision of Dr. Fini Schulsinger. In the first of these studies (Kety et al., 1968), we were interested in the incidence of

schizophrenic disorders in the biological and adoptive relatives of schizophrenics and nonschizophrenics, respectively. The design of the study is shown in fig. 1. Because the focus of the study is the relatives of the adoptees rather than the adoptees themselves, we may call it the Adoptees' families design. In this study we are testing two opposed hypotheses.

RELATIVES

Probands	Biological	Adoptive
Schizophrenic		
Control (nonschizophrenic)		

Fig. 1. Adoptees' families design.

(1) If schizophrenic disorders are heritable, we should find a higher prevalence of such disorders among the biological relatives of our schizophrenic index cases than among the biological relatives of the matched controls.

(2) If schizophrenic disorders are transmitted behaviorally, and at least in good part by rearing parents whose own behavior is confused, disorganized, erratic or chaotic, to mention some of the terms cited in the literature, we should expect that the index cases would have a greater number of adoptive relatives with schizophrenic disorders than would be found in the adoptive relatives of the controls.

To carry out this design, we began by collecting identifying information on all persons who had formally been given up for non-family adoption at an early age in the greater Copenhagen area between 1923 and 1947. There were almost 5500 such adoptions. From the records we learned the name and birthdate of the adoptee, and the names and other identifying information of the adopting and biological parents. From the Psychiatric Register, we found out which of the approximately 5500 adoptees had been admitted to a psychiatric facility. The hospital records for each admitted adoptee were examined by two Danish psychiatrists, and the main information provided by one psychiatrist was sent to the American investigators. All five made their own independent diagnoses. By this procedure, we were able to select 33 index cases. Of these, 16 were chronic or process schizophrenics; 7 were acute schizophrenic reactions of the schizophreniform, schizo-

affective or paranoid type, and 10 were cases of borderline schizo-phrenia.

We selected from among the remaining adoptees in the total pool a control group who did not have a file in the Psychiatric Register and who were matched individually to the index cases with respect to sex, age, pretransfer history, and socioeconomic status of the rearing family.

In determining the rates of schizophrenic disorders among the relatives of our 66 probands, we did not examine the relatives person-ally. Instead, we first identified each biological or adoptive relative who was either a parent, sib or half-sib of a proband, and we then identified each one of these relatives who had a known psychiatric history. These histories were abstracted from records by a Danish psychiatrist who did not know if the individual case he was abstracting was the biological or adoptive relative of an index case or a control. The psychiatric abstract was then sent to the U.S. investigators who independently made their own diagnoses while they were similarly blind regarding the relationship of the relative to the proband. Diagnostic differences among the four major investigators were settled by discussions based on more complete data from the records before we broke the relationship code.

At this point, I would like to call to your attention two important features of our research. The first is that, wherever possible, we keep all examiners blind with respect to the index or control status of the subject under examination. We are almost always successful in this respect. This procedure insures against the possibility of bias either for or against any preferred hypothesis that the examiner may hold. The second feature has to do with the fact that we have included a broad spectrum of disorders in the ones I am calling schizophrenic. These include not only the classical chronic, process types of cases, but patients called doubtful schizophrenic, reactive, schizo-affective, borderline or pseudoneurotic schizophrenic, or schizoid or paranoid. If we dealt only with hardcore schizophrenia, our *n*s would be too small to make any of these studies meaningful. However, a more positive reason for including the spectrum of disorders is that in the process, we hope to be able to determine whether any or all of these disorders, which phenotypically have strong resemblances to hardcore schizo-phrenia, are genetically related to it as well (Rosenthal, 1970).

With respect to fig. 1, the major finding was that we obtained the

highest concentration of schizophrenic spectrum disorders among the biological relatives of the schizophrenic index cases. The rates for such disorders did not differ appreciably in the other three cells. Thus, this finding provides strong evidence for an hereditary contribution to such disorders. However, I want to point out that fig. 1 does not comprise a true fourfold table. That is why a double line is drawn to separate the biological and adoptive halves. The reasons for this are practical rather than theoretical. I will mention only the major reason. It is important to understand that both the adopting and biological parents of our adoptees represent screened populations. The screening with respect to adopting parents is well-known, since adoption agencies have long taken the view that mentally ill people do not make the kinds of parents that serve the best interests of the child. But biological parents are also screened in that if they are known to be schizophrenic, adoption agencies may be reluctant to place their children for formal adoption. Instead, the children may be reared in foster homes or in institutions. Moreover, at least in Denmark, schizophrenic women, or women with schizophrenia in their families, may request and have legal abortions. Thus, fewer such children are born and cannot come into the pool of probands in fig. 1. We do not know the extent of screening in the biological and adopting families, but the screening may be unequal. This fact limits the possible range of differences that might otherwise be found in this type of study, but it does not invalidate the procedure. It also means that we can compare the two groups of biological relatives, and the two groups of adoptive relatives, but we cannot now make valid comparisons between biological and adoptive relatives.

The second model (Rosenthal et al., 1968) is shown in fig. 2. We call it the Adoptees study design because the focus of study is the

BIOLOGICAL PARENTS

| Schizophrenic	Nonschizophrenic
1	1'
2	2'
ADOPTEES 3	3'
4	4'
⋮	⋮
n	n'
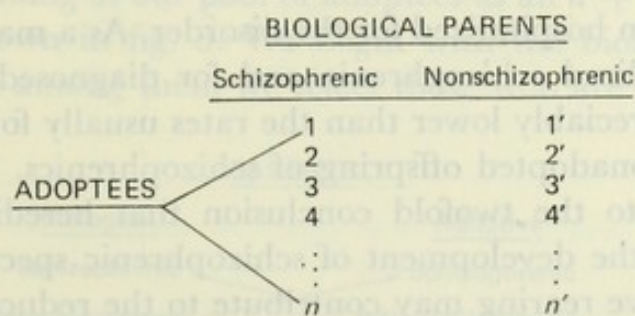
Fig. 2. Adoptees study design.

adoptees themselves rather than their relatives. The design asks the question: What is the fate of offspring of schizophrenic parents when these offspring are reared adoptively? In this study, the starting point is the approximately 10,000 biological parents of our pool of adoptees. A search was conducted to see who among these parents had a file in the Psychiatric Register. The hospital records of each such parent were reviewed in detail by a psychiatrist who completed a prescribed form which was reviewed independently by the American investigators. If we agreed that the parent's diagnosis belonged in our spectrum of schizophrenic disorders, or was a clearcut or possible case of manic-depressive psychosis, the adopted-away child of that parent was chosen as an index case. From among the remaining adoptees, we chose as controls those whose both biological parents had no known psychiatric history, i.e., neither parent had a file in the Psychiatric Register. Controls were matched to the index cases for sex, age, age at transfer to the adopting family, and the socioeconomic status of the adopting family.

The index and control subjects were invited to participate in a study of the relationship between environment and health. We were able to achieve almost 80% cooperation, an acceptable figure, and the two groups did not differ in this respect. At this time, we are able to report on 76 index cases and 67 controls. The subjects were given a semi-structured psychiatric interview by Dr. Joseph Welner that lasted from 3 to 5 hours. Each subject also had one and a half days of psychological testing, but we will not be able to present the test findings now. The examinations of all subjects spanned a period of four years.

The main finding of this study is that there is a significantly greater number of schizophrenic spectrum disorders among the index cases than among the controls. Three cases were called clearcut schizophrenia by Dr. Welner. All three were index cases. However, only one of these had been hospitalized for the disorder. As a matter of fact, the rate for hospitalized schizophrenia and for diagnosed schizophrenia tends to be appreciably lower than the rates usually found in Scandinavia for the nonadopted offspring of schizophrenics. Therefore, this study leads us to the twofold conclusion that heredity contributes significantly to the development of schizophrenic spectrum disorder, and that adoptive rearing may contribute to the reduced expressivity of such disorder. In both studies presented, evidence is accumulating

that the disorders in our spectrum are genetically related, with the probable exception of reactive schizophrenia, which may have to be excluded from the spectrum.

Now I would like to show you a research model that is based on an experimental design that has been used in the past by behavioral geneticists (Ginsburg and Allee, 1942; Fredericson, 1952; Broadhurst, 1961; Ressler, 1963). It has generally been referred to as a cross-fostering or reciprocal fostering model. To review briefly the essentials of this model, let us assume that the experimenter is interested in learning whether he can breed in a trait such as social dominance. He would first decide on a test criterion for the trait. He would then run his starting pool of animals through this test and separate those who test high (called dominant) and those who test low (called submissive). He would then inbreed the dominant animals and inbreed the submissive animals, and repeat the test with the next generation. This procedure is continued as long as the respective inbreedings continue to increase the test discrimination between the dominant and submissive groups. Let us say that at the nth generation, the experimenter decides that he can no longer increase the discrimination. At this point, he must ask himself whether he has successfully bred in the trait or whether each generation had become more dominant or more submissive because it had, in turn, been reared with successively more dominant or more submissive parent populations. Therefore, he checks this possibility with the $n + 1$ generation. He does this by transposing the $n + 1$ dominant animals to be reared by submissive dams, and $n + 1$ submissives to be reared by dominant dams. Then he runs the $n + 1$ adult generation through his test to see what effect the transposed rearing may have with respect to the test performance.

We cannot control human breeding, but we can follow the model somewhat by thinking of our pool of adoptees as an $n + 1$ generation. The design is shown in fig. 3. We begin with the biological parent generation. From among them we select those who are schizophrenic
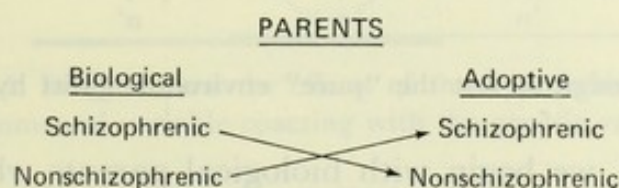
PARENTS

Fig. 3. Cross-fostering design.

and who are presumably breeding the trait. Among their adult off-spring, we select those who were reared by adoptive parents who had had no schizophrenic disorder, as far as we can tell. These offspring constitute one testing group. Then we select from among those biological parents who had had no schizophrenic disorder, as far as we can tell, those whose offspring had been reared by an adopting parent who did have some schizophrenic disorder. These offspring comprise our second testing group. The two groups of offspring are then compared with respect to the trait in question. Although we have not yet analyzed the data in this study, a preliminary look at the data suggests that the incidence of schizophrenic spectrum disorders tends to be about equal for the two cross-fostered groups. Should this tentative observation prove true, it would not mean that heredity is irrelevant, but rather that rearing by a schizophrenically disordered parent may also be influential in the development of spectrum disorders.

Although the cross-fostering design has its own built-in elegance, what it does in effect is to pit two competing hypotheses against one another. However, we also want to know in more detail the effect of each independent variable considered separately. Now that some statistical evidence is accumulating to the effect that rearing by a schizophrenic parent may itself produce spectrum disorders in off-spring, it is important that we have a research model that provides a clean test of this hypothesis. This model is shown in fig. 4.

BIOLOGICAL PARENTS

Nonschizophrenic

REARING PARENTS

Schizophrenic   Nonschizophrenic

ADOPTEES

|	
1	1'
2	2'
3	3'
4	4'
:	:
n	n'
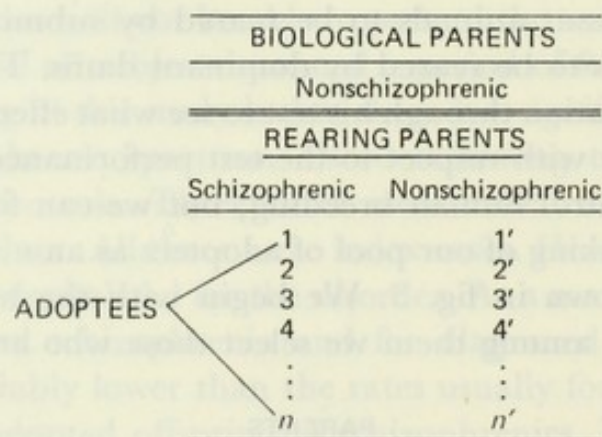
Fig. 4. Design to test the "pure" environmentalist hypothesis.

In this model, we begin with biological parents who do not have any schizophrenic spectrum disorder, as far as we can tell. This is done

to insure to the maximal extent possible that the offspring under study are as free of genetic contamination as we can make them. Preferably, all biological parents should be examined personally and in depth to make the determination of no spectrum disorder, but we have not as yet been able to do this. Now we ask the question: When there is minimal or no genetic predisposition in the child, will rearing by a schizophrenic parent induce spectrum disorders in the child? Thus, we have two groups of adoptees. The first or index group are reared by a schizophrenic spectrum parent, the second or control group by rearing parents who are free of spectrum disorder. The second group, which is matched to the first group for various relevant variables, constitutes as ideal a control group as we can find in that both their biological and rearing parents are free of spectrum disorders. Any psychopathology that we find in these offspring should arise from other factors. Any psychopathology in the index group in excess of that occurring in this idealized control group represents the contribution of rearing by a schizophrenic parent. We cannot at this time report any findings on this study, but will do so in the future.

We must be alert to another alternative. It may be that rearing by a schizophrenic parent is insufficient per se to induce spectrum disorders in offspring, but that such rearing could raise havoc with genetically predisposed individuals. To test this possibility, we require a research model such as that shown in fig. 5.
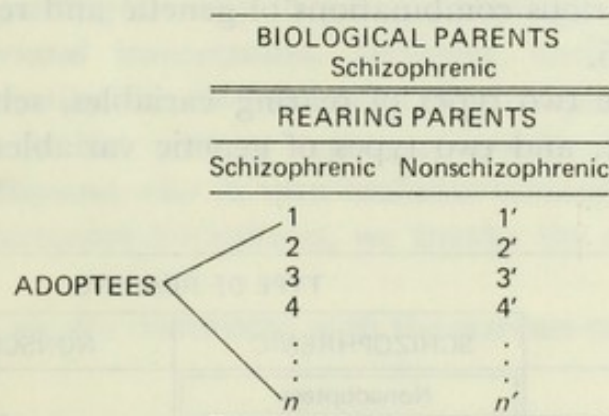

Fig. 5. Design to test the effects of the hypothesized environmental variable coacting with the genetic variable.

This design is exactly like that of the previous design, with one im-

portant exception: this time all subjects must have a biological parent who has schizophrenic spectrum disorder. Thus, from a genetic standpoint, the amount of hereditary predisposition for such disorder should be the same for our two groups, and it should be considerable. Again the difference between the groups occurs in the rearing variable. Actually, it is not possible to carry out such a design in pure form, at least not in Denmark, since this would require that both groups of subjects should be adoptees. However, the likelihood of generating a sample in which the subjects have a biological parent who is schizophrenic and are then given up for adoption to a rearing parent who is also schizophrenic is, fortunately, very small. Thus, to carry out the intent of the design, we have had to substitute for adoptees a group of subjects who had a schizophrenic parent and who were reared in the parental home at least during their first fifteen years of life. This represents the group in which the hypothesized genetic and rearing factors would be truly coacting to produce the schizophrenic phenotype. The comparison group of adoptees provides a baseline that represents only the genetic contribution, without the superimposition of rearing by a schizophrenic parent. Any difference between the two groups should represent the coaction or true interaction effect. We have collected a matched sample of nonadoptees to carry out this design, but the research material has not yet been subjected to analysis.

We are now in a position to bring together several of the samples of subjects we have collected and arrange them in a fourfold table that represents the various combinations of genetic and rearing variables, as shown in fig. 6.

Thus, we have two types of rearing variables, schizophrenic and nonschizophrenic, and two types of genetic variables, schizophrenic

Genetic Background	TYPE OF REARING	
	SCHIZOPHRENIC	NONSCHIZOPHRENIC
Schizophrenic	Nonadoptees	Cross Fostering
Nonschizophrenic	Cross Fostering	Controls

Fig. 6. Modified design to test for statistical interaction between the hypothesized genetic and environmental variables.

and nonschizophrenic. Three of the four cells contain adoptees. Two diagonal cells represent subjects in the cross-fostering design. The adoptees in the lower right cell are obtained from the control group in the adoptees study design. The upper left cell, unfortunately, has to be represented by the nonadoptees obtained in the previous design, and that is why it is represented by a double line. Thus, in one cell the factor of adoption does not hold and we do not know to what extent this fact invalidates the findings of this otherwise neat design. Nevertheless, we may carry out such an analysis if we have reason to think it will be worthwhile.

The next study I want to present was carried out in Bethesda (Wender et al., 1968). It represents the kind of study that can be done without requiring the cooperation of adoption agencies. The design is based on the following rationale. Many investigators have maintained that a child develops a schizophrenic disorder because his parents have subjected him to various kinds of noxious rearing. In accounting for the elevated incidence of schizophrenia among the parents of schizophrenics, they point out that such parents are more likely than normal parents to emit these noxious behaviors in regard to their children and that, therefore, the elevated incidence of schizophrenia among parents of schizophrenics is to be expected on rearing grounds alone. Alanen et al. (1966) reported that parents of schizophrenics had a higher rate of severe psychopathology than did the parents of neurotics, and inferred that the correlation between parents and children regarding severity of psychopathology represented evidence for behavioral transmission. However, such findings could equally well imply that the elevated rates of schizophrenia and severe psychopathology in the parents represent genetic factors that are transmitted to offspring who in turn manifest schizophrenic disorder. To test these alternative hypotheses, we invoke the design shown in fig. 7.

In this design, we are concerned with the parents of schizophrenics.

	DIAGNOSIS OF PROBANDS		
REARING PARENTS	Schizophrenic	Schizophrenic	Nonschizophrenic
	Adoptive	Biological	Adoptive

Fig. 7. The adoptive parents study design.

Since in the type of study done by Alanen and other investigators the genetic and rearing variables are confounded in the same parents, we again resort to adoption to separate the two variables. We begin by finding young adult schizophrenics who had been given up for adoption early in life. This can best be done by interviewing all new admissions to mental hospitals, and their parents. It is a tedious job, but it is feasible. From among other schizophrenic admissions who were home reared, we find a group that is matched to the adopted schizophrenics with respect to the variables deemed most relevant. The third group in the design shown is used to control for the factor of adoption. However, this group of adoptees is free of schizophrenic disorder. The subjects studied are not the offspring, but the parents. The particular focus of the study is the adoptive parents of the schizophrenics. Our reasoning goes like this: If the schizophrenia in the children represents primarily genetic influences, the degree of psychopathology in their adoptive parents should not be severe, as Alanen had reported, and should be less than that of the biological parents of schizophrenics. If the schizophrenia in the children represents the effects of noxious behavioral influences, the degree of psychopathology among the adoptive parents should be the same as that found in the biological parents.

Our findings indicated that the degree of psychopathology in the adoptive parents of schizophrenics was significantly less than that of the biological parents of schizophrenics but significantly greater than that of the adoptive parents of normal subjects. Thus, it is possible to have schizophrenia in offspring who are not subjected to the noxious influences associated with severe psychopathology in the rearing parents. The finding of a difference in degree of psychopathology between the adoptive parents of schizophrenics and the adoptive parents of normals could have any of several explanations which I will not take the time to discuss here. It is interesting that on a word association test, the biological parents of schizophrenics produced more unusual responses than did the adoptive parents of schizophrenics.

To carry out the last design that I shall present, I went to Israel. This study was done without the collaboration of my two brilliant colleagues, Dr. Kety and Dr. Wender. As noted earlier, our attempts to generate a clean fourfold-table design by using adoption fell short of our goals. However, we can forego the advantages conferred by adoption if we can

specify two different environments that bear on the kinds of rearing we have been talking about. Israel provided two such environments, the kibbutz and the nuclear family types of rearing. The reasoning underlying the study is: In the typical nuclear family, if a parent – let us say the the mother – is schizophrenic, the child is likely to endure the following psychological hazards: the mother may be too autistic to attend or to be responsive to the child's needs and she may program reinforcements haphazardly and unpredictably, thus impairing the child's cognitive training and his affective and motivational integration; during the times she is not hospitalized, she is likely to be the only person in the child's environment during most of each day, so that during the greater part of the time that he is awake, the child has no other model with whom to identify during his formative years; sometimes the parent undergoes successive hospitalizations, so that the child may suffer increased insecurity each time he loses her, and he may develop a deep sense of mistrust of the world around him; sometimes the home will be broken, the child may be reared by relatives or friends, in institutions, or he may be shuttled back and forth in various combinations of such rearing; he may be isolated from other children; if he has siblings, they are likely to be similarly influenced and they may tend to influence each other noxiously in turn.

Although kibbutzim vary among themselves in a number of ways, in the main they may provide greater protection for the child who has a schizophrenic parent. For example, the child grows up in children's houses under the guidance of trained caretakers. During the greater part of each day, he receives the same tutelage and training as do other children. During evenings and holidays when the children and parents visit together, the child will visit with both the well parent and the sick parent, and the well parent may help to neutralize any noxious impact of the sick parent. Usually, the child is well-known to other adults in the kibbutz and they may serve as parent surrogates. If the sick parent requires hospitalization, the child suffers minimal disruption of his life. He remains in the same children's house with the same caretakers, teachers, and friends. He lives in the same community, and he can still visit with the well parent during the evenings and holidays.

The design for this study is shown in fig. 8.

This study was carried out under the supervision of Dr. Shmuel Nagler and Dr. Sol Kugelmass. The key cell is in the upper lefthand

corner. We had to find children who were born and reared in a kibbutz and who had a schizophrenic parent. We were able to find 25 such cases. We then found 25 matched cases who lived in the usual nuclear family situation and who also had a schizophrenic parent. For kibbutz controls, we selected a group of children who were reared in the same children's houses as the index cases, but whose parents had no spectrum disorder, and for nuclear family controls we selected children from the same neighborhood and classroom, but without a schizophrenic parent.

PARENTAGE	TYPE OF REARING	
	Kibbutz	Nuclear family
Schizophrene	25	25
Nonschizophrene	25	25

Source	df
Parentage	1
Rearing	1
Parentage X Rearing	1
Error	96
Total	99

Fig. 8. Generalized design for estimating the relative contributions of heredity, environment, and heredity-environment interactions.

The children had two days of examination. They were brought in pairs, each index case and his control, but all examiners were kept blind as to which child was which. Thus, we had the rare opportunity to observe and test both the index and control subjects in the same situation. The children ranged in age from 8 to 14. Our major dependent variables involve the degree and type of psychopathology found in the four groups of subjects. With respect to each variable, we can apportion the amount of variance contributed by genetic background or parentage, the amount contributed by type of rearing environment, and the amount contributed by the genetic-rearing interaction. At this time, data are being analyzed. We hope to begin reporting our findings in the next year. It is worth noting that this is a generalized design that avoids the problems confronting us in adoption studies, and that can be applied whenever the investigator can specify two contrasting types of environment, whether they have to do with rearing or with other

kinds of environmental or experiential phenomena. The latter can be conceptualized narrowly or broadly, depending on the investigator's theoretical predilection.

Outlook

In closing, I would like to say that only a decade ago there existed a widespread air of pessimism about the possibility of ever unraveling the hereditary and environmental factors involved in the etiology of the behavioral disorders. Today, the outlook is completely opposite. During the seventies we should see a marked acceleration in the accumulation of knowledge in this important field.

A high-risk project

The first paper in this section is of interest inasmuch as it includes the first public proposal of the high-risk longitudinal method – previous discussion had been confined to a small research conference (Mednick and Higgins, 1960). However, the main reason for opening the section with this paper is that it outlines the theoretical orientation which generated many of the hypotheses tested in the project (a detailed and documented theoretical statement may be found in Mednick, 1958). The paper further illustrates the Institut's commitment to a program of research grounded in and guided by an organizing conceptual framework.

SCHIZOPHRENIA:
A LEARNED THOUGHT DISORDER*

SARNOFF A. MEDNICK

From the great variety of deviance, peculiarity, and debasement which presented itself to Bleuler, that aspect of his schizophrenic patients which most arrested his attention was their disturbance of sequential associative thought. Perhaps this is the aspect of the disorder which for centuries has set its victims apart from the rest of humanity. But from one point of view it is not surprising that people manifest such a disorder; what is surprising is that more of us do not. After all (assuming random sampling) at any given point in thought the probability of the development of a "reasonable" sequence of ideas is astronomically small. Let me assure you that I never allow myself to dwell too long on this threatening associative sequence for fear that I'll suffer the fate of the centipede who found himself unable to walk when he began to study the synchrony of his hundred legs. However let it suffice if I make the point that rational thought is a narrow and improbable path. This afternoon I shall discuss the thought and behavior of individuals who have strayed from this narrow path.

On the basis of conditioning and psychophysiological research and clinical experience I am going to suggest that the origin of the schizophrenic disorder lies in the interaction of hypersensitive autonomic nervous systems and unkind environments. In the context of behavior theory (mainly learning theory) I will first try to reconstruct how an individual may have an acute breakdown. I will then explain the transition from the acute state to the chronic state. [...]

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* This paper was first presented to the XIV Congress of Applied Psychology which was held in Copenhagen during 1961. It was subsequently included in Volume 4 of the *Proceedings of the XIV International Congress of Applied Psychology* edited by G.S. Nielsen, and published by Munksgaard International during 1962.

I will conclude with the discussion of a research project with which we are currently struggling at the University of Michigan.

Learning and thinking research

This research in schizophrenia began some years ago when I was reviewing the literature on learning, problem solving and thinking in schizophrenia.

What immediately struck me in this literature was the uniformly poor performance of schizophrenics relative to normals. On any task imaginable (I must say some defy imagination) schizophrenics' performance was inferior to that of normals. In view of this it was with great excitement that I began to note study after study in which schizophrenics were showing performance superior to normals in the ease and rapidity of classical conditioning. Responses which have been studied include the kneejerk reflex, the psychogalvanic response, and the eyeblink reflex. To my great surprise the literature discloses that schizophrenics consistently condition more easily than normals.

There is a phenomenon related to conditioning which also pointed up an unusual aspect of the experimental behavior of the schizophrenic. This phenomenon is stimulus generalization; when a response trained to one stimulus is also elicited by similar stimuli, stimulus generalization may be said to have occurred. (Having been bitten by dog A we fear dog A; through stimulus generalization we also fear dog B who is similar to dog A.) Paul Schilder, on the basis of his clinical experience, was one of the first to take explicit note of the schizophrenic's tendency to show exaggerated generalization reactiveness. Several researchers have provided experimental and clinical support for his early observations. In our own laboratory several studies have been completed which support these findings, including the recent work of Gaines et al. (1963), on temporal generalization.

These two findings in conditioning and generalization which have been repeatedly observed are in many ways counter to expectation and merit careful examination and interpretation. There are a number of variables which might be responsible for organisms displaying relatively rapid conditioning and brisk generalization responsiveness. Among these, two of the principal possibilities are faster habit accrual and a

heightened arousal state. While it is too early to cast any possibility aside, faster habit accrual does not appear to be a likely explanation. On the other hand, heightened arousal certainly merits some further consideration since it is a state which can be produced by autonomic reactions such as anxiety. There is a good deal of experimental evidence that organisms in aroused states (precipitated by hunger, thirst, anxiety, etc.) demonstrate faster conditioning and greater generalization responsiveness. In addition the poor showing that schizophrenics make on highly complex tasks is quite in keeping with what one would expect of individuals performing under aroused conditions.

Critical reading of the research on the arousal state in schizophrenia lends background support to the arousal interpretation of the conditioning and generalization findings. While the literature may hardly be characterized as unequivocal there is certainly very strong support for Arietti's description of the first phase of schizophrenia as a "period of intense anxiety and panic". Psychophysiological studies strongly point to a low threshold of emotional arousal in the schizophrenic. These include studies of heart rate, the psychogalvanic response, the startle reflex, etc.. Also of very great importance is the repeated finding that once aroused, schizophrenics take longer to recover from an affective imbalance than do normals. Let us summarize what has been said to this point:

(1) The schizophrenic more easily acquires a conditioned response.

(2) The schizophrenic shows more stimulus generalization responsiveness.

(3) These two facts may reasonably be interpreted as being due to a state of heightened arousal.

(4) The clinical and experimental arousal literature lends strong support to this interpretation. In addition we have noted in the schizophrenic consistent evidence of a markedly retarded rate of recovery from autonomic imbalance.

Explanation of acute breakdown

Now I shall attempt to take these factors and describe how an acute schizophrenic episode might ensue in an individual with such predispositions. In this instance we shall deal with an incipient reactive schizophrenic.

In reactive schizophrenia we almost invariably find a precipitating event or series of events. Let us closely examine the effect of such a stress. As is shown in fig. 1, a normal individual will show an arousal response to stress. Because of his heightened sensitivity, the preschizophrenic will show a larger response and will recover at a slower rate than the normal. If a this point the individual can get away from the
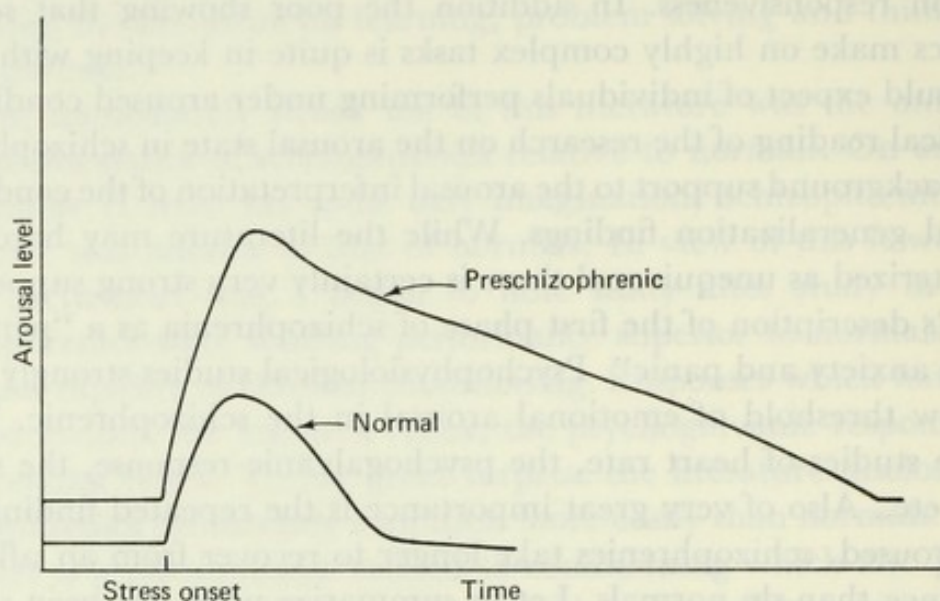

Fig. 1. Depiction of arousal and recovery following stress onset.

troublesome situation, if he can take a rest or vacation and allow his anxiety to subside to its resting level then we would expect no further untoward consequence to this specific upset. However, if he continues to operate in society, for example, if he is an individual from a lower socio-economic group and must stick with his job, there are certain consequences which might ensue.

For one thing, the increase in anxiety or arousal level will cause an attendant increase in the level and breadth of stimulus and associative generalization. This increase will affect all of the individual's habits including those related to learned fear reactions. The increase in the breadth of generalization will cause many new stimuli to become potential anxiety arousers; in addition those stimuli which previously elicited anxiety reactions will elicit stronger anxiety reactions. Because of the increase in the breadth of the gradient of stimulus generalization, the probability that he will encounter an anxiety-arousing stimulus has

increased. If he continues in society and does encounter such stimuli this will increment his arousal level. This in turn will cause his generalization responsiveness to increase. This will increase the probability of his encountering fear-arousing stimuli by increasing the *number* of such stimuli and the *magnitude* of his response to such stimuli. This will cause an increase in his anxiety level which will in turn again increase his generalization responsiveness and so forth.

In fig. 2 we have a schematic depiction of this reciprocal augmentation. For the purpose of illustration it uses the father as a conditioned stimulus for a fear reaction and generalization stimuli which vary in their similarity to the father. Each level of generalization represented
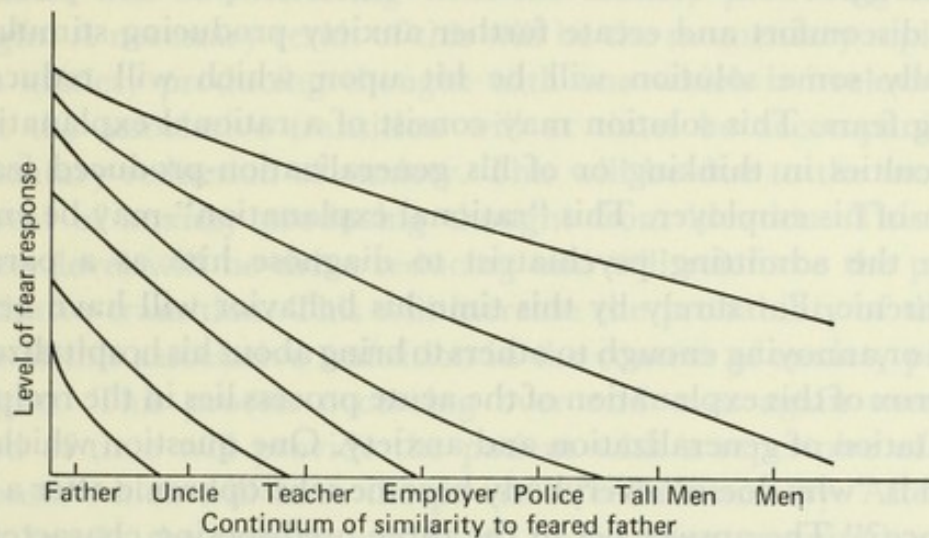
Fig. 2. Depiction of increasing generalization of a fear response due to reciprocal augmentation of fear and generalization.

by the rising curves is *brought about* by increasing levels of arousal and in turn brings about increased arousal. The pictured heightened levels of generalization represent augmented generalization responsiveness across *all* learned responses.

The subjective experience

This rather cold and ominous sounding mechanistic talk leaves the patient out of the picture. But what will be the subjective feelings of this individual?

For one thing he is going to experience uncomfortable levels of anxiety. Things which used to soothe him may now begin to make him uneasy. As generalization mounts, he will experience atypical thought sequences and tangential intrusions into his stream of ideation. These will be due to associative generalization. His perception will be distorted through stimulus generalization. Noises in the plumbing will sound like speech; shadows will resemble people. Because of the uncontrolled nature of some of his thought and the irreality of some of his perceptions, he will begin to fear that he is going crazy. This will only lead to further anxiety. His psychophysiological state will be producing internal stimuli which will partially cue ongoing thought processes. These thoughts will therefore tend to dwell on previous periods of anxious discomfort and create further anxiety producing stimulation. Eventually some solution will be hit upon which will reduce the torturing fears. This solution may consist of a rational explanation of his difficulties in thinking or of his generalization-produced fears of police or of his employer. This "rational explanation" may be enough to cause the admitting psychiatrist to diagnose him as a paranoid schizophrenic. For surely by this time his behavior will have become atypical or annoying enough to others to bring about his hospitalization.

The crux of this explanation of the acute process lies in the reciprocal augmentation of generalization and anxiety. One question which may be asked is "why doesn't everybody become schizophrenic after a stress experience?" The answer lies in the three predisposing characteristics of the preschizophrenic:

(1) Low threshold for anxiety arousal.
(2) Slow recovery rate.
(3) High generalization reactiveness.

An individual may have a low threshold for anxiety arousal but recover quite quickly. Such an individual will not suffer a reciprocal augmentation process since the building up of anxiety would be prevented by his fast recovery. He would only be threatened by such a process in conditions where stresses followed one another at a very rapid pace. Such circumstances may be found under severe military combat conditions. And indeed there is good evidence that combat experience produces acute psychotic breakdowns.

Chronicity in schizophrenia

We have discussed the essentials of the explanation of the onset of schizophrenia in a reactive schizophrenic. Now we shall follow him into chronicity. Meyer and Kraeplin have both described schizophrenia as an evasion of life. I believe that this evasion or avoidance is learned. I believe that the learning takes place gradually over a period of time and that *it is this avoidance learning which is schizophrenia*. This learning is especially prevalent during periods of high anxiety. During such periods, thought with anxiety producing content is dominating the thinking of the patient. Due to generalization, remote, tangential associates will be interfering with the anxiety producing stream of thought. A necessary result of this will be the momentary replacement of an anxiety producing thought with one which is irrelevant. As a result the associative transition will at times be accompanied by a momentary reduction of anxiety. This will be due to the momentary removal of anxiety producing thought from ideation. This drop in anxiety level will be drive reducing and will reinforce the preceding associative transition. This will increase the probability of the occurrence of this associative transition in the context of anxiety provoking thoughts. This process occurring over and over again over a long period of time will provide the patient with a repertoire of thought responses which will have the power to reduce anxiety. After several acute breaks the patient will have, by learning, acquired a built in anxiety governor which will remove him from any stimulation with a hint of threat. If at this point the patient responds with the anxiety provoking thought, "I am going crazy", he can defend against it by making an immediate associative transition to an irrelevant, tangential thought or by making use of a well learned rationale such as "the radiators are broadcasting to me". This avoidant thinking will be continually self-reinforcing since it will enable him to evade anxiety producing stimuli. It will assume the status of a conditioned response which will be elicited automatically upon the presentation of anxiety producing stimulation. This will make it extremely difficult to reach his awareness with any stimulation which is even mildly anxiety arousing. As more of these avoidant associates are learned the patient will experience less and less anxiety and may very well be described as having "flat affect". What is especially damning is the effectiveness of

this means of reducing anxiety and the fact that it is automatically self sustaining through secondary reinforcement. Whenever an anxiety producing stimulus presents itself, the individual's anxiety level will momentarily rise. An avoidant associative transition will remove him from the threatening stimulus and result in a reduction in anxiety which will once again reinforce the learned avoidant thinking mechanism. At this point it is difficult for me to see how this avoidant habit can be extinguished. Most avoidant responses are quite resistant to extinction because of their built-in self reinforcement. Sometimes by physically preventing the avoidant response in the presence of the danger signal and omitting the punishment, extinction may be hastened. At the moment, it is difficult to see how an avoidant thought might be physically prevented.

One aspect of this explanation should be emphasized. Schizophrenia is here seen as a learned disorder of thought and emotion. The acute phase of the illness in the reactive patient is not in and of itself schizophrenia. It is the learning of the avoidant thoughts which is the essence of the schizophrenic disorder. Chronicity is a function of the degree to which the patient's thinking is dominated by avoidant thought sequences and I believe that chronicity may best be measured in this manner. [...]

A proposed research project

This orientation to research has provided the background for a series of experiments on learning and thinking in schizophrenia. I have refrained from presenting these to you since the complete explication of the methods of any one might have taken up all of my time. Instead I would like to close with a very brief description of a study we are attempting to carry out at the University of Michigan. In this study we are taking a group of "normal" individuals and observing them with measures suggested by the theory. Using these measures we will attempt to predict which of them will become schizophrenic. In order to maximize the number of cases of schizophrenic which occur in the group we are testing individuals whose parents have both been hospitalized for schizophrenia. The literature suggests that from 40% to 68% of these individuals will themselves become schizophrenic. If

we can isolate a group of measures which will reliably identify those individuals in society who may become schizophrenic; then we can begin to institute preventive measures and be able to assess their value. In addition if we are successful in predicting which of our *S*s will become schizophrenic, then this will lend support to the general theory which could then be used to suggest preventive measures. I am presenting this research plan to you in the hope that you will find it worthy of your attention and will give me the benefit of your suggestions and criticisms in what I recognize as an extremely difficult project.

A LONGITUDINAL STUDY OF CHILDREN
WITH A HIGH RISK FOR SCHIZOPHRENIA:
A PRELIMINARY REPORT*

SARNOFF A. MEDNICK AND FINI SCHULSINGER

At the time when the first author was proposing the Michigan high-risk project to his audience in Denmark, Higgins was making the discovery that the study was clearly not feasible in Michigan, nor, for that matter, in the United States. It was, however, during his attendance at the Copenhagen Congress that the author learned of the very real possibility of conducting such a study in Denmark.

This paper describes in detail the rationale, design and methodology of the subsequent Copenhagen high-risk project.

It might be of interest to point out that the high-risk method is based upon the empirical finding that a relatively high percentage of children of schizophrenics themselves become schizophrenic. Because of the anticipated size and duration of the 1962 high-risk project, Mednick and Schulsinger deemed it prudent to check this empirical finding in Denmark. Neils Reisby, a young psychiatrist, was supported in conducting such a study (Reisby, 1967) which encouraged the initiation of the experimental high-risk research at the Institut.

In the past 14 months in Copenhagen, Denmark, we have examined 207 children whose mothers are severely and chronically schizophrenic. We have also examined 104 control children carefully matched with the 207 for age, sex, father's occupational status, rural-urban residence, years of formal education, and institutional versus family rearing conditions. The examination included biochemical, psycho physiological, social, cognitive, and personality measures.

Our long range plan is to follow these children until some appre-

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ciable number become schizophrenic. We will then be in a position

(1) to look back at the results of our current examinations and determine the childhood characteristics which distinguish those that succumbed,

(2) investigate the interaction of these characteristics with life circumstances including conditions surrounding the onset of psychosis,

(3) observe characteristics which differentiate these children and plot them as they change from the time of the first examination to frank psychosis.

We study high-risk children because the prevalence rate of the disorder in the general population is only approximately 0.29% (Lemkau and Crocetti, 1958). In view of the extensive testing involved the project would not be possible if subjects were selected without bias. It would be necessary to examine 10,000 individuals in order to include perhaps 29 who would subsequently become schizophrenic. To maximize the number of cases of schizophrenia which will occur in our sample we study individuals whose mothers have been schizophrenic. The psychiatric genetics literature suggests that 16% to 21% of individuals with one schizophrenic parent will become schizophrenic (Fuller and Thompson, 1969).

Check on psychiatric genetic literature

We are studying children with schizophrenic mothers because it has been reported that the probability of schizophrenia is high in such samples. In view of the reliance we place on this assumption it seemed prudent to check these reports on a sample more or less identical to our sample. Dr. Niels Reisby and Dr. Fini Schulsinger conducted this investigation in 1963. We shall summarize some of the relevant findings.

First, they found the names of 98 women patients in four mental hospitals. From the hospital records, the Folke register (an up-to-date record of the current address of every individual in Denmark), and the Human Genetics Institute they prepared a list of their children. Again, at the Human Genetics Institute (where every psychiatric hospitalization is registered) they checked to see the percent of these children that had been hospitalized for schizophrenia. This figure proved to be 12.7%. (They used Strömgren's modification of the Weinberg

correction. The average age of the children was 34.8 years.) The average age at first admission for those children who succumbed was 24.6 years. We can consider 12.7 to be a sizable under-estimation of the prevalence of schizophrenia in this sample because well over 50% of the children live on small farms in isolated areas of Denmark, but only 27% of those who were hospitalized for schizophrenia were from such farm areas. In terms of clinical experience and from surveys done in equivalent areas, it is known that the farm people shelter many harmless "trouble-free" schizophrenics and avoid hospitalization if at all possible. They are currently doing a follow-up to obtain a reduction of the number of unidentified children; this will probably increase the estimate of risk. In any case, the figure, 12.7%, is not far from Kallmann's (1938) figure of 16%.

Of great interest in this study is the distribution of ages of the children at first admission (table 1). In view of the fact that the

Table 1

Children with schizophrenic mothers*

Children's age of first hospitalization for mental illness

Age	%
Below 20	38
21–25	14
26–30	10
31–35	24
36–40	10
41 and over	5

* The total number of cases is 21. The total number of mothers is 98. The mean age of the mothers at the time of investigation was 61.5 years; the children were 34.8 years.

mothers were selected on the same basis as the mothers of the proposed long-term study, this table should enable us to estimate the ages of breakdown of the children in the long-term study. Of course, since we propose to re-examine the children periodically we should be able to diagnose the illness well in advance of the first hospitalization. [...]

With respect to the major aim of this study, it is clear that the results are consonant with Kallmann's (1938). They suggest that our sample of younger children of schizophrenic mothers will yield schizophrenics

in numbers sufficient for purposes of our research. We have two additional pieces of information. We can maximize our rate of hospitalization for schizophrenia by concentrating on an urban sample. In addition to schizophrenia, the children of these mothers manifested a number of other varieties of socially deviant behaviors, e.g., suicide, mental deficiency, and psychopathy. While the resulting Ns for each of these deviancies may not reach levels appropriate for statistical analysis, by having followed such individuals from childhood we may be able to formulate hypotheses concerning etiology. It will be of special interest to relate differential pathological outcome within sibling groups to differential individual characteristics and environmental conditions.

Selection of site for study

The senior author first attempted this study in Michigan in 1960 (Mednick, 1962).* The attempt had to be abandoned because the hospital records proved inadequate and the high residential mobility rate made it improbable that we could follow our subjects for any appreciable amount of time. Fifty percent of the entire Detroit population moves every 4 years. When the mobility patterns for individuals in the age range of greatest danger of incidence of schizophrenia were examined, a 47% change of address every year was noted. This figure is even greater for the low-income non-home-owner. The group of greatest interest is also the most mobile (U.S. Bureau of the Census, 1956). If 10 of the subjects should move to California one would be hard pressed to locate them there. If one were able to do so it would cost up to $ 5000 to bring them with a responsible adult for one day of testing. On the basis of these data and other considerations the decision was made not to attempt this study. Anything less than certainty of 90% follow-up success was unacceptable.

Such certainty seemed unattainable until an address by the internationally eminent Danish research worker in psychiatric genetics, Professor Erik Strömgren, directed the attention of the senior author to opportunities for research in Scandinavia. As an example, Fremming

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* See the preceding paper by Mednick.

(1951) carried out a 60-year follow-up of 5500 individuals. He was successful in locating 92% of his sample. Now, Myschetzky, in Denmark, is attempting (with great success) to locate this same sample. At this point his effort represents a 78-year follow-up.

Clearly the study just abandoned as impractical was readily feasible in Scandinavia. Further investigation and a visit to Scandinavia in the summer of 1961 revealed that the epidemiological aspects of schizophrenia are about what we experience here in the United States (Lemkau and Crocetti, 1958). A tour of the mental hospital system of Denmark in the summer of 1961 suggested that the clinical picture which emerges is not essentially different from what we observe in U.S. hospitals. The remarkable and complete national psychiatric register at the Copenhagen University Institute for Human Genetics would greatly facilitate various aspects of the study. The Folke register (which maintains an up-to-date record of the current home address of every individual living in Denmark) completely explained the excellent record of the longitudinal research mentioned above.

What further recommended Denmark as a site for the proposed research was the compact size of the country (16,619 square miles, somewhat smaller than Massachusetts and New Hampshire combined). The population is concentrated in greater Copenhagen. These factors all tend to minimize the distance that subjects must be transported. The major loss of subjects in a longitudinal study in Denmark will be through external emigration. If any *S*s from our sample do emigrate an attempt could be made to locate them. The low rate of emigration of Danes suggests that in any case this will not be a serious problem in our research (Statistiske Meddelelser, 1961).

Finally Dr. Schulsinger (Director of the Department of Psychiatry, Kommunehospitalet) became actively interested in the study and was able to solve the subtle and difficult organizational problems which the project presented.

Method

Sample procurement

Our procedure entailed several steps. First, we sent social workers

to state hospitals in the vicinity of Copenhagen. (We wanted most of our children to be urban residents so as to make it more likely that they would be hospitalized upon becoming psychotic.) The social workers obtained lists of resident female patients who had children between the ages of 10 and 18. These lists were checked with the University Institute for Human Genetics and the Folke register. The mothers' hospital records were examined by two psychiatrists who certified chronic schizophrenia. (After almost perfect reliability of diagnosis was established only one psychiatrist was used.) Social workers then went to the homes of the children and enlisted their cooperation and the cooperation of the responsible adults. The children were then scheduled for testing.

After some children of schizophrenic mothers (Experimental group) had been tested we began forming *pairs* of matched Experimental (*E*) subjects. When some of the Experimental subjects begin to become schizophrenic we shall already have made an unbiased selection of comparison *E* subjects who did not become schizophrenic. The pairs of *E* subjects were matched on sex, age, father's occupation (the best measure of social class in Denmark; Svalastoga, 1959), rural-urban residence, years of education, and upbringing in a children's home versus family life. Next, a single Control (*C*) subject was selected who was matched on these same variables "individual for individual" with each *E* pair. We wrote to a school attended by one or both of the *E* subjects and asked for the names of children, at that school, meeting all the matching criteria. The school typically would send through some names. The name of the *E* child was removed; the other names were then sent to the Institute for Human Genetics, which returned a report on each child concerning *any* history of psychiatric hospitalization or civil disturbance for the child, his parents or his grandparents on either side. For example, on Child A we may have learned that his grandfather on his mother's side had been hospitalized for two months in 1936 for severe depression. Child B's record might be clean. We would choose Child B, of course, as our control subject. A social worker would visit Child B's home and engage the cooperation of the child and his guardians.

In the case that an *E* child was in a children's home, he would be paired with another child in a children's home. *C* children were also sampled from children's homes. These were checked as usual with the

Institute for Human Genetics. In most of these *C* cases the parents had divorced, died, or were alcoholics or criminals. These controls from children's homes will be examined carefully in the data analysis. In any case, they represent some degree of control for the broken home aspects of being a child of a schizophrenic mother. Having summarized our subject-procuring methods, we shall now back-track and present some of the stages in greater detail, discuss problems which arose and our solutions.

Selection of schizophrenic mothers

We chose to study children whose *mothers* are *process* schizophrenics for a number of reasons.

(1) Paternity is sometimes questionable in normal middle class families. It might be difficult to be quite sure of our major independent variables with alleged fathers, especially if they are schizophrenic.

(2) Schizophrenic women have more children than schizophrenic men (Goldfarb and Erlenmeyer-Kimling, 1962) giving one the luxury of a larger subject pool. In a pilot study in Nykøbing, Sjælland, we found schizophrenic women had about five times as many children as schizophrenic men.

(3) Psychodevelopmentally, mothers presumably play a greater role in shaping children (Sanua, 1961). Studying mothers has permitted us to carry out some research on the effects of being reared by a schizophrenic mother.

(4) The offspring of process schizophrenic mothers yield a higher rate of schizophrenia (Schulz, 1939, 1940; Lewis, 1957).

There are aspects of family dynamics that will be biased because we chose mothers. For example, Rosenthal (1962) has shown that in a family with a schizophrenic the family members of the same sex are more likely to be concordant for schizophrenia. We shall expect more of our Experimental girls to become schizophrenic.

Diagnosis of mother

Two experienced psychiatrists trained together and then independently tested their reliability in making judgments from hospital records on the form prepared to record the mothers' symptoms. Their agreement

as to diagnosis on 20 test cases was found to be 100%. They merely had to judge whether the mothers were typical schizophrenics. They were instructed to discard any questionable cases. Following this reliability check only one psychiatrist checked each record.

Table 2
Characteristics of the experimental and control samples

	Control	Experimental
Number of cases	104	207
Number of boys	59	121
Number of girls	45	86
Mean age[1]	15.1	15.1
Mean social class[2]	2.3	2.2
Mean years education	7.3	7.0
Percent of group in children's homes[3] (5 years or more)	14%	16%
Mean number of years in children's homes[3] (5 years or more)	8.5	9.4
Percent of group with rural residence[4]	22%	26%

1. Defined as age to the nearest whole year.
2. Determination based on Svalastoga (1959).
3. We only considered experience in children's homes of five years or greater duration. Many of the Experimental children had been to children's homes for brief periods while their mother was hospitalized. These experiences were seen as quite different from the experience of children who actually had to make a children's home their home until they could go out and earn their own living.
4. A rural residence was defined as living in a town with a population of 2500 persons or less.

Characteristics of the sample

An initial letter was sent to the family informing them of the project and the fact that they have been included in the sample. The project had received copious newspaper, radio, and TV coverage, so that in most cases the family was already somewhat prepared. Both *C* and *E* families were told that we were interested in the effect of "nervous breakdown" on the members of the family. They were also informed of our need for normal families. We did not identify to which group we thought they belonged, but this was usually obvious to them.

Table 2 presents the identifying characteristics of the *E* and *C* groups.

Procedure

Until testing was complete none of the researchers was informed regarding whether the children tested that day were *C* or *E*. (The interviewing psychiatrist could usually guess from the interview material.) The social worker scheduled all visits. The procedure was identical for *C* and *E* subjects.

The subject's day

Testing began at 8 a.m. First *S* had his height and weight taken. He was then escorted to the psychophysiological laboratory where he underwent mild stress, conditioning, and stimulus generalization procedures. He then received a full Wechsler Intelligence Scale for Children and an abbreviated MMPI. Then came lunch. After lunch he took two Word Association Tests (single word response and continual association) and completed an adjective check list describing himself. He then returned for a second psychophysiology session where he underwent mild stress, semantic conditioning, and mediated generalization procedures. Finally, *S* was interviewed by a psychiatrist and given an honorarium. A sub-sample also provided urine samples.

Morning session

Recording was done on an Offner Type R Dynograph. We made use of a device designed in Dr. Ax's laboratory to reverse polarity of the electrodes every 1.2 seconds. The psychophysiology laboratory was in the basement of a hospital, in a room separated by two tight-fitting doors from a lightly traveled corridor. The humidity and temperature of the laboratory were relatively constant but recorded before and after each session. After washing and alcohol sponging at points of electrode placement, *S* reclined on a hospital bed and was asked to relax. Respiration, heart rate, GSR and EMG electrodes were attached.

Respiration. An Offner respiration transducer was fastened just above the waistline and below the diaphragm.

Heart rate. Electrodes were attached with rubber straps to the ankles and to the left arm just below the elbow. Electrode paste was vigorously rubbed in.

EMG electrodes. EMG electrodes were fastened with elastic tape 2 cm above the eyebrows and 5 cm on either side of the noseline. Electrode paste was vigorously rubbed in.

GSR electrodes. GSR electrodes consisted of zinc, 7 mm in diameter, embedded in a plastic cup. Small sponges saturated in zinc sulfate solution were inserted into the plastic cup.

When the transducers were attached, recording was started and was continuous until the conclusion of generalization testing, S was permitted to relax for 15 minutes. Earphones were then attached.

Conditioning and generalization procedure

Approximately 30 seconds after the tape recorder was started, S heard instructions informing him of the procedure to follow. At the end of the instructions there was a silence of 70 seconds followed by 8 desensitization presentations of the CS (conditioned stimulus – 1000-cps tone). Nine seconds after the final "desensitization trial," conditioning trials began. Unconditioned stimulus (UCS) was an irritating noise of 96 db (where 0 db $= 0.002$ dynes/cm^2) presented for $4\frac{1}{2}$ seconds following 1/2 second after the onset of CS (54 db). There were 14 partial reinforcement trials (9 CS–UCS pairings, and 5 interspersed presentations of the CS alone). Trials were separated by intervals which varied from 17 to 77 seconds.

Following the final conditioning trial, there was an interval of 3 minutes, following which conditioning and stimulus generalization testing began. Generalization stimuli were tones of 1311 cps (GS$_1$) and 1967 cps (GS$_2$). There were 9 trials, 3 each of CS, GS$_1$, and GS$_2$. Duration of CS, GS$_1$, and GS$_2$ was 2 seconds. The order of the CS, GS$_1$, and GS$_2$ was counterbalanced.

The final conditioning and stimulus generalization testing trial marked the end of the morning session, which took approximately 50 minutes. S was disconnected from the apparatus and escorted from the laboratory.

Afternoon psychophysiology session

Word association norms

Before beginning this pilot study we obtained and tabulated word

association norms for the Kent-Rosanoff List from 145 Danish school children between the ages of 9 and 16 years. This was in preparation for the semantic conditioning and mediated generalization procedures of the afternoon psychophysiology session and the Word Association Test.

In this procedure a psychophysiological response was conditioned to the word "light" ("lys" in Danish). In mediated generalization testing we presented the stimuli "lamp" ("lampe" in Danish), "dark" ("mørk" in Danish), and "fruit" ("frugt" in Danish). These words as stimuli vary in the probability that they will elicit "light" as an associate (61%, 20%, 0%, respectively in the Danish norms). "Lamp" or "dark" elicit the implicit association "light" which elicits the conditioned psychophysiological response. The strength of this response has been shown to vary with the strength of association between the generalization test stimulus and the original conditioned stimulus (M.T. Mednick, 1957; Mednick and Wild, 1962).

The conditioning and generalization test procedures in the afternoon were otherwise equivalent to the morning session.

Wechsler Intelligence Scale for Children. A Danish translation of the WISC in common use in Denmark was used. Danish norms will be available in the future. All subtests were administered.

MMPI. A Danish translation was used. It should be noted that norms do not exist for Danish scales. We intend to attempt to develop a preschizophrenia scale. The test was shortened to 304 items by removing items deemed inappropriate or offensive to children.

Word Association Test (WAT). A Danish version of the Kent-Rosanoff Test was administered. The word "mutton" was omitted since it is rather unusual in Danish. The words "sun" and "star" were added to make a total of 101 words. The words were read to *S* with the instruction to respond to each word with the first word that came to mind. Response latency was recorded.

Continuous Association Test (CAT). Subjects were also presented with 30 other words and asked to associate continuously to each of them for one minute. Responses and response latencies were recorded.

We attempted to avoid associative chaining by having the stimulus word on a card before *S* during the entire minute period.

Adjective Check List (ACL). A specially constructed list of 241 adjectives was administered to each *S* with instructions to check those items which he would use to describe himself. The interviewing psychiatrist, WISC, and WAT administrators also used the ACL to describe each *S*.

Psychiatric interview

Each *S* underwent a psychiatric interview to assess his current diagnostic status. The interview was largely precoded and highly structured. The questions concerned *S*'s mental status, social history, and attitudes. There are 94 coding items in the interview. Two coders independently coding 20 cases agreed in 100% of the 20 cases on 69 of these coding items, 95% on 9 of these items, 90% on 10 of these items, and 85% on 6 of these items. We considered the coding reliable for these items. Six other items were discarded since they could not reach 85% agreement.

The psychiatric interview took 30–40 minutes.

Measures obtained outside of testing day

Parental interview

The social workers interviewed the individual responsible for the child on questions concerning the child's current behavior, social development, school behavior, parental behavior, and parents' socioeconomic status. The interview was highly structured. Working with 30 cases and 88 coding items, two coders achieved 100% agreement on 61 items, 95% agreement on 11 items, 90% agreement on 13 items, and 85% on 3 items. We considered the coding reliable.

School report

A questionnaire was mailed to each *S*'s school. Items concerned *S*'s

relationship to the teacher and classmates as well as academic achievement. Of 311 forms sent out, 310 have been received to this date. Items were in the "true, not true" form. The questionnaire was filled out by the teacher most familiar with *S*. [...]

After completion of subject testing in 1964, an alarm network was established to detect subjects who broke down. Under the national health insurance program, each subject had a family doctor. These physicians were alerted to the fact that their patients were participants in the project and were requested to provide information concerning future contacts with the subjects. Further, all psychiatric facilities in Denmark (and all health facilities in Sjælland) were requested to notify the Institut immediately upon hospitalization of any of the subjects.

SOME PREMORBID CHARACTERISTICS
RELATED TO BREAKDOWN IN CHILDREN
WITH SCHIZOPHRENIC MOTHERS*

SARNOFF A. MEDNICK AND FINI SCHULSINGER

A brief resume of the project design is given in this paper. It summarizes the findings which relate to high- and low-risk group differences. A detailed discussion of the first 20 subjects reported by the alarm-network is provided.

The reader should note that one additional data source was discovered after the main project had commenced. Every birth in Denmark, except in extraordinary circumstances, is attended by a trained midwife who completes a detailed form covering the pre- and post-birth condition of the mother together with information on the birth process and the condition of the neonate. These forms were obtained for the appropriate subjects and subjected to subsequent data analyses.

Schizophrenics excite a good deal of behavioral research, the goal of much of this research is to produce information concerning the *etiology* of schizophrenia. It may be difficult, however, to isolate such etiological factors through studies carried out with individuals who have lived through the process of becoming and being schizophrenic. The behavior of these individuals may be markedly altered in response to correlates of the illness such as educational, economic and social failure, pre-hospital, hospital and post-hospital drug regimens, bachelorhood, long term institutionalization, chronic illness and sheer misery. In research with non-schizophrenics, these same factors have been shown to measurably affect behavioral research results. If researchers used control groups which were equated with their schizophrenic groups for

all of these correlates of schizophrenia, then any observed differences could reasonably be ascribed to the variable of schizophrenia. But such control groups are apparently not readily available. Consequently, in comparisons of normals and schizophrenics, it is often difficult to judge what portion of the reported differences have unique relevance to schizophrenia. If, for example, comparisons of non-psychiatric prisoners and normals produced identical differences we might tend to attribute the schizophrenic–normal differences to the effects of institutionalization rather than some intrinsic quality of the schizophrenic.

In view of these considerations we decided to attempt to study the schizophrenic before he became ill. We turned to the study of young, high-risk populations (children with schizophrenic mothers). There are certain advantages in examining such subjects:

(1) They have not yet experienced many aspects of the schizophrenic life such as hospitalization and drugs. Thus, these factors do not yet color their reactions.

(2) The researchers, relatives, teachers and the subject himself do not know that he will become schizophrenic. This relieves the data of a certain part of the burden of bias. The bias is certainly not greater for the future schizophrenic than for other high-risk subjects who do not succumb.

(3) The information we gather is current, not retrospective. That part of our inquiry which is retrospective is less so than it would be if the subjects were adults.

(4) The data are uniformly and systematically obtained. This is in contrast to retrospective studies which make use of childhood and school records concerning adult schizophrenics.

(5) One advantage of this method which may not be immediately apparent is the fact that the ideal controls for the high-risk subjects who become schizophrenic, are the high-risk subjects who develop other deviances and the high-risk subjects who do not become deviant. We consider it an advantage that such controls are an integral part of the design. (See fig. 1.).

Our method involved the intensive examination of 207 "normally functioning" children who had chronic schizophrenic mothers and 104 control children. We estimate that the group of 207 children (high-risk group) contains more than 25 children who will some day be hospitalized for schizophrenia. We intend to follow these 311 children for 20 years from the inception data of the study, 1962.

	HIGH-RISK Children with schizophrenic mothers		LOW-RISK Children with "normal" mothers	
Level I	200		100	

	Eventually deviant	Eventually not deviant	Eventually deviant	Eventually not deviant
Level II estimated number	100	100	10	90

	Eventually schizophrenic	Eventually deviant	Eventually not deviant		
Level III estimated number	30	70	100	10	90

Fig. 1. Example of design of study of high-risk samples.

Note: This in an illustration of a study using high-risk samples of 200 children with schizophrenic mothers and 100 low-risk control subjects. The design can be conceptualized as developing at three levels. At the first level we can study the distinguishing characteristics of children with schizophrenic mothers in comparison with children with no familial psychiatric background. At the second level we can estimate that about 50% of the high-risk children will become seriously socially deviant. Rather good controls for these deviants are the children with schizophrenic mothers who do not become deviant. At the third level we can estimate that perhaps 30 of the 100 high-risk deviants will be diagnosed schizophrenic. The remaining 70 high-risk deviants may be considered appropriate controls for these 30 schizophrenics, as may the nondeviant, high-risk children and the low-risk children.

Such a study may not be readily or at least easily replicated. Others using even the same design may not be attracted to the same variables. In view of this fact a form of replication can be built into the design. At level II the 100 eventually deviant individuals may be conceived of as suffering breakdown in five waves of 20 subjects each. Thus there are four potential replications of the first data analysis. (It should be mentioned that the precision of the replication might be attenuated if the waves differ in age of breakdown or diagnosis.) At level III, the 30 schizophrenics may be conceived of as suffering breakdown in two waves of 15 subjects each.

The study had a number of aims:

Aim 1. An immediate aim was to compare the high-risk and low-risk subjects on a broad range of measures. Since about 50% of the high-risk group seems to be heading for some serious deviancy (Heston, 1966), differences between these two groups may relate to factors pre-

disposing to deviance. Since the schizophrenics will represent a large subgroup of the deviants some of these differentiating characteristics may relate to schizophrenia.

Aim 2. We intend to follow both high- and low-risk samples and periodically retest them. Changes in personal characteristics and/or life conditions or their interactions which instigate or signal developing illness may make themselves evident through such procedures.

Aim 3. As mentioned above, 50% of the high-risk group may be expected to become seriously deviant. At some future time it will be possible to look back at our initial assessment and discover which (if any) of our test variables could have differentiated this deviant group from the high-risk subjects that develop more normally. Of the 50% of the high-risk group expected to become seriously deviant (approximately 100 individuals), about 30% may be expected to develop some form of schizophrenia. It will be of great interest to see which (if any) premorbid characteristics and life circumstances differentiate the schizophrenics from the other varieties of deviance, from the "non deviant" high-risk subjects, and from the low-risk controls. We will give special attention to the interaction of premorbid personal characteristics and life circumstances as possible factors contributing to mental illness. [. . .]

Results

The project is now in its fifth year. We shall present two data analyses that will serve to illustrate the manner in which this "follow-up high-risk" design may be exploited.

(1) The first analysis compares the behavior and characteristics of the high- and low-risk groups. This comparison is relevant to Aim 1. Due to limitations of space, and in view of the fact that much of this material has appeared earlier (Mednick and Schulsinger, 1965a, 1965b; Mednick, 1966) this presentation will take the form of a narrative summary of some of the significant findings.

(2) Twenty of the high-risk subjects have suffered psychiatric breakdown since the inception of the study. The second analysis reports on characteristics which differentiate these individuals from comparable high- and low-risk subjects. These results are relevant to Aim 3.

High-risk vs. low-risk group comparisons

Birth data. There is a general trend for the birth of the H subjects to have been attended with more difficulties. This is in conformance with previous reports on pregnancy and delivery in schizophrenic women. Significantly more of the mothers of the H subjects tended to be unwed. The birth process took much longer for the H subjects and was perhaps therefore attended by significantly more exploratory examinations. Perhaps most significant is the fact that abnormal placentas were evidenced by 11.3% of the H subjects and only 1.2% of the L subjects. Many of the placental disturbances took the form of infarcts.

Psychophysiologic findings. Extremely consistent and highly significant differences were observed in the latency of the galvanic skin response (GSR). These differences, however, seem to be rather complex. Unequivocally and without exception, the H group responds with a shorter period of latency to each of the nine stress stimuli. In every case the differences are significant and marked. This short latency period suggests that the H group is characterized by a volatile autonomic nervous system that is easily and quickly aroused by mild stress.

The differences between the two groups in latency of response to more neutral stimuli are not as marked. Although the H group continues to respond more quickly, there are many instances in which this trend becomes reversed.

We predicted differences in amplitude of response, speed of recovery, and generalization responsiveness. The two predictions concerning amplitude of response and generalization were strongly supported. The H group responds with much greater amplitude to the stress and to the generalization stimuli than does the L group.

In complete contradiction to our prediction is the fairly consistent finding that the H group recovered from its response to the stress stimuli at a relatively greater rate of speed. For the past 10 years our hypothesis in research in schizophrenia has been that the preschizophrenic should show slower recovery from stress. Our data seem definitely to contradict this hypothesis. We will discuss some interpretations of this finding below.

The H subject is an individual quick to react with extremely vigorous autonomic responses. His autonomic responses are not discrimi-

nating but overgeneralized. (Perhaps the overgeneralization is in part due to the excessively quick latency of the response system.) This very rapid, highly vigorous responding is balanced by an equally labile rate of recovery from autonomic imbalance.

Cognitive findings. The single-word association and intelligence tests yielded few differences between the H and L groups. The H group tended to give more idiosyncratic and fragmented associations. While the H groups performed a bit more poorly on most of the subtests of the WISC, the differences only reached significance on the Arithmetic and Coding subtests.

In a thesis at the University of Copenhagen, Diderichsen (1967) compared the H and L group on the CAT. The H group gave a significantly greater number of responses; they also gave a greater percentage of clang associates, chain associations and repetitions of the response words. These findings suggest that disorders of association are already discernible in the thought processes of some members of the H group. Whether or not these are the individuals slated for schizophrenia remains to be seen. The low magnitude of the single-word association and intelligence test differences probably reflects the fact that no member of either group was mentally ill at the time of the first examination.

Level of adjustment. At the conclusion of the psychiatric interview, the psychiatrist rated the state of adjustment of each subject, taking into consideration personal and environmental factors. This resulted in a five-point scale: (1) poor, (2) relatively poor, (3) doubtful, (4) relatively good, (5) good. Twenty-four per cent of the H group was rated 1 or 2; only 1% of the L group fell into these categories.

Social-developmental factors. In the brief narrative summary which follows we will combine many individual findings.

The first characteristic that all of the H subjects have in common, of course, is that they have mothers who are schizophrenic. Their home life has not been harmonious, but has been marked by frequent parental quarrels. The mother has apparently been relatively dominant in the home. However, her influence has not been benign; the child sees her as scolding and unreliable and not worthy of his confidences.

This difficult environment has been imposed upon (or perhaps has been responsible for producing) a child whose autonomic nervous system is highly labile, reacting to threat abnormally quickly and with abnormal amplitude. To make things still more difficult, reactions are not specific, but overgeneralized. This serves to broaden the range of stimuli that are adequate to provoke this sensitive autonomic nervous system.

In school, the child's teachers recognize his tendency to get upset easily. He seems to react to excitement by withdrawing. He handles peer relations and classroom challenges by passivity. Perhaps this mode of reaction is learned, since it is usually followed by the reduction of his anticipatory fear. Despite the use of passivity and withdrawal, the child is still approachable and is performing relatively adequately. He shows his "nervousness" enough for his teacher to remark on it. However, having begun to learn avoidance behavior, it is difficult for the child to stop, since this takes him away from the very social situations in which he might learn more direct means of dealing with his anticipatory anxiety. His autonomic recovery being more rapid, his withdrawal is even more effectively rewarded. Since he withdraws, his peers reject him; and the circle gets tighter and more difficult to break.

Although, in general, the child performs adequately, he has already learned to effect momentary withdrawal responses whenever pressures build up. In tasks that require continuous concentration and effort (Arithmetic and Coding the WISC), his performance will begin to slip.

The child is a "loner" much of the time. He does not share associations with his peer group as much as does his schoolmate. In addition, he is beginning to learn to escape from autonomic arousal by drifting off into idiosyncratic thought.

Every statement in the preceding summary is based on a statistically significant finding separating the H and L groups. Two points should be made. First, the groups overlap on all of the measures mentioned. Second, the summary is written as though all of these characteristics were present in a single group of individuals. What is more likely is that different subgroups of the H group were responsible for the significant findings on different items.

Twenty high-risk subjects who succumbed

Since the 1962 assessment the Alarm Network and the follow-up interview have identified 20 H risk subjects who have manifested severely abnormal behavior. We shall call these individuals the Sick Group. Of these, 12 have been admitted to psychiatric facilities or placed under psychiatric care. The remaining 8 are severe schizoids, delinquents, alcoholic or have manifested bizarre symptomatic behavior. Case summaries are presented in table 1.

Why did these particular H subjects become ill? How are they different from the other H subjects? The answers could lie in certain personal characteristics (physiological, psychological or early experiential) which they already possessed at the time of the 1962 assessment; the answers could lie with the experiences they have had since 1962; the answers could lie in the interaction of these factors. We have recently completed a personal examination and home interview of the H and L samples. Two aims of this personal examination were to obtain information on the course of the subject's recent life and observe the subject interacting with his family in his home. This information may help us to evaluate the role of recent experience in contributing to breakdown. These data are not yet available. In this report we limit ourselves to an attempt to fulfil Aim 3, to "discover which (if any) of our test variables could have differentiated this sick group from the high-risk group that developed more normally".

Selection of comparison groups

At an early stage of this research the H subjects were set off in matched pairs. If was hoped that these matched pairs would provide us with a preselected control for subjects who break down. This strategy failed for two reasons. First, while not ill enough to be in the Sick Group, may of the erstwhile controls are likely candidates and could hardly be said to have "developed more normally". In addition, the original matching variables did not include any indicant of the subject's psychiatric status at the time of the first examination (such as the interviewing psychiatrist's rating of Level of Adjustment). Many of the otherwise matched pairs were widely discrepant for Level of Adjustment. Any differences in the 1962 assessment data between such pairs of subjects might not be prognostic but might simply reflect already existing differences in Level of Adjustment.

Table 1

Descriptions of conditions of sick group

Male, born 16 March 1953; extremely withdrawn, no close contacts, 2 months' psychiatric admission following theft, currently in institution for boys with severe behavior difficulties, still performing petty thieveries.

Female, born 19 January 1943; married, one child, extremely withdrawn, nervous. Evidence of delusional thinking, pulls her hair out, has large bald area.

Female, born 29 March 1946; promiscuous, highly unstable in work, no close contacts, confused and unrealistic, psychiatric admission for diagnostic reasons, recent abortion, some evidence of thought disorder.

Male, born 1 July 1946; under minor provocation had semipsychotic breakdown in Army, expresses strange distortions of his body image, thought processes vague, immature.

Male, born 2 May 1944; severe difficulties in concentrating; cannot complete tasks; marked schizoid character; marginally adjusted.

Male, born 3 June 1947; lonely in the extreme; spends all spare time at home; manages at home only by virtue of extremely compulsive routines; no heterosexual activity; marked schizoid character.

Male, born 1 October 1953; no close contact with peers, attends class for retarded children, abuses younger children, recently took a little boy out in the forest, undressed him, urinated on him and his clothes, and sent him home.

Male, born 17 January 1954; has history of convulsions, constantly takes antiseizure drug (Dilanthin), nervous, confabulating, unhappy, sees frightening "nightmares" during the day; afraid of going to sleep because of nightmares and fear that people are watching through the window, feels teacher punishes him unjustly.

Female, born 18 March 1944; nervous, quick mood changes; body image distortions, passive, resigned; psychiatric admission, paranoid tendencies revealed, vague train of thought.

Male, born 14 March 1952; arrested for involvement in theft of motorbike; extremely withdrawn, difficulties in concentration; passive, disinterested, father objected to his being institutionalized; consequently he is now out under psychiatric supervision.

Male, born 19 October 1947; level of intellectual performance in apprenticeship decreasing, private life extremely disorderly; abreacts through alcoholism.

Male, born 20 January 1944; severe schizoid character, no heterosexual activity; lives an immature, shy, anhedonic life, thought disturbances revealed in TAT.

Female, born 25 May 1947; psychiatric admission, abortion, hospital report suspects pseudoneurotic or early schizophrenia; association tests betray thought disturbance, tense, guarded, ambivalent. Current difficulties somewhat precipitated by sudden death of boy friend.

Male, born 13 August 1950; sensitive, negativistic, unrealistic; recently stopped working and was referred to a youth guidance clinic for evaluation. Is now under regular supervision of a psychologist.

Male, born 28 May 1947; history of car stealing, unstable, drifting, unemployed, sensitive, easily hurt, one year institutionalization in a reformatory for the worst delinquents in Denmark. Now hospitalized for schizophrenia.

Female, born 1 June 1945; psychotic episode, one year of hospitalization; diagnoses from 2 hospitals: (1) schizophrenia, (2) manic psychosis.

Male, born 3 September 1946; severe schizoid character; psychotic breakdown in Army, preceded by arrest for car thievery. Now hospitalized, for schizophrenia.

Male, born 28 January 1953; perhaps border-line retarded; psychiatric admission for diagnostic reasons; spells of uncontrolled behavior.

Male, born 23 June 1948; repeatedly apprehended for stealing; severe mood swings, sensitive, restless, unrealistic; fired from job because of financial irregularities.

Female, born 5 July 1941; highly intelligent girl with mystical interests. Very much afflicted by mother's schizophrenia. TAT reveals thought disorder. Receiving psychotherapy.

In view of these two considerations we rematched each subject in the Sick Group, individual for individual, with one H subject and one L subject. The matching variables were: the psychiatrist's rating of Level of Adjustment at the time of the initial assessment, age, sex, and social class. In addition, we imposed the restriction that the H group controls must have either maintained or improved in their Level of Adjustment since the time of the first assessment. This rating was independently obtained by the junior author from the material of the personal follow-up mentioned above. Of the 20 controls from the H Group, 11 had shown definite improvement in Level of Adjustment; 9 had maintained their Level. These controls from the H Group will be called the Well Group. Comparable follow-up Level of Adjustment ratings are not yet available for the matched L Group control subjects.

The mean values for each of the matching variables may be found in table 2. "Control Group" refers to the L comparison group. The socioeconomic status (SES) of these groups is somewhat lower than that of the parent H and L groups which had SES scores of 2.2 and 2.3, respectively. This is mainly due to the presence in the Sick Group of a disproportionate number of children raised in children's homes. (This factor was matched for both the Well and Control Groups.) SES is zero for such children. Notice also that the Control Group could not be perfectly matched with the Sick and Well Groups for Level of Adjustment because too few L subjects had low enough Level of Adjustment scores for this purpose. We have, however, selected the worst of the L Group for the Control Group.

Table 2

Identifying characteristics of Sick, Well and Control Groups

	Sick	Well	Control
Mean age	15.1	15.1	15.1
Mean socio-economic status	1.45	1.05	1.85
Mean level of adjustment	3.0	3.0	3.3
Number of females	5	5	5
Total N	20	20	20

Note: The figures in the table refer to the subjects' status at the time of the initial assessment. The social class scale was adapted from one developed for Denmark by Svalastoga (1959). The scale runs from 0 (Low) to 6 (High). The Level of Adjustment rating is drawn from the Psychiatric Interview.

This matching process yielded three groups. Two of these groups (Sick and Well) are drawn from the H sample, i.e. they have schizophrenic mothers. An experienced psychiatrist found these two groups to be equivalent in Level of Adjustment in 1962. Since that time the members of the Sick Group have suffered severe psychiatric breakdown; the members of the Well Group have tended to maintain or improve their level of adjustment. The matched Control Group, drawn from the L Group, is at the lower end of the "normal" psychiatric spectrum. We will now turn to a consideration of the variables in the 1962 assessment that differentiate these groups.

Results

The latest member of the Sick Group was brought to our attention 3 weeks before this Conference. Consequently not all variables and tests have been analyzed. This is a preliminary report; more findings may be added in the future. The report of results will concentrate on differences between the Sick and Well Groups.

Birth data

The factors examined included mother's age, marital status, previous pregnancies, time for the birth process, explorations, irregularities, anaesthetic, prematurity, weight, length, and characteristics of the

newborn. While there was a slight general tendency for the Sick Group to have had a more difficult birth, none of the differences reached statistical significance.

Parent interview

Of all the 88 coded items in the Parent Interview only a few significantly differentiated the groups. Most significant is the fact that the Sick Group tended to lose their mothers to a mental hospital quite early and permanently. These figures are shown in table 3. It is important

Table 3

Per cent of group with mother completely absent from home during specified periods in the child's life

Child's age in years	Sick	Well	Control	χ^2	p
0–1	7	5	0		n.s.
1–2	11	5	5		n.s.
3–5	30	10	10		n.s.
5–10	65	15	30	20.6	< 0.01
11–13	81	40	35	15.1	< 0.01
14–17	85	42	46	11.8	< 0.05

Note: The Sick and Well Groups differ significantly for ages 5–10 ($\chi^2 = 6.5$, 1 *df*, $p < 0.01$), for ages 11–13 ($\chi^2 = 18.63$, 1 *df*, $p < 0.01$), and for ages 14–17 ($\chi^2 = 4.96$, 1 *df*, $p < 0.05$).

to emphasize that the tabulated percentages refer to the *total* absence of the mother from the home during the specified period. Thus if the mother was in the home for 3 months during the third to fifth year of the child's life and absent thereafter, this absence was first coded in the 5–10 year category. It should be noted that the absence of the mother from the home occurred at about the same time and frequency for the Well and Control Groups. In every case where there is overall significance between the three groups the Sick and Well Group taken by themselves are also significantly different.

For the Sick and Well Groups, the absence of the mother from the home was in every case occasioned by psychiatric hospitalization. On the basis of length of hospitalization, degree of recovery between hospitalizations, and treatment received, the illness of the mother was

rated as Very Severe or Moderately Severe. Of the Sick Group mothers, 75% were rated as Very Severe; 33% of the Well Group mothers were rated as Very Severe ($\chi^2 = 6.35$, 1 *df*, $p < 0.05$). The mothers who were Very Severely ill left the home for the hospital at a time when the child was significantly younger.

In view of the greater severity of illness of the mothers who left the home early, these data concerning the mother's absence from the home could be interpreted in relatively environmental or relatively genetic terms. It is also of interest that absence of the mother from the home was correlated with signs of disturbed behavior even in the initial assessment.

School report

The teacher found it characteristic of 67% of the Sick Group that when upset or excited their reaction persisted and they continued to be upset. He reported this for only 22% of the Control Group and 23% of the Well Group ($\chi^2 = 6.69$, 2 *df*, $p < 0.01$).

The Sick Group was also rated by the teacher as being more disturbing to the class. We can identify subjects who were either rated as being class disciplinary problems, domineering, aggressive and creating conflicts, or disturbing the class with chatting. Fifty-three per cent of the Sick Group, 18% of the Well Group and 11% of the Control Group were listed in one or more of these three categories. The frequencies for the three groups are significantly different as are the Sick–Well differences taken by themselves.

WISC and WAT

There were *no* statistically significant differences on these tests between the Sick and Well Groups. On all 12 of the WISC subtests the Well Group achieved a higher mean raw score than did the Sick Group. The three groups differed significantly on the Picture Arrangement Subtest; however, the Sick–Well Group differences were not significant.

Continual association test

In this test where the subject is asked to give multiple single-word associations to a stimulus word, the Sick Group distinguished itself by frequently rattling off a whole series of words which were interrelated but contextually relatively irrelevant. (*Opremsning* in Danish). This

series might be given to the stimulus word "afraid" as follows: "Mother is afraid; father is afraid; brother, sister, aunt, uncle, etc." The mean *Opremsning* scores (corrected for Total Number of Response) for the Sick, Well and Control Groups were 1.33, 0.11, 0.33, respectively (F = 4.33, 2/51 *df*, *p* < 0.05). The Sick *vs.* Well Group differences were also significant (*t* = 2.30, 36 *df*, *p* < 0.05).

Another characteristic of the associations of the Sick Group is a tendency to slide away from the original stimulus word, despite cautions by the examiner. This characteristic has been named "drifting"; each of the Sick and Well Groups' sets of associations to each of the 30 stimulus words has been rated on a scale from 1 (no drifting) to 3 (much drifting). The Sick Group had a mean Drifting score of 1.72, the Well Group 1.33 (*t* = 2.10, 38 *df*, *p* < 0.05).

Electrodermal measures

Basal level

There were no significant differences among the three groups in basal level at any point. The basal levels all hovered around the mean H Group levels. The relatively low basal skin resistance of the Control Group is probably related to their relatively low Level of Adjustment rating.

Responsiveness-stress stimuli

Table 4 presents the mean GSR amplitude for the three groups for the stress stimuli. As can be seen, the Sick Group gives the largest responses to the stress stimuli with the Well Group falling in the middle. On 3 of the 9 trials differences between the Sick and Well Groups were significant. On most of the stress trials the variance for the Sick Group proved to be 5–7 times that of the Well Group. This suggests that a subgroup of the Sick Group might have given abnormally large responses which were producing the mean differences in response amplitude. This point will be discussed below. A count was made of the number of individuals responding to the stress stimuli. As almost everyone responded on almost every trial, there were no differences between the groups on this measure.

Table 4

Mean amplitude of GSR response to Stress Stimuli, Conditioned Stimuli and Generalization Stimuli (comparison of Sick, Well and Control Groups)

Points of measurement	Mean GSR response in ohms			
	Sick	Well	Control	p^a
UCS trials				
CS–UCS I	25,859	17,194	9,238	$< 0.01^b$
CS–UCS II	14,467	10,472	6,583	< 0.05
CS–UCS III	11,128	8,167	4,133	0.01
CS–UCS IV	10,823	11,567	5,365	n.s.
CS–UCS V	10,759	6,859	4,900	< 0.05
CS–UCS VI	10,900	5,494	3,606	$< 0.05^b$
CS–UCS VII	8,778	6,728	2,922	n.s.
CS–UCS VIII	10,983	5,761	4,241	$< 0.05^b$
CS–UCS IX	9,682	7,217	3,244	< 0.05
CS trials				
CS 1	3,744	2,917	3,189	n.s.
CS 2	5,394	1,959	4,094	n.s. ^{b}
CS 3	6,139	1,617	2,853	n.s. ^{b}
CS 4	5,694	2,067	1,433	n.s.
CS 5	6,178	3,106	1,711	n.s.
Generalization trials				
CS (1)	6,611	2,717	1,300	< 0.05
GS I (1)	6,189	2,822	422	$< 0.05^b$
GS II (1)	3,739	1,422	233	< 0.05
GS (2)	5,222	2,389	756	< 0.05
GS I (2)	4,400	2,139	50	n.s.
GS II (2)	2,088	1,278	0	< 0.05

[a] Significance of differences was tested in all cases by analysis of covariance. Basal level just preceding response was the covariance control.

[b] Significant *t*-test between Sick and Well.

A comparison of the Sick and Well Groups with the total H Group reveals that on most trials these two groups fall on either side of the total H Group. However, reversals occur and the differences are not large.

Responsiveness-conditioned stimuli

There seems to be some evidence that the Sick Group showed more conditioning than the other groups. This may be seen in fig. 2. The Well and Control Groups show almost no evidence of conditioning. The mean summated GSRs to the conditioned stimuli for the Sick and Well Groups were 5430 and 2311 ohms respectively. This difference was significant ($t = 2.15$, 38 *df*, $p < 0.05$). As may be seen in table 4, the Sick and Well Groups differed significantly on the second and third conditioning trials.

A count was made of the number of CRs per subject. This conditioning score could vary from 0 to 5. The Sick, Well and Control Groups had means of 3.28, 2.00 and 1.28 respectively. These three means were significantly different ($F = 4.72$, 2/53 *df*, $p < 0.05$) as were the Sick and Well means ($t = 2.00$, 38 *df*, $p < 0.05$).
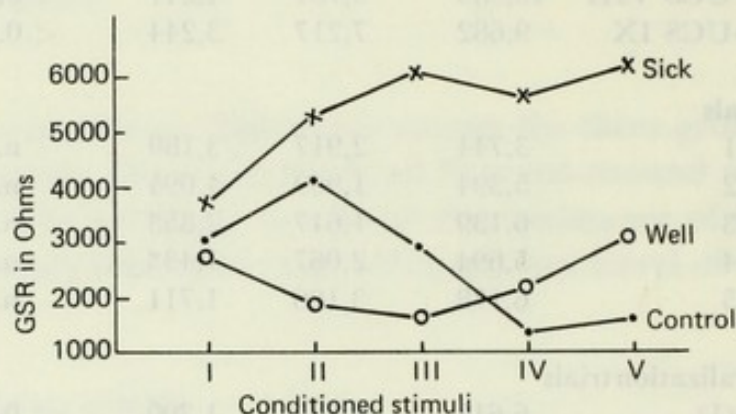
Fig. 2. Amplitude of conditioned responses for 5 test trials with CS alone (for Sick, Well and Control Groups).

Demonstrating a conditioned response with the GSR as a response measure has always proven difficult because of the relatively rapid adaptation of the GSR. This suggests that rapid adaptation could have been a reason for the poor conditioning shown by the Well and Control Groups (see fig. 2). On the other hand, it could be taken as an indication that the Sick Group is not so much evidencing conditioning as failing to habituate. This argument can be countered by pointing to the fact that from trials 1 to 5 the CRs of the Sick Group tended to increase in amplitude (unfortunately this increase was not significant). This increase was taking place while their responses to the UCS (among which the CS trials are mixed) were decreasing.

The weight of the evidence slightly favors the conclusion that the Sick Group evidenced superior GSR conditioning. When the conditioning performance of the Sick and Well Groups is compared with that of the total H Group this conclusion is strengthened. The Well Group behaves like a somewhat enfeebled version of the total H Group.

Generalization

The CS and GS_1 and GS_2 were presented in extinction test procedures 3 times each in counterbalanced order at the conclusion of conditioning. Table 4 and fig. 3 present the mean amplitude of the generalization responses for the first 2 test trials. The third test trial data are not presented since very few subjects were responding.

The generalization responsiveness of the Sick Group is well above the level of the Well and Control Groups; the differences are significant on 5 of the 6 trials. When each subject is given a generalization score by adding together the amplitude of his responses to the first presentations of GS_1 and GS_2, the Sick Group evidences significantly more generalization than the Well Group (U = 222, Ns = 18, 18, $p < 0.04$). It should also be pointed out that the shape of the gradients are
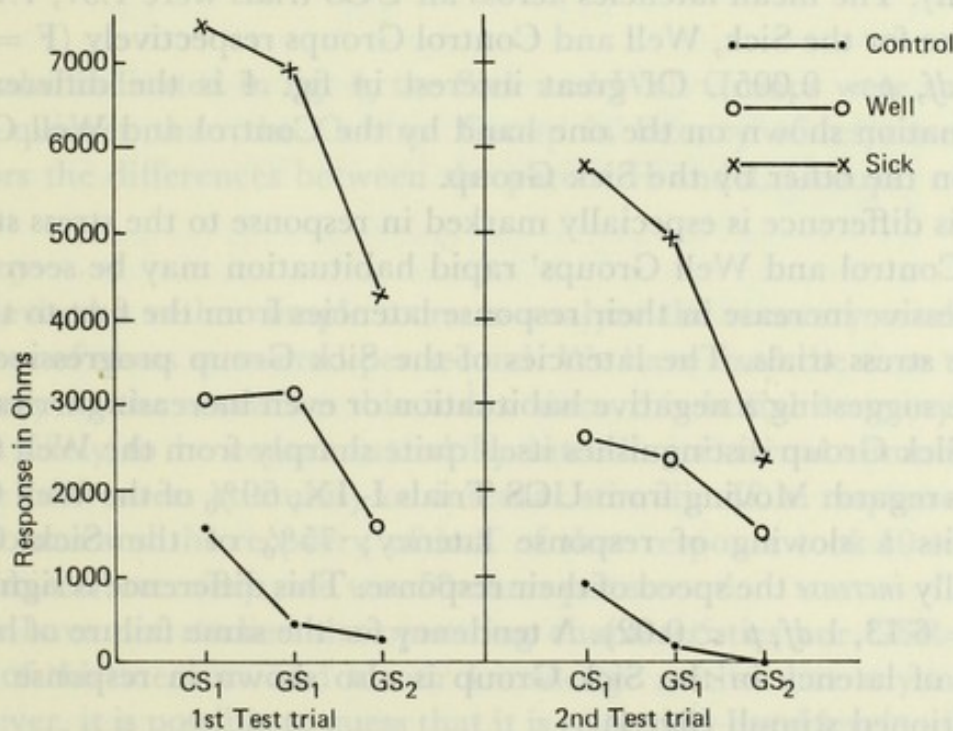
Fig. 3. Generalization gradients for Sick, Well and Control Groups.

approximately the same for the Sick, Well and total H Groups (concave downward) while the gradients for the Control and total L Groups are in the normal concave-upwards form (Mednick and Freedman, 1960). This is also shown in the fact that the amount of relative generalization (ratio of generalization responsiveness to conditioned responsiveness) is about the same for the Sick and Well Groups. Another way of saying this is that the Sick and Well Group generalization curves are essentially parallel and different from the Control curve. The earlier comparison of the H–L gradients demanded the interpretation of an essential difference between these groups in generalization responsiveness. Both the Sick and the Well Groups continue to evidence this heightened generalization responsiveness. The fact that the Sick and Well Groups evidence parallel curves suggest that some additional factor might be acting to increase the overall responsiveness of the Sick Group. This factor could either be a higher level of arousal or a failure of habituation or both.

Latency

A summary of the latency data may be found in fig. 4. The groups differed significantly on all but one of the trials with the UCS (stress stimuli). The mean latencies across all UCS trials were 1.57, 1.77 and 2.47 sec for the Sick, Well and Control Groups respectively ($F = 8.63$, $2/52$ *df*, $p > 0.005$). Of great interest in fig. 4 is the difference in habituation shown on the one hand by the Control and Well Groups and on the other by the Sick Group.

This difference is especially marked in response to the stress stimuli. The Control and Well Groups' rapid habituation may be seen in the progressive increase in their response latencies from the first to the last of the stress trials. The latencies of the Sick Group progressively decrease suggesting a negative habituation or even increasing irritability. The Sick Group distinguishes itself quite sharply from the Well Group in this regard. Moving from UCS Trials I–IX, 69% of the Well Group exhibits a slowing of response latency; 75% of the Sick Group actually *increase* the speed of their response. This difference is significant ($\chi^2 = 6.13$, 1 *df*, $p < 0.02$). A tendency for the same failure of habituation of latency in the Sick Group is also shown in response to the conditioned stimuli (fig. 4).
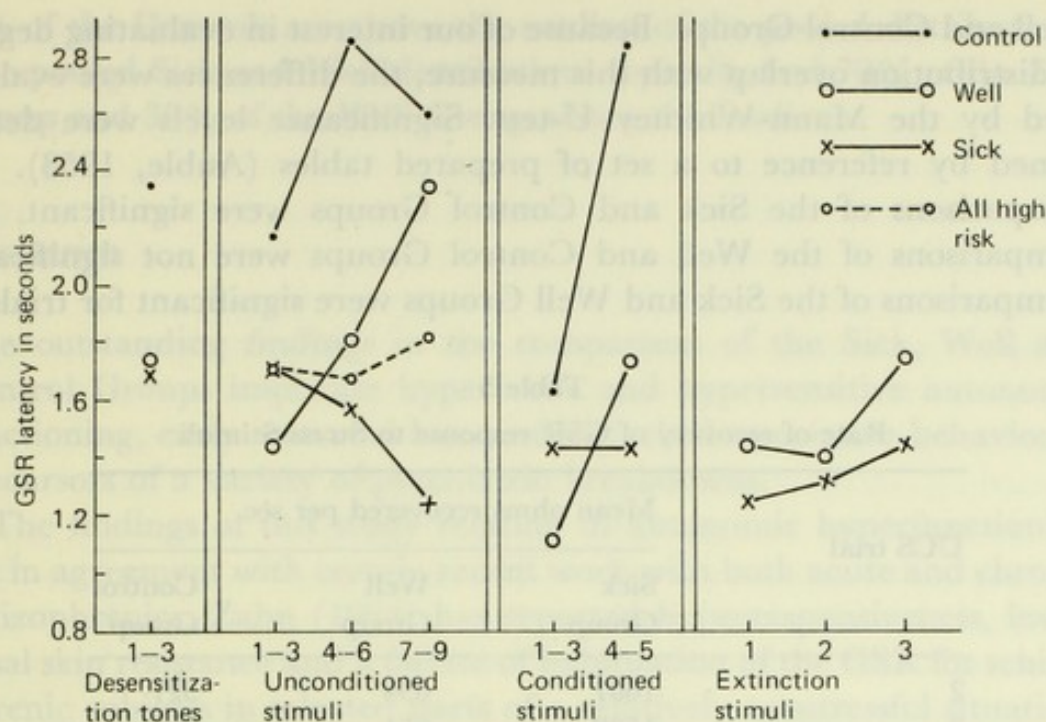
Fig. 4. Mean GSR latencies for the 3 groups for the entire session. Note that the Control Group latencies are omitted for the Extinction Stimuli trials 1, 2 and 3. These were omitted since there were very few responses and the latencies were completely off the figure. The mean latencies for the Control Group for trials 1, 2 and 3 were 2.63, 3.12 and 4.83 sec respectively.

As is also indicated in fig. 4, the Sick and Well Groups were substantially quicker than the Control Group in latency of response. This mirrors the differences between the parent H and L Groups.

Recovery

We devised a rather simple score to analyze the recovery results, the number of ohms recovered per second. We have used the time to *half-recovery* as the score for this index since this initial recovery phase is less likely to be contaminated by intruding external stimuli (such as the next stress stimulus) or internal stimuli. If a response were 1000 ohms and the recovery of half of that response took 10 sec then the subjects' recovery rate was 50 ohms per second.

We have not studied the operating characteristics nor GSR correlates of this measure and to our knowledge neither has anyone else. However, it is possible to guess that it is related to basal level.

Mean ohms recovered per second is reported in table 5 for the Sick,

Well and Control Groups. Because of our interest in evaluating degree of distribution overlap with this measure, the differences were evaluated by the Mann-Whitney U-test. Significance levels were determined by reference to a set of prepared tables (Auble, 1953). All comparisons of the Sick and Control Groups were significant. All comparisons of the Well and Control Groups were not significant. Comparisons of the Sick and Well Groups were significant for trials 2,

Table 5

Rate of recovery of GSR response to Stress Stimuli

UCS trial	Mean ohms recovered per sec.		
	Sick Group	Well Group	Control Group
2	1607	634	521
3	1538	651	595
4	1386	764	394
5	1230	615	582
6	1282	606	331
7	1816	749	401
8	1490	884	392
9	1406	691	590

Note: (1) The rate of recovery is computed for the first half of the ohms recovered. If a response were 1000 ohms and recovery of half of that response took 10 sec then the recovery rate was 50 ohms/sec.

(2) UCS trial 1 was omitted since most subjects did not succeed in recovering half of their response to this stimulus before the onset of UCS 2.

3, 4, 5, 6 and 9. Trials 7 and 8 were not significantly different. The recovery rate of the Sick Group is substantially greater than that of the Well or Control Groups. The latter two tend to be relatively similar to one another.

The measure separates the groups better than any other in our test battery. The overlap between the Sick and Control Groups is not large. Typically we find 80% of the Sick Group and 20% of the Control Group above the median of the pooled distribution on any one stress stimulus trial. On UCS trial 6 all but one of the Sick subjects and only

two of the Controls are above the median of the pooled distributions. The pooled Sick and Well distributions typically find 70% of the Sick Group and 30% of the Well Group above the median.

Discussion

The outstanding findings in the comparison of the Sick, Well and Control Groups implicate hyperlabile and hypersensitive autonomic functioning, early maternal loss, and disturbed associative behavior as precursors of a variety of psychiatric breakdowns.

The findings of this study relating to autonomic hyperfunctioning are in agreement with certain recent work with both acute and chronic schizophrenics. Zahn (1964) has reported hyperresponsiveness, lower basal skin resistance and a failure of habituation of the GSR for schizophrenic subjects in selected parts of a relatively nonstressful situation. Other recent and methodologically sophisticated studies, in which schizophrenics have been subjected to stress have produced evidence of extremely high autonomic responsiveness in even the chronic schizophrenic (Ax et al., 1962; Malmo et al., 1951; and Ray, 1963). A review by Venables (1966) of recent research in this area seems to place the general form of the hyperresponsiveness hypothesis on a rather firm empirical footing.

When the senior author first advanced the hypothesis of autonomic hyperresponsiveness, as one of several hypothesized etiological precursors of schizophrenia (Mednick, 1958) there were only a few supportive studies that could be cited. "The majority of these studies reported lowered autonomic responsiveness in chronic schizophrenics" (Zahn, 1964, p. 167). The sense of the more recent empirical work on the schizophrenic, and the results of the present study bolster this hypothesis which is central to the theoretical orientation of this project. Two additional preschizophrenic characteristics, which were first hypothesized in 1958, were excessive generalization of autonomic responses and excessively *slower* recovery from stress. The first of these, generalization responsiveness, has found support in the present study. Both the H and Sick Groups evidenced elevated generalization gradients. However, the same cannot be said for the hypothesis of slow recovery. Both H and Sick Groups unequivocally showed abnormally

fast rates of recovery from autonomic imbalance. It seems clear that this hypothesis of slow recovery merits abandonment. It may be of interest to try to reshape the theory to see what role *quick* autonomic recovery could play in the development of schizophrenia.

The theory identifies schizophrenia as a learned disorder of thought and suggests that there are certain physiological and environmental factors that predispose individuals to such learning.

The thought disorder consists of a set of conditioned avoidance responses which help the schizophrenic to control his autonomic hyperresponsivity. The avoidant responses (associations or thoughts) are learned on those occasions when the preschizophrenic escapes from some arousal-producing stimulus by switching to a thought which interrupts this arousal stimulus. The intruding association may then enable the individual to avoid (perhaps for just a moment) the arousal stimulus. This will automatically result in a momentary reduction in arousal level. (Such a reduction in arousal has been shown to have great reinforcement value.) This reduction in arousal level will reinforce the association between the arousal stimulus and the avoidant thought. This, in turn, will increase the probability of an avoidant associate response to future arousal stimulation. Each time this "arousal-avoidant thought" pairing occurs, it will be automatically reinforced by a reduction in arousal and will increase in probability. Notice that the "avoidant thought-reinforcement" relationship is completely internal to the subject. It is a truly autistic process requiring no physical or social interaction for successful operation. After many such learning trials the individual will have built up a single avoidance response or a small repertoire of responses which will have the ability to remove him from arousal stimulation or at least modulate his arousal stimulation.

This repertoire of avoidant responses will be *automatically* cued whenever the individual senses a stressful stimulus. Perhaps we are observing the beginnings of this process in our Continual Association Test results. This automatic avoidance response will seriously interfere with sustained thought processes and long term sets. It is at the point when these conditioned avoidant responses begin to dominate the individual's thinking that he may be classified as schizophrenic.

According to the earlier version of the theory the preschizophrenic is especially prone to learning this avoidant pattern because of his

extreme hyperresponsivity, excessive generalization and slow recovery from autonomic imbalance. However, the hypothesis of slow recovery has always caused critics to point out that this would cause the preschizophrenic to be reinforced more slowly and meagerly for avoidance than even the normal. The finding of an abnormally fast rate of recovery has forced us to alter the theory. It is now our hypothesis that one of the determining features of the preschizophrenic is his abnormally fast recovery; because of this fast rate of recovery he is more easily, quickly and thoroughly reinforced for avoidance than the normal. This taken together with his tendency to chronic hyperarousal will, in a harsh environment, inexorably push him to learn conditioned avoidant thought mechanisms. The revised theory then implicates a rapid autonomic recovery from states of autonomic imbalance as a key factor in a complex of factors predisposing individuals to schizophrenia.

As mentioned above the finding of a failure of habituation has been reported by Zahn (1964). At first glance this finding may be seen as antagonistic to the findings on quick recovery. However, the recovery finding refers to single instances of states of imbalance while failure of habituation refers to a tendency to continue to respond to stimuli over an entire experimental session as though they had never been experienced before. Failure of habituation may prove to be an independent factor. Before accepting this assertion, however, we shall explore the relationship between this variable and GSR latency, responsiveness and generalization.

Maternal loss

Early maternal loss through psychiatric hospitalization was a common precursor of breakdown in the Sick Group. This finding might be compared with research which has found a greater frequency of schizophrenics suffering early maternal loss by death (Hilgard and Newman, 1963). Both of these findings suggest an environmental-stress etiological contribution. However, in our sample we found that the mothers of the Sick Group not only were lost to the family earlier but were also more severely schizophrenic. In view of the findings reported by Kety et al. (1968) we cannot disregard the possibility of a heavier genetic burden in the Sick Group as evidenced by the greater severity

of their mother's illness. Two findings within the Sick Group reflect on this possibility. First, we found that within the Sick Group the very severely schizophrenic mothers were separated from their children when the children had a mean age of 3.75 years; the children of the moderately severe mothers were 8.80 years of age at separation ($t = 2.33$, 18 *df*, $p < 0.025$). The second finding concerns those members of the Sick Group who have been admitted to a psychiatric hospital or who are under psychiatric care. These subjects tend to be the more overtly ill members of the Sick Group with promiscuity and criminality as common symptoms. Eighty-eight per cent of these have very severely schizophrenic mothers; of those Sick Group subjects who have not been hospitalized, 50% have very severely schizophrenic mothers ($\chi^2 = 4.40$, 1 *df*, $p < 0.05$). What is suggested tentatively by these results is that the very severely ill schizophrenic mothers (who had less contact with their children) had children with symptom-rich, acutely disturbed, psychiatric involvement. The Sick subjects, who spent more time with their moderately severely schizophrenic mothers tend to be classed as severely schizoid, anhedonic, overconforming, and obsessive. They also tended strongly to manifest more severe associative drifting ($t = 2.90$, 18 *df*, $p < 0.005$); these subjects also had significantly poorer Level of Adjustment scores ($\chi^2 = 4.8$, 1 *df*, $p < 0.05$). They also tended to be in a subgroup of individuals chosen as fast GSR responders, poor in habituation, high in generalization, fast in recovery and high amplitude responders ($\chi^2 = 11.22$, 1 *df*, $p < 0.005$). These results are highly congruent with those of Reisby (1967). He found that schizophrenics who had spent a relatively long time with their schizophrenic mother tended to develop a more process schizophrenic condition with slow, insidious onset. Schizophrenics having been separated earlier from their schizophrenic mother developed more acute, symptom-rich, reactive schizophrenia.

We present these results on the Sick–Well–Control comparisons with great tentativeness. While the groups are rather well matched and the Sick Group carefully selected, there is a total of only 60 cases. Our tentativeness is even greater regarding the comparisons relating to time spent with the schizophrenic mother. Here our N is only 20. We hope to increase the interpretability of these results by selection of both "relatively sick" and "well" subgroups of the total L Group instead of just a single Control Group. We have one other safeguard built into the

research design. As indicated above, we can expect approximately 50% (100 subjects) of the H Group to develop some form of manifest psychiatric disturbance. This means that we have just observed the first wave of 20 disturbed subjects. We can expect four more waves of 20 subjects each. These waves offer opportunities for cross validation. As the number of cases mounts it will be possible to separate out diagnostic groups (such as schizophrenia) for differential data analysis.

BREAKDOWN IN INDIVIDUALS AT HIGH RISK FOR SCHIZOPHRENIA: POSSIBLE PREDISPOSITIONAL PERINATAL FACTORS*

SARNOFF A. MEDNICK

It will be recalled that the previous paper reported that "While there was a slight general tendency for the Sick Group to have had a more difficult birth, none of the differences reached statistical significance." (page 74). This paper reveals that this was a premature conclusion. Here, it is reported that there is indeed a close relationship between pregnancy and birth complications and aberrant autonomic functioning in those subjects who have succumbed to psychiatric breakdown. Drawing on data from animal studies, the author speculates as to which neuroanatomical, neurophysiological and biochemical mechanisms might play a mediatory role in this relationship.

In 1962–1963 in Copenhagen, Denmark, Dr. Fini Schulsinger and I intensively examined 207 "normally functioning" children with a high risk of becoming schizophrenic. (They have chronic and severely schizophrenic mothers.) We also examined 104 controls. The study is prospective and longitudinal. We intend to follow these 311 subjects for 20–25 years. During the course of these years we estimate that approximately 100 of the high-risk children will succumb to some form of mental illness, twenty-five to thirty should become schizophrenic.

Fig. 1 presents a schematic picture of the research design of this type of study. There are certain research advantages in the longitudinal study of such high-risk populations.

	HIGH-RISK		LOW-RISK	
Level I	Children with schizophrenic mothers 200		Children with "normal" mothers 100	

| Level II | Eventually deviant 100 | Eventually not deviant 100 | Eventually deviant 10 | Eventually not deviant 90 |

| Level III | Eventually schizophrenic 30 | Eventually deviant 70 | Eventually not deviant 100 | 10 | 90 |

Fig. 1. A schematic representation of the high-risk research design.

Note: The design can be conceptualized as developing at three levels. At the first level we can study the distinguishing characteristics of children with schizophrenic mothers in comparison with children with no familial psychiatric background. At the second level we can estimate that about 50% of the high-risk children will become seriously socially deviant. Rather good controls for these deviants are the children with schizophrenic mothers who do not become deviant. At the third level we can estimate that perhaps 50 of the 100 high-risk deviants will be diagnosed schizophrenic. The remaining 70 high-risk deviants may be considered appropriate controls for these 30 schizophrenics, as may the non-deviant, high-risk children and the low-risk children.

Such a study may not be readily or at least easily replicated. Others using even the same design may not be attracted to the same variables. In view of this fact a form of replication can be built into the design. At level II the 100 eventually deviant individuals may be conceived of as suffering breakdown in five waves of 20 subjects each. Thus, there are four potential replications of the first data analysis. (It should be mentioned that the precision of the replication might be attenuated if the waves differ in age of breakdown or diagnosis.) At level III the 30 schizophrenics may be conceived of as suffering breakdown in two waves of 15 subjects each.

(1). They have not yet experienced many aspects of the schizophrenic life such as hospitalizations and drugs. Thus, these factors do not yet color their reactions.

(2) The researchers, relatives, teachers and the subject himself do not know that he will become schizophrenic. This relieves the data of a certain part of the burden of bias, which is certainly not greater for the future schizophrenic than for other high-risk subjects who do not succumb.

(3) The information we gather is current, not retrospective. That part of our inquiry which is retrospective is less so than it would be if the subjects were adults.

(4) The data are uniformly and systematically obtained. This is in contrast to retrospective studies which make use of childhood and school records concerning adult schizophrenics.

Since 1962, 20 of our high-risk children have suffered severe psychiatric breakdown. I will briefly summarize the 1962 premorbid characteristics that distinctly differentiated these 20 sick children from controls.

Methods

The high- and low-risk samples were matched, individual for individual, for certain variables.

The average age of the sample was 15.1 years (range was 9–20 years). There would have been some advantage in testing a younger group; however, it will take 20–25 years for the present sample to pass through the major risk period for schizophrenia. The subjects' mean age was selected so as to maximize the probability that the investigators would still be alive at the conclusion of this risk period. Studies of three-year-old and ten-year-old high-risk samples are being undertaken. A study of prenatal high-risk children is being planned.

Procedures

In addition to weight and height the following measures were taken in the intensive 1962 examination:

(1) *Physiological-conditioning-extinction testing.* Continuous recording was made of heart rate, muscle tension, respiration, and galvanic skin response (GSR) during rest, conditioning, generalization and extinction procedures. The CS was a 54 db tone of 1000 cps. The UCS (also considered the stress stimulus) was a very irritating, loud (96 db) noise presented via earphones.

(2) *Wechsler Intelligence Scale for Children* (Danish adaptation). All subtests were administered.

(3) *Personality Inventory*. This consisted of a group of items translated from the MMPI.

(4) *Word Association Test*. This was a translation of the Kent-Rosanoff list.

(5) *Continuous Association Test*. We observed the flow of the subject's associations to a single word over a one-minute period. Thirty stimulus words were used.

(6) *Adjective Check List*. A list of 241 items was used by professional personnel to describe the subject. The subject also described himself using the same list.

(7) *Psychiatric Interview*. A pre-coded psychiatric interview was included for diagnostic pusposes and to elicit reports from the subject on his current social and interpersonal functioning. A rating of Level of Adjustment was made for each subject.

(8) *Parent Interview*. A pre-coded interview was conducted with the individual with major responsibility for the child's rearing.

(9) *School Report*. A questionnaire was obtained from the teacher who knew each subject best.

(10) *Midwife's Report*. This is a detailed, legally required, standard form prepared by the midwife attending the subject's birth.

Results

In 1969 the first wave of 20 breakdowns (which we call the Sick Group) had been identified. Thirteen have been admitted to psychiatric hospitals with many diagnoses including schizophrenia. The seven not admitted include some who are clearly schizophrenic. The clinical status of these individuals was ascertained by our follow-up procedures. To each of these 20 we have matched another high-risk subject (Well Group) of the same age, sex, social class, and institutional rearing status. In addition we have matched these subjects for the psychiatrist's 1962 Level of Adjustment rating. We tried as much as possible to select individuals for the Well Group who, since 1962, had shown some improvement in Level of Adjustment. Also, 20 Controls were selected from the low-risk group for comparison purposes. This matching yielded two groups of high-risk subjects. In 1962, both were judged to be equal in Level of Adjustment. Yet since 1962 one

group has improved in level of mental health, the other group has suffered severe psychiatric breakdown. Why? Part of the answer could lie with the predisposing characteristics measured in 1962 at the time of the intensive examination.

The most important characteristics distinguishing the Sick Group from the Well and Control Group were:

(1) The Sick Group lost their schizophrenic mother to psychiatric hospitalization much earlier in their lives than did the other two groups. These early-hospitalized mothers were also more severely schizophrenic. The Well Group lost their mothers at approximately the same time as did the Control Group. In view of the greater severity of illness of the mothers who left their home early, these data may be interpreted in relatively genetic or environmental terms.

(2) The teachers' reports indicate that the Sick subjects tended to be disturbing to the class. They were disciplinary problems, domineering, aggressive, created conflicts and disrupted the class with their talking. This was true of 53% of the Sick Group, 18% of the Well Group, and 11% of the Control Group.

(3) On the Continual Association Test, where the subject is asked to give, in one minute, as many single-word associations as he can to a stimulus word, the Sick Group showed two distinctive patterns. They had a strong tendency to rattle off a whole series of words which were interrelated but contextually relatively irrelevant, "Opremsning", in Danish. Their associations also tended to "drift" away from the stimulus word. Contrary to instructions and cautions they might begin responding to their own responses; for example to the stimulus word "table" they might respond "chair, top, leg, girl, pretty, sky...". Those in the Sick Group who do not evidence drifting can apparently manage to avoid this only by restricting themselves to one or two responses per stimulus word for the entire one-minute period.

(4) Some of the variables most sharply differentiating the Sick Group from the Well and Control Groups were the electrodermal measures taken during the psychophysiological testing. These measures largely reflect the functioning of the body's stress mobilization mechanisms.

(a) The latency of the GSR was substantially faster for the Sick Group than for either of the other two groups.

(b) The GSR latency for the Sick Group did not show any signs of habituation. This was especially marked in their responses to the nine

UCS stress stimulus trials. The Control and Well Groups rapid habituation of latency was seen in the progressive increase of their response latencies from the first to the last of the stress trials. The latencies of the Sick Group progressively decrease suggesting a negative habituation or even increasing irritability. Moving from UCS trials I–IX, 69% of the Well Group exhibit a slowing of response latency (habituation); 75% of the Sick Group actually increase the speed of their response.

(c) A well-documented characteristic of conditioned GSR behavior is the rapidity with which it demonstrates experimental extinction and/or adaptation. In both the Well and Control Groups electrodermal responsiveness was already dropping off by the end of the stress stimulus trials. Following those stress trials we presented a series of nine non-reinforced test trials for generalization and speed of extinction of the conditioned response. The Well and Control Groups evidenced very rapid extinction, i.e. they responded to only one or two of the extinction test trials. The Sick Group exhibited great resistance to extinction, in many cases responding with tenacity until the very end of the extinction series.

(d) The Sick Group showed remarkably fast recovery from momentary states of autonomic imbalance. Once a GSR was made we measured the rate at which recovery to basal level proceeded. On some trials rate of recovery almost perfectly separated the Sick and Control Groups. The pooled Sick and Well Groups' distributions for rate of recovery typically found 70% of the Sick and 30% of the Well Group above the median. [. . .]

(5) In a previous report of the differences between the Sick, Well and Control Groups we pointed out that while in our analyses of data on birth complications "there was a slight general tendency for the Sick Group to have had a more difficult birth, none of the differences reached statistical significance". (See the preceding article.) Subsequent, more careful, examination of these data revealed that while it was true that no single complication significantly differentiated the groups, 70% of the members of the Sick Group had suffered one or more serious pregnancy or birth complication (PBC). This contrasted sharply with the 15% of the Well Group and 36% of the Control Group with PBCs. The PBCs included anoxia, prematurity, prolonged labor, placental difficulty, umbilical cord complication, mother's illness during pregnancy, multiple births, and breech presentations. Careful perusal

of these data brought out an additional striking relationship within the Sick Group (and the entire high-risk group). There is a marked correspondence between PBC and the anomalous electrodermal behavior reported above. All the GSR differences between the Sick and Well Groups could be explained by the PBCs in the Sick Group. In the Control Group and low-risk group the PBCs were not strongly associated with these extreme GSR effects. This suggests that the PBCs trigger some characteristic which may be genetically predisposed. The PBCs seem to damage the modulatory control of the body's stress-response mechanisms. PBCs are associated with rapid response onset, poor habituation of the response, poor extinction of the conditioned electrodermal response, and very rapid recovery from the response. In terms of the theoretical orientation guiding this project (Mednick, 1958, 1962, 1966) this lack of modulation may be viewed as an important etiological factor in the development of mental illness, especially schizophrenia.

The finding that immediately raised fertile questions was the high frequency of PBCs in the Sick Group. What damage might these PBCs have done and where? We first sought for inklings of brain sites particularly sensitive to being damaged by PBCs. We then examined animal studies in which analogous damage had been inflicted by surgical lesion to particularly sensitive brain sites. The reports of the behavior of animals suffering surgically inflicted lesions to these same areas were then searched for instances of behavior similar to that which we observed in our PBC-Sick subjects. We hoped in this manner to generate hypotheses regarding specific sites of brain lesions in our PBC subjects.

Brain sites of selective vulnerability

PBCs result in future difficulties for the fetus chiefly because of the great sensitivity of neural tissue to anoxia. (Mechanical damage probably plays a less significant role, although through vascular obstruction it can also lead to anoxia.) Researchers have singled out particular brain structures as being "selectively vulnerable" to the effects of anoxia. These areas include most prominently, the hippocampus, and Purkinje cells of the cerebellum (Blackwood et al., 1967). Of these two areas, Spector (1965) singles out the hippocampus as

being the most vulnerable. He evaluates the effects of anoxia by studying "biochemical lesions", i.e. "the initial chemical changes in tissues following the application of harmful agents and preceding anatomical evidence of damage". The chemical changes he has studied as a function of anoxia have been losses in certain enzymes which precede "histological evidence of cell injury by approximately 10 hours. It is noteworthly that chemical changes appear in the hippocampus immediately after anoxia, whilst the other areas show earliest loss of enzymes after 1–6 hours. The enzyme loss in the hippocampus involved the neurones and was not apparent in the glia or neuropil. This observation suggests that, in this site at least, the neurones are more susceptible than are the surrounding cells to oxygen lack" [pp. 552–553].

Friede (1966) also indicates that the hippocampus (Ammons Horn) represents one of "the most striking examples of selective vulnerability in the brain and in particular Sommer's Sector, H 1 is known to be a characteristic site for anoxic damage". (Friede links this vulnerability of H 1 to relatively low levels of lactate dehydrogenase in Sommer's Sector).

Animal ablation literature

Thus, with the hippocampus as our chief, and most likely suspect, and the amygdaloid and the cerebellum (Purkinje cells) as an additional suspect we next turned to the animal ablation literature. The strategy here was to see if we could find any similarity between the behavior of our Sick subjects with PBCs and the behavior of animals with circumscribed lesions to each of these suspect areas. Conditioning and extinction behaviors are frequent dependent variables in animal ablation studies. This facilitated comparisons with our data since our subjects have gone through a conditioning and extinction session.

Briefly stated, the literature on the Purkinje cells did not strongly relate to the conditioning data of our PBC subjects. On the other hand the behavior of hippocampal animals was in some surprising ways like that of our PBC-Sick subjects. At this point we must sound a strong note of caution; below we will be relating rat, instrumental, and human, classical conditioning data. It is doubtless a questionable

procedure to draw analogies across two species and two types of conditioning. In this case it has proven of great value for hypothesis formation. These ideas are presented in this spirit.

There are several aspects of the behavior of hippocampal rats which are of interest to us in the present context.

(1) Rats with hippocampal lesions manifest relatively fast response latency (Rabe and Haddad, 1969; Roberts et al., 1962).

(2) Rats with hippocampal lesions evidence very poor habituation of the latency of their responses. While normal and cortically damaged control groups exhibit habituation by responding with increasing latencies across a series of test trials, the response latencies of the hippocampal rats do not slow down. They continue to respond as though they were experiencing the stimulus for the first time (Kimble, 1968).

(3) Rats with hippocampal lesions evidence great resistance to the experimental extinction of conditioned behavior (Isaacson et al., 1961; Niki, 1965).

(4) Rats with hippocampal lesions are hyperactive (Kimble, 1963; Roberts et al., 1962).

(5) Rats with hippocampal lesions acquire a conditioned avoidance response in a shuttle box more quickly than control or cortically damaged rats (Isaacson et al., 1961; Kimble and Gostwell, 1968; Roberts et al., 1962).

In comparing these characteristics with the characteristics described above for the Sick Group we can detect some considerable similarity. Both the Sick subjects with PBCs and the hippocampal rats evidence fast response latency, very poor habituation and poor extinction of a conditioned response. We can also tentatively link the hyperactivity of the hippocampal rats to the unruly classroom behavior of our Sick Subjects. The two points that do not immediately relate to each other are the fast avoidance conditioning of the hippocampal rats and the fast GSR recovery of the Sick Group with PBCs. In terms of some of the components of a theory of schizophrenia advanced earlier (Mednick, 1966; Mednick and Schulsingner, 1968) these seemingly independent points may actually be closely related. Thus, if we assume that the fast GSR recovery of the Sick Group with PBCs is also characteristic of the hippocampal rats we can postulate some basis for the puzzling and consistent finding of unusually fast avoidance learning on the part of the hippocampal rats. Whether one takes a reinforcement or contiguity

position, one crucial variable influencing speed of avoidance conditioning in a shuttle box is the rapidity and amount of fear reduction following a successful avoidance response.

After the avoidance response has been made, the speed and the amount of reinforcement depends in large part, on the speed of fear reduction and hence on the rate of recovery from the stress response (Zeaman and Wegner, 1954). Any rat who recovers unusually rapidly from a stress response will receive a correspondingly rapid reward of fear reduction when he leaps from the shuttle box' electrified grid floor into the safe compartment. His reinforcement will be greater than that of a rat with normal recovery rate or slow recovery rate. Fast recovery from stress-response could conceivably explain the otherwise rather mysterious rapid avoidance learning of hippocampal rats. If such fast recovery were directly demonstrated, the similarity of hippocampal rats to our PBC-Sick subjects would be striking. In the light of the sensitivity of the human hippocampus to the anoxic effects of PBCs, this similarity would suggest the hypothesis that the PBCs in our high-risk children have resulted in damage to their hippocampus. What is further suggested is the possibility that the resultant behavioral anomalies are in some way predispositional to psychiatric breakdown and schizophrenia in individuals with schizophrenic mothers.

Implications

In summary:

(1) The most likely site of brain damage resulting from PBCs seems to be the hippocampus, especially Sommer's Sector, H 1.

(2) High-risk children who have suffered PBCs exhibit a specific and unique pattern of conditioning, habituation, extinction and GSR behavior. (This pattern is also exhibited by low-risk children with PBCs but at a diminished level.)

(3) This pattern is strikingly similar to the conditioning, habituation and extinction behavior of rats who have experienced surgical lesions to the hippocampus. These surgical lesions encompass what in the human would be Sommer's Sector, H 1 (Kimble, personal communication).

Another important aspect of behavior which is characteristic of

hippocampal rats has been observed in infants who may have suffered anoxia and hence hippocampal damage at birth. Kimble (1968) indicates that "damage to the hippocampus should impair the process of habituation to novel stimuli, as has been reported (Leaton, 1965)". This same failure of habituation to novel stimuli has been reported for infants at the ages of two days, five days and 30 days in those cases where the mother had undergone heavy anaesthesia during delivery. Controls were infants of the same age where the mothers had undergone mild or no anaesthesia (Conway and Brackbill, 1969). Maternal heavy anaesthesia during delivery can effect the fetus, producing retarded respiration and anoxia (Moya and Thorndike, 1963). In the context of this general discussion it is tempting to postulate that in this study anaesthesia-induced anoxia produced some hippocampal damage in these children which, in turn, manifested itself in the form of a failure of habituation.

We are suggesting the existence of a relationship between a pattern of observed habituation-conditioning-extinction findings in our PBC-Sick Group and hypothesized hippocampal damage. It is tempting to consider what biochemical and neurophysiological mechanisms could possibly be at the basis of this hypothesized relationship. One interesting lead is recent evidence of a link between hippocampal functioning and ACTH secretion. Damage to the hippocampus has been shown to result in a failure of inhibition of ACTH released by the pituitary gland (Knigge, 1963, 1966). Weiss, McEwen and DeSilva (personal communication) have evidence that this inhibitory influence is only called into play during states of stress reaction. During such stress states a damaged hippocampus does not provide an adequate inhibitory influence on the pituitary gland and thus permits an oversecretion of ACTH. Interestingly enough, such ACTH oversecretion may be expected to prolong the extinction of a conditioned response. (De Wied 1965, 1966; De Wied and Bobus, 1966). Such prolonged extinction effects were, of course, observed in our PBC-Sick subjects and are observed in hippocampal rats. It may be suggested that one basis for this failure of extinction was an oversupply of circulating ACTH due to the failure of a damaged hippocampus to sufficiently inhibit ACTH-pituary secretion during the stressful psychophysiological session.

This failure to inhibit ACTH secretion because of hippocampal in-

adequacy may also partially explain the state of hyperarousal that seems characteristic of the schizophrenic. (Ax et al., 1962; Cohen and Patterson, 1937; Goldstein et al., 1965; Malmo et al., 1951; Mirsky, 1969; Ray, 1963; Venables, 1966; Venables and Wing, 1962; Zahn, 1964). The explanation of the state of hyperarousal may also follow a relatively non-biochemical, neurophysiological route. On the basis of a series of studies observing cortically evoked potentials to visual and auditory stimuli, while concurrently stimulating the hippocampus, Redding (1967) concluded that the hippocampus exerts an inhibitory influence on the brain stem reticular formation. An inadequate hippocampus exerting a less than normal inhibitory influence on the reticular formation could contribute to the existence of a chronic state of hyperarousal in an individual. Mechanisms by means of which this hyperarousal and fast GSR recovery and latency could translate themselves into the clinical symptoms and life condition of schizophrenia have been elaborated in detail in earlier publications and need not be repeated here (Mednick, 1958, 1962, 1966; Mednick and Schulsinger, 1968).

We are, perhaps, now at a point where we can hypothesize that PBC factors lead to defective hippocampal functioning which in combination with genetic and environmental factors could conceivably play a vital predispositional role in at least some forms of schizophrenia. This linking of hippocampal functioning and schizophrenia is not an entirely new idea. Necrosis of neural tissue in Sommer's Sector of the hippocampus has been very regularly found in neuropathological studies of the epileptic (Blackwood et al., 1967). Chapman (1966) and Slater, Beard, and Glithero (1965) among others have pointed to the great similarity of epileptic states of consciousness, especially psychomotor epilepsy, to the disturbances of consciousness in the schizophrenic. Roberts (1966) conceptualized schizophrenia "as a disordering of an entire brain system [...] correlated with malfunction in the dorsal hippocampal limbic system." There has also been a considerable amount of research linking PBCs with serious behavioral disturbances and schizophrenia in children (Knobloch and Pasamanick, 1962; Pasamanick et al., 1956; Pollack, M., and Woerner, 1966; Taft Goldfarb, 1964) and adults (Lane and Albee, 1966; Stabenau and Pollin, 1967). There are studies in the literature which have demonstrated "typical" hippocampal-lesion behavior in the schizophre-

nics. Milstein et al. (1967) demonstrated very poor habituation and very fast latency of the alpha attenuation response for chronic adult schizophrenics. As early as 1937, Cohen and Patterson reported poor habituation of the cardiac response in schizophrenics. Zahn (1964) has reported poor habituation of the GSR in chronic schizophrenics. Vinogradova (1962) has demonstrated that chronic schizophrenics take an unusually large number of trials to extinguish a conditioned plethysmograph response.

The adjective "chronic" has been used above to modify the noun "schizophrenia". It may well be that hippocampal dysfunction is an important contributing predispositional factor in only some types of schizophrenia. These may be the more typical, process, chronic, or poor premorbid types. Our Sick subjects tend to be "early onset" cases suggesting that many of them may have a relatively poor prognosis. It is also possible that degree of hippocampal dysfunction will relate to degree of seriousness of illness.

The emphasis on neurophysiological, biochemical and traumatic variables and materials in this paper should not be read as a denigration of the capability of genetic forces to produce identical hippocampal insufficiency or a disregard for the necessity of an appropriate environment to cultivate the learning of schizophrenic modes of behavior and thought. The emphasis on PBCs should not be read as denying the possibility that postnatal injury or high fever could also produce similar brain damage. Finally we have dealt exclusively with the possible impact of hippocampal injury. We could have also brought the septum and other limbic areas into the discussion. The functioning of the entire temporal lobe is also not irrelevant in this area. However, for reasons that are made evident above, the hippocampus seems the best candidate for our attention.

Implications for future study

In terms of the theoretical orientation of the author, the condition of schizophrenia (predisposed by a variety of conditions and circumstances) is a pattern of well-learned avoidance responses. In terms of treatment considerations, such well-learned avoidance responses are difficult to extinguish. Every time an avoidance response is successfully

made it is automatically and immediately reinforced. In animal research a shuttle-box-avoidance response can be extinguished by physically preventing the rat or dog from performing the avoidance response in the presence of the avoidance stimulus and not delivering the punishment. However, the bulk of the schizophrenics' avoidance responses are thoughts. These are difficult if not truly impossible to prevent or control. Thus, for theoretical as well as practical and humane reasons our research thinking centers on primary prevention rather than treatment. In view of our findings, one potentially useful field of intervention that suggests itself is the pregnancy and birth process. If a sound hippocampus is a prerequisite for sound mental health and if we can avoid PBCs in high-risk populations, we may avert hippocampal damage and hence reduce the probability of mental illness. A research project on this very matter is currently being planned. Secondly, in view of the possible involvement of poorly modulated hormonal secretions, research on psychopharmacological intervention at an early premorbid age would seem indicated. Such a study is now in its early stages. We are also conducting further prospective studies on the longterm consequences of PBCs in children with schizophrenic parents.

Acknowledgement

STUDIES OF CHILDREN AT HIGH RISK
FOR SCHIZOPHRENIA*

SARNOFF A. MEDNICK AND FINI SCHULSINGER

This paper was given at the 1972 annual meeting of the American College of Psychiatrists held in San Diego on the occasion of Mednick and Schulsinger's receipt of the Stanley R. Dean Research Award. The initial portion of the address which was devoted to a rapid review of the design, methodology and previous results has been omitted: it begins with an elaboration of the finding that faster autonomic recovery is evident in those subjects who have succumbed.

In earlier papers Mednick (1958, 1962) has attempted to formulate specifically how this pattern of avoidance could result in some of the common symptoms of schizophrenia. If fast recovery does constitute such an aptitude, one would expect that those subjects in the high-risk group who manifested a fast rate of recovery will have, in the course of their lives, learned a large number of avoidance responses. As a test of this hypothesis Mednick et al. (1971) determined the individual rate of GSR recovery for the Sick and Well subjects and correlated this with a score for avoidant associates ("Chaining" Score from the Continuous Association Test; Diderichsen, 1967). The two scores correlated positively ($r = 0.48$, 25 df, $p < 0.05$). As predicted, those subjects who have a faster rate of recovery had learned more avoidant associates.

This formulation would also predict that the schizophrenic would perform well in a situation where an avoidant response is functional or correct. For example such a response might avoid noxious stimulation or punishment. In general, censure or punishment produces marked deterioration in schizophrenic's performance (Rodnick and

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Garmezy, 1957). If, however, the situation is constructed so that the schizophrenic can learn to avoid the censure (response-contingent censure) his performance improves disproportionately (Cavanaugh, 1958; Johannesen, 1964; Losen, 1961; McCarthy, 1963). Unlike normal subjects, schizophrenics learn faster when their response can avoid punishment than when their response merely produces reward (Atkinson and Robinson, 1961).

This formulation would also predict that schizophrenics would perform better than normals in eyelid conditioning. Their task here is to learn to close their eyelid to a warning signal in order to avoid the noxious effects of a puff of air on the eyeball. Spain (1964) demonstrated that schizophrenics learned this avoidance response faster than normals. In addition, those schizophrenics that evidenced most withdrawn ward behavior manifested the fastest avoidance conditioning in this situation!

Since within this learning theory orientation, learned avoidant associates are the essence of the schizophrenic disorder, the aptitude of fast recovery must be interpreted as a crucial factor predisposing to schizophrenia. Empirically, we would expect to find this aptitude in schizophrenic patients. Stimulated by our reports of fast recovery in the Sick subjects, Ax and Bamford (1970) reanalysed psychophysiological data on schizophrenics in order to score their recovery rates. The results support our findings. Schizophrenics evidence markedly faster GSR recovery rates than do controls. Gruzelier and Venables (1972) conducted two new studies with schizophrenics, studying their GSR behavior. Their data replicate ours very well in almost all details including the crucial recovery variable. Lidsky et al. (1967), observed unusually fast recovery from contraction of pupils (redilation) of their psychiatric patient population (mainly schizophrenic) in comparison to controls. This study is interesting since it involves another response modality sensitive to autonomic influences.

Our theory suggests that the combination of:

(1) an autonomic nervous system that responds too quickly and too much,

(2) an inability to habituate to mild stress,

(3) an abnormally fast rate of recovery,

provides an aptitude for learning avoidance responses. These ANS variables may be profitably classified into two categories, those that

can produce ANS distress (fast latency, exaggerated response amplitude and lack of habituation) and the variable (fast recovery) that helps resolve the distress by providing an aptitude for learning to avoid distressing stimuli. If an individual is to become schizophrenic he must possess both of the types of ANS characteristics. If an individual is rapidly, exaggeratedly, and untiringly emotionally reactive he may become anxious or psychotic but won't tend to learn schizophrenia unless his rate of recovery tends to be very fast. It also seems likely that an extraordinarily reactive ANS will only require moderately fast recovery while an extraordinarily fast recovery will only require moderate reactivity. Both very high reactivity and very fast recovery will result in a very heavy predisposition for schizophrenia.

The greater the autonomic responsiveness and lack of habituation, the more protective avoidance will be necessary to fend off potentially distressing internal and external stimuli. The ultimate protection is perhaps the almost totally avoidant thought pattern and behavior or the truly chronic schizophrenic. In this case, thoughts and behavior are almost totally dominated by avoidant associative and motor responses. If from among the chronic schizophrenics we select those who evidence a pattern of most extreme withdrawal, we should find these withdrawn chronics to be characterized by perhaps the most responsive ANS. This is precisely what has been found (Fowles et al., 1970; Venables, 1966; Venables and Wing, 1962). It also follows that *chronic* schizophrenics should exhibit a lack of ANS habituation, as indeed Zahn et al. (1968) and Milstein et al. (1969) have found.

One final point. We have stressed the importance of the physiological predispositions. But the hypothesized ANS predispositions will only result in distress in *response* to unpleasant environments or noxious thoughts. An individual who is treated kindly is far less likely to evidence distressing ANS overexcitement and will have relatively little provocation to learn a massive pattern of avoidant responses. The development of schizophrenia depends then on an interaction of reactive, sensitive and quickly recovering autonomic nervous systems and unkind environments. Let us turn now to a consideration of the relationship between unkind environments and the ANS variables.

Speculations and data on the origins of ANS abnormalities

The ANS variables play a crucial role in our theoretical constructions concerning the etiology of schizophrenia and were distinctive, empirically, in differentiating the Sick Group. It was consequently inevitable that our interest turned to exploring the possible origins of this autonomic deviance. There is evidence that some aspects of the GSR can be influenced by genetic factors and that schizophrenia has a genetic component. It seemed clear that genetic factors could not be excluded as possible origins of the ANS deviance in the Sick Group. On the other hand, it seemed a good bet that early environmental stress could also produce chronic autonomic aberrations. This factor also had to be considered. Finally the autonomic variables studied have proven to be relatively independent of one another. (The correlation between log conductance response and the rate of recovery from that response hovers around 0.10.) Consequently, it seemed very possible that some autonomic factors could be influenced by genetic and some by environmental variables. We could tentatively explore the genetic factors in a rather imprecise way by comparing our High and Low-Risk groups which differ in their familial loading for schizophrenia.

Parental separation and ANS factor

We looked for an important, reliable way of dividing the subjects on the factor of environmental stress. Many of the children were separated from their parents quite early in life in both the High and Low-Risk groups. In view of the pervasive stressful influence of such separation we chose parental separation as an environmental stress whose chronic effect on GSR we would explore. In Western society, a young child lacking a special adult who will love, protect and educate him has a relatively elevated probability of leading a difficult early life. There are implications for almost every aspect of his existence from his nourishment to his intellectual competence. Our goal in this next study was to compare risk, separation and their interaction as possible determinants of autonomic deviance, and thus possibly as predispositional to schizophrenia. The study involved groups varying in risk but "equated" for separation, and groups varying in separation but "equated" for risk. Thus, we had the opportunity to observe the

effects of separation with the influence of psychiatric familial background greatly reduced or eliminated. It is in such a situation, where genetic variance is restricted, that environmental variance such as parental separation can have an opportunity to show its influence. Parenthetically, we might mention that it is likely that the lack of such genetic control in the parental-separation literature may be in part responsible for the conflicting findings in that area. This parental-separation study is being conducted by Edna Herrmann at the New School for Social Research. She is making use of the data from the 1962 high-risk study.

Herrmann developed several scales relating to the quantity and continuity of parent or substitute-parent contact in the first five years of life. These several scales proved to intercorrelate so highly that she expressed them as one scale score: the Separation Scale. This scale gives a score indicating the degree to which a child has been free of, or deprived of, the direct and individual care of a parent or parent substitute in the first five years of life. The children with high scores have led rather chaotic lives. High-Separation and Low-Separation groups were chosen from both the High and Low-Risk groups. All four groups were matched, individual for individual, for sex, age, social class, and years of education. The High and Low-Risk, High-Separation groups were matched for Separation Scale scores as were the High and Low-Risk, Low-Separation groups. With all this careful matching, Herrmann's N's have come down to 30, each, in the Low- and High-Separated, High-Risk group and 15, each, in the Low- and High-Separated, Low-Risk group.

Results of separation study

The High-Risk group evidenced markedly poorer mental health than the Low-Risk group on a series of items based on teacher's judgment and interviewing psychiatrist's judgment ($F = 18.39$, 1/87 *df*, $p < 0.01$). Note that this was true with amount of separation equated. The poorer mental health of the High-Risk group probably could not be ascribed to aspects of their life experiences related to separation from their parents. It would seem possible here to attribute their adjustment difficulties to genetic factors. However, in the groups differing in separation, but "equated" for genetic background, the Separation

Scale proved *equally effective* in predicting to level of mental health. Poorer mental health was associated with more separation ($F = 16.33$, 1/87 *df*, $p < 0.01$). It is difficult, however, to postulate a direction of causality. Were these children separated because they manifested poor mental health and perhaps were irritating to care for? Did they develop the poor mental health *because* of the separation? (Or was it some spiralling combination of these circumstances?)

There is another possible interpretation of the effectiveness of separation. The mothers of the High-Separated group may differ in some specific heritable characteristic which is related to separation. The children of the High Separation mothers might have inherited this specific characteristic which might have given them some predisposition to poor mental health. We are currently checking severity of illness of the High-Risk mothers and some limited information we have on pre-separation characteristics of the children in order to evaluate these alternate interpretations.

But in any case these very well-matched groups enable us to assess the relationship between psychophysiology and separation while holding risk constant, and between risk and psychophysiology while holding separation constant. Both High Risk and High Separation produce a significantly faster latency (F (risk) $= 7.25$, 1/87 *df*, $p < 0.01$; F (separation) $= 3.51$, 1/87 *df*, $p < 0.03$, one-tail test). (A significant statistical interaction was not observed). The effect of separation does seem a bit greater in the Low-Risk group but it should be recalled that the latency of the High-Risk group is working against a physiological limit. The mean GSR latency of 1.81 sec. for the High-Risk, High-Separation group is rather fast. What we can conclude from this is that even when the High and Low-Risk groups are equated for separation, large differences still exist in latency of the GSR. We might permit ourselves the speculation that this finding represents a genetic effect. Likewise where the risk variable is controlled (implying some genetic control) separation also proves to be a powerful variable influencing latency. Granting some of the cautions we have mentioned above, we might consider that this finding represents an environmental effect. These two variables having independently demonstrated effectiveness in influencing latency, produce a clear additive effect. That is, if you have been separated from your parents you will have an unusually fast GSR latency; if you also happen to be born to a schizophrenic woman your latency will be that much quicker.

The same pattern is observed in amplitude where both the risk and separation variables are again independently significant (F (risk) $= 9.82$, $1/87$ df, $p < 0.01$; F (separation) $= 3.35$, $1/87$ df, $p < 0.03$, one-tail test). The interaction of the two is not statistically significant. But again these variables are additive in their effect. Having been both born to a schizophrenic mother and having also been separated from her produces an extremely highly reactive autonomic nervous system.

The pattern for recovery is different. Here while the risk variable is highly significant ($F = 9.32$, $1/87$ df, $p < 0.003$), the separation variable is not at all so ($F = 0.02$, $1/87$ df, n.s.), nor is the interaction of the two significant. This pattern suggests that we have in recovery a variable that is not sensitive to the type of environmental stress implied in the separation variable. You will recall that the recovery variable separated the Sick, Well, and Control groups better than any of the other measures in our test battery. The recovery variable occupies a central position in our speculations concerning the development of the clinical behavioral pattern called schizophrenia. There is a reasonable possiblity that important, uncontrolled, environmental variables, correlated with risk status and unrelated to genetics, produced the rate of recovery effects in the children with schizophrenic mothers. It is tempting, however, to speculate that (being the only ANS variable uninfluenced by the environmental variables related to early parental separation) recovery may be an important part of the genetic pattern passed on to the child by the schizophrenic parent. (See page 144 for a later test of this hypothesis.)

From these analyses we concluded that the aspects of autonomic functioning which are sensitive to and associated with distress can be chronically influenced by the early environmental stress of separation from parents. Recovery was not so influenced. In continuing our search for the origins of the observed pattern of autonomic deviance we turned next to the perinatal data.

Perinatal complications and ANS factors

As noted above, the Sick Group had suffered considerably more pregnancy and birth complications (PBCs) than the Well and Control group. Perusing the midwife data for the Sick group we noted a very

marked correspondence between presence of PBCs and the deviant ANS behavior. In fact, much of the GSR differences between the Sick and Well Groups as well as the Control group could be explained by the PBCs in the Sick group. In the Control group the PBCs were not as strongly associated with these extreme GSR effects. The PBCs in the Sick group seem to trigger some characteristic which may be genetically predisposed. We determined to explore the PBC-ANS relationship in the entire High and Low-Risk groups. These data were submitted to a Stepwise Multiple Regression Analysis (MR) with the autonomic measures as the dependent variable and risk and degree of PBC as independent variables. We have modelled the analysis along the lines suggested by Cohen (1968). We wish to acknowledge Dr. Cohen's invaluable advice in this analysis. When PBCs were analysed, the constant was the mean of the group with no PBCs. When interaction effects were analysed the constant was the Low-Risk group with no PBCs. Variables were forced into the regression equation so as to test the hypothesis that severity of PBCs would predict the autonomic variables.

The PBCs are ineffective in influencing the GSR latencies of the Low-Risk subjects but have a significant effect in the High-Risk group. This matches our findings for the Sick, Well and Control groups. The interaction term is significant ($F = 20.67$, $1/241$ df, $p < 0.001$). An analysis for the data on GSR amplitude as a function of risk and PBCs was carried out. The PBCs, in this case, produce highly significant effects in both the High and Low-Risk groups. There is no interactive effect as there was in the Sick, Well and Control groups. As is the case with the separation data, the effect seems to be additive. Having a schizophrenic mother is associated with elevated responsiveness of the ANS, if in addition the individual has suffered PBCs his autonomic responsiveness will be even more exaggerated. The effects of PBCs were significant ($F = 9.07$, $1/241$ df, $p < 0.01$) as were the effects of the risk variable ($F = 13.49$, $1/241$ df, $p < 0.01$).

Much the same pattern is seen with recovery. Both the risk and the PBC variables are related to significant changes in the recovery rate of the GSR (F (risk) $= 7.67$, $1/241$ df, $p < 0.01$; F (PBC) $= 11.97$, $1/241$ df, $p < 0.01$). The High-Risk subjects with severe PBCs recover at a mean rate of 1054 ohms per sec in the stress trials. This puts them well up into the range of recovery rates observed in the Sick group.

It is difficult to compare magnitude of PBC effects across the variables of latency, recovery and amplitude because different units of measurement are involved and different physiological ceiling effects are doubtless operating. However, visual inspection suggests that amplitude was most strongly affected by PBCs. We ranked the pooled High and Low-Risk distribution of amplitudes and divided this pooled distribution into Large, Medium and Small Responders. We then looked to see which PBCs were associated with being a large Responder. Especially strongly associated were: dry birth, use of ether during labor, severe prolonged labor, use of quinine during labor, intrauterine asphyxia, and umbilical cord complications. Most of these complications tend to occur together, and would very likely result in fetal anoxia and/or mechanical damage (pressure) to brain tissue. This type of analysis might suggest hypotheses regarding the mechanisms by which PBCs might affect autonomic functioning.

At this point we hasten to add two cautions. First, it is possible to suggest that it is not the PBCs that are causing the autonomic deviance. It could be argued that genetically determined, autonomic deviance in the fetus was in some unknown way responsible for provoking the PBCs. Maternal stress during pregnancy might also be responsible for autonomic deviance in the fetus (Sontag, 1944) and also for the delivery complications. Secondly, we find the results of these more detailed exploratory attempts quite exciting and suggestive. However, they are based on midwife reports whose reliability we will discuss below. Until these findings are replicated we would urge that your attention be drawn more to the problems and methods than to the individual results.

Summary: possible factors etiologically related to autonomic deviance

To sum up this exploration of some possible etiological factors related to autonomic deviance, we can tentatively put forth the following assertions:

(1) High risk, separation from parents, and perinatal disturbance are associated with deviance in autonomic functioning.

(2) Amplitude of response seems to be most heavily influenced by PBCs and separation. There is some hint that delivery difficulties which could have produced fetal anoxia were the instrumental PBC variables.

(3) Rate of recovery was not at all influenced by separation but was affected by PBCs. Rate of recovery was consistently faster for the group with schizophrenic mothers. We were tempted to speculate that this variable is, in part, related to genetic factors.

(4) Early separation from parents produced a quick GSR latency in both risk groups; PBCs and risk had an interactive effect on latency. The latencies of the Low-Risk group were unaffected by the PBCs; PBCs in the High-Risk group, however, related to significantly enhanced speed of autonomic response.

This interaction is reminiscent of the interactive effect of risk and PBCs found in the Sick–Well–Control comparisons. Perhaps, in the vulnerable High-Risk children the PBCs were triggering or exacerbating some genetically determined sensitivity of the ANS. This finding attracted our attention; we turned to see if we could find parallels in the genetics literature and discovered that this type of perinatal-genetic interaction was not unknown. Fraser and Fainstat (1951) subjected pregnant mice to a heavy dose of cortisone and *in a genetically vulnerable strain* radically increased the frequency of cleft palates. Joffe (1969) subjected a group of pregnant rats to repeated, severe, and inescapable electric shocks. In comparison to controls, the resultant pups demonstrated significantly faster response latency and interestingly enough faster avoidance conditioning. These results are startlingly similar to those of the hippocampal rats and our PBC-Sick subjects. Again these effects of gestational stress varied markedly as a function of rat genetic strain. Ingalls et al. (1953) reduced atmospheric pressure in the environment of mice 9 days pregnant and differentially caused an increase in sternum malformations in the litters of genetically predisposed strains. A genetic predisposition could very well be exacerbated by perinatal complications. Research by Kalter suggests "that the factors controlling PBC susceptibility [. . .] involve both the maternal and fetal genotypes" (1954, p.195).

We stopped to consider our position at this point. The perinatal data were exciting but suffered from limitations:

(1) The midwife is an adequate but not ideal recorder of the pregnancy and delivery,

(2) She did not produce her records for purposes of research. Danish investigators working with midwife records have noted that the midwife would tend to err in the direction of omitting mention

of some difficulties. If she did record complications we could be sure they had occurred.

In view of these limitations of our data and in view of our perception of the importance of the problem, we determined to launch a new longitudinal study of children of schizophrenic parents. We were lucky enough to be able to contact children who were part of a massive Danish perinatal study of 9006 consecutive deliveries at the University Hospital in Copenhagen from 1959–1961; excellent pregnancy and delivery information is available for them. As controls we have selected from this same perinatal-study population, children with normal parents, and children with parents who have suffered non-schizophrenic psychiatric disorders. These children are currently being brought in for intensive assessment. Because of the high quality of the perinatal data these groups give us an excellent opportunity to attempt to replicate and extend our earlier PBC findings.

At this point, I can very briefly sketch for you the course of the pregnancy, delivery and first year of development o. these high-risk children. (Greater detail may be found in the introductory article in Part IV, p. 231, by Mednick et al.) It was our hypothesis that while there would be no differences between the three groups in the amount of pregnancy or delivery complications, we would observe a genetic-perinatal casualty interaction. That is, the same level of perinatal difficulties would have a more pronounced effect in the Schizophrenic group than in the other groups.

The subjects had been examined during pregnancy and delivery, immediately after birth, and at one year of age. The Schizophrenic Parents, Psychiatric Controls, and Normal Controls were matched, individual for individual, for the following factors (in order of importance): sex of ill parent, sex of child, race, multiple birth, (twins), pregnancy number, mother's age, mother's height, father's age.

We devised several scoring systems for the pregnancy and delivery. The different scoring systems intercorrelate very highly. I will present results for the simplest system – a count of the number of complications of pregnancy – a count for delivery – a count of the number of neurological and physical disorders in the neonatal and in the one year exams and a count of developmental anomalies in the one year exam. In this simple system more serious complications or conditions get more points because their effects are more widespread. For example,

severely low birth weight would receive only one point but it would get additional points for use of incubator, associated difficulties of the fetus in beginning to breathe, various signs of prematurity, and disturbances in heart-beat.

Results

There were no impressive differences in the progression of the pregnancies and deliveries of the Schizophrenic, Psychiatric Control, and Normal Control groups. In the neonatal examination both the Psychiatric and Schizophrenic group children evinced more abnormalities. The abnormalities for the children of schizophrenics tended to come in the absence or weakness of their motor reflexes. These results agree well with those reported by Fish and Alpert (1963). Most remarkable in the one year examination was the retarded motor development of the children of schizophrenics. In almost every item they are retarded in the age of attainment of motor milestones.

The relationship between the pregnancy and delivery complications and the neonatal and one year examination scale scores was explored by intercorrelating these scores. In this manner, high scores on the birth factors indicating complications and high scores on the postnatal examinations indicating abnormalities should tend to go together and yield positive correlations. As expected, almost all correlations were positive. Difficulties in pregnancy and delivery, however, showed no significant correlations with neonatal status for any of the groups except the schizophrenics. For the children of schizophrenics, both pregnancy and delivery scales correlated positively and significantly with the child's appearance at the time of the neonatal examination.

Low birth weight was consistently related to difficulties in the neonatal examination for all groups. For all groups but the Schizophrenics it proved to be unrelated to the status of the child at the one year exam. Exclusively in the case of the schizophrenics, and especially so in the case where the mother was schizophrenic, birth weights below 3000 grams were associated with retarded development during the first year.

The Schizophrenic group suffered levels of PBCs which were quite similar to those of the two control groups. Despite this, the effect of these PBCs was much greater for the Schizophrenic group in the

neonatal and one year examinations. This result may be considered support for the hypothesized PBC-genetic interaction.

All of the 10–12 year old children described in this study are currently being brought into our Institut in Copenhagen for intensive examination. An important purpose of this new longitudinal study is to seek out the details of the PBC-genetic interaction. To further this aim a new control group is being gathered. This group with normal parents will be matched to the Schizophrenic group for the nine matching variables listed earlier. In addition, they will be matched individual for individual for the course of their pregnancy and delivery. Each pattern of abnormality noted in the pregnancy or delivery of a Schizophrenic group subject will be found in a normal mother from the pool of 9006 deliveries. This group of children will also be brought in for examination. The new Control group will thus be matched to the Schizophrenic group for a rather impressive list of factors. The great difference between the two groups of children will be the schizophrenia in their mother or father. This group will further enable us to assess the result of "identical" perinatal difficulties in two groups of children differing in genetic background.

Perinatal factors and prevention

If the importance of perinatal factors in schizophrenia is confirmed this will suggest a course of prevention involving perinatal care for high-risk mothers. Prevention, along with understanding, has been an important goal of our research program from its inception. This is, in part, because of the theory guiding this research. Learned avoidance responses are difficult to change. Every time the avoidance response is made, the relief it brings reinforces the avoidance. It is thus self-reinforcing. In the shuttle box the rat's avoidance response can be extinguished by closing the door to the safe compartment and not delivering any shocks. By physically preventing the response it can be extinguished. This method is useless in the case of avoidant thoughts. But because the theory suggests that treatment will be unrewarding, our effort has been directed toward the goal of prevention. It is for this reason we developed the high risk method; one of the important products of this method is the identification of measures to identify children at high risk. Such children might then be helped by preventive

efforts aimed at the anomalies for which the children were selected. In the case of our research, the psychophysiological measures, the word association measures, classroom behavior and, extensive parental separation could be seen as potential premorbid, identifying characteristics. If one wanted to work in prevention with very young children, however, the classroom behavior, associations and parental separation might not be useful. In that case one just might choose to identify high-risk children by means of their psychophysiology. [...]

THE RECOVERY LIMB OF THE SKIN CONDUCTANCE RESPONSE IN "HIGH-RISK" RESEARCH

PETER H. VENABLES

This paper presents a comprehensive review of the literature dealing with the recovery limb of the skin conductance response. The coverage ranges from a discussion of the problems of measurement to the possible determinants of recovery. The author concludes by suggesting some promising areas for future research.

In the work on high-risk samples carried out so far in Copenhagen skin conductance activity has shown considerable potential promise as an indicator of future breakdown and abnormal genetic environment (see the next article). This work receives a degree of support from work carried out on adult patient subjects, but analyses of the determinants of the recovery limb are limited and what is known about the phenomenon is based on a small number of empirical studies. This review, therefore, aims to outline what is known and to delineate what seem to be useful areas for future research.

Definitions

The skin conductance response has four measurable aspects, three temporal and one concerned with magnitude (fig. 1). The three temporal aspects are *latency* (time between stimulus onset and response onset), *rise time* (time between response onset and response peak), and *recovery* (time between response peak and a defined fall in response amplitude. The amplitude is the change in conductance between the level of conductance at response onset and that at response peak.

It is to be noted that these four measures are derived from aspects of *phasic* responsivity having recognisable morphological characteristics. Some confusion is possible if a distinction is not made between these

and changes of a longer term nature in tonic activity. In this case changes do not show the identifiable shapes of phasic responses. There
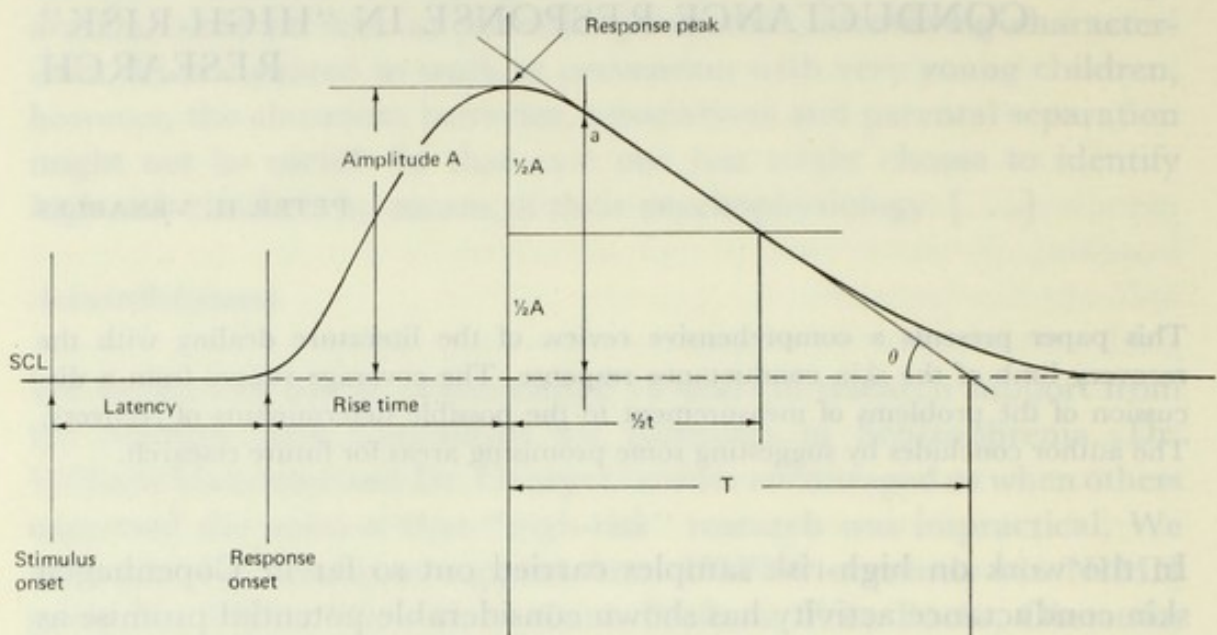
Fig. 1. Schematic representation of the Skin Conductance Response.

is particular difficulty in the case of *recovery* where some work has been done which examines the extent to which skin conductance *level* returns to baseline after some behavioural disturbance (e.g., Freeman and Katzoff, 1942). It is most likely that the mechanisms involved in tonic recovery are different from those in phasic recovery which is the main concern of this review. How far, however, they can be separated in circumstances while a subject exhibits an abnormally long phasic recovery is somewhat doubtful.

It should be noted that the definitions given are minimal ones; thus, for instance, another measure might be derived from rise time, and entitled "recruitment" which would be related to the slope of response onset and measured in micromhos/sec. Many other metrics than change in conductance have been suggested as measures of amplitude, however, it has been argued (e.g., Venables and Christie, 1973) that conductance change is physiologically reasonable and other conversions should be undertaken for statistical rather than for other reasons. The question of the metric of the recovery limb will be considered below.

Measurement of recovery

The recovery limb was first described by Darrow in 1932 and he concluded in 1937 that it was exponential in form. The exponential form of the recovery limb is generally supported by the work of Edelberg (1970). If in general the recovery limb closely approximates to exponential form then recovery rate is *theoretically* independent of the response peak from which recovery takes place. Measures based on the exponential form of the recovery limb should thus reflect this independence. There are three possibilities which are outlined by Edelberg in an unpublished manuscript. These are the *rate constant*, the *time constant*, and the *half-time* measures.

If we take as the expression for exponential decay

$$C = C_\mathrm{p}\mathrm{e}^{-kt} \tag{1}$$

where C_p is the starting conductance (i.e., response peak), C is the instantaneous conductance at time t, and k is the rate constant (rc). When $t = 1/k$

$$C = C_\mathrm{p}/\mathrm{e} \tag{2}$$

(i.e., 37% of its original value); t the reciprocal of the rate constant is called the *time constant* (tc).

Rather than measuring when the conductance has decayed to 37% of its peak value it is more convenient to measure the time taken to decay to 50% of its peak value (i.e., 0.7 tc), this measure, too, is theoretically independent of amplitude and is termed half recovery or half time ($t/2$). In practice it is possible to directly measure tc or $t/2$ but not rc on the conductance write-out from the polygraph. Edelberg (1970) has described the measurement of tc by a curve matching technique, using a transparent overlay consisting of a family of exponential curves of known time constants. This method is particularly useful when responses do not recover to 50% of their value before a subsequent response is given, however, as Edelberg says (1970) "The curve-matching method is somewhat [...] difficult; it soon becomes clear that many depart from the exponential shape and matching is ambiguous". The departure from exponential shape could be theoretically important and also may explain why in practice correlations between response amplitude and recovery are found. The half-time

measurement ($t/2$) is simpler to apply in practice and is also facilitated by the use of a transparent overlay. Reference to figure 1 shows how $t/2$ may be measured.

The rate constant (rc) is calculated as the reciprocal of the time constant (tc) and is reported by Edelberg to have more uniform variance than (tc). If measurements are taken in the form of $t/2$, rc may be calculated as $1/1.43$ ($t/2$).

In an attempt to move towards a more automatic measure of recovery Edelberg (unpublished) has suggested the following steps. If

$$dC/dt = -kC \tag{3}$$

where k is the rate constant as before then

$$k = -C'/C \tag{4}$$

where C' is the slope of C, i.e. its first derivative. By this means the rate constant may be obtained by taking the slope and amplitude at any point on the recovery limb. In practice a point beyond the inflection point is chosen (a in fig. 1) and

$$k = -(\tan \theta)/a. \tag{5}$$

Edelberg found empirically that a was very highly correlated to A (peak amplitude) where it was possible to achieve greater precision of measurement. Using this technique and comparing it to the curve matching measure of tc ($k = \text{rc} = 1/\text{tc}$) he obtained a correlation of 0.81 between the two measures.

$$\text{If rc} = -(\tan \theta)/a \quad \text{then} \quad \text{tc} = -a/(\tan \theta) \tag{6}$$
$$\text{or approximately tc} = A/(A/T) = T$$

where T is the distance along the baseline included by the extension of the recovery limb slope at (a). Correlations between T and tc obtained by curve matching were of the order of 0.82.

Edelberg (1967) showed that the maximum slope of the onset limb was closely related to peak amplitude. It therefore is possible to substitute the maximum value of the first derivative of the pre-peak waveform for a or A and the maximum value of the first derivative of the post-peak waveform for $\tan \theta$. Thus, by the use of a hardware differentiation two values may be more automatically obtained for substitution in (5) or (6) to measure rc or tc.

Mednick has made use of what seems to be intuitively a possibly more satisfactory metric, namely half recovery rate. This is calculated by measuring half recovery time as above and dividing half the peak response amplitude by it. This is, of course, approximately equal to tan θ in the earlier discussion and hence is approximately equal to the rate constant, rc multiplied by the peak amplitude and is thus theoretically not independent of amplitude.

However, it must be recognised that the theoretical considerations in the measurement processes described need to be investigated empirically at much greater length. As a postscript it may be noted that Mednick's earlier work employed the measurement of the recovery of the skin resistance response (SRR) rather than that of the SCR. Edelberg (1970) provided data to show that there were high correlations (0.83, 0.82, and 0.95) between SRR and SCR $t/2$ derived from measurements on three subjects. There is thus a fairly close relation between recovery data derived from SR and SC methods of measurement. Data provided by Edelberg suggest, however, that the SR data shows a slightly longer $t/2$ than that from SC.

Recording methods

The data from Edelberg just reviewed used a constant current method of measuring SR and a constant voltage method of measuring SC. It is possible that these two types of measurement have effects on recovery limb measurement. To determine whether this is so, SR data recorded from a constant current system would have to be converted to conductance units before recovery limb calculations were made in order to establish whether it was the units of measurement or the method which was responsible for any differences found.

More importantly it is almost certain that the electrolyte medium used will have an effect on recovery. While many workers now use Ag/AgCl electrodes with NaCl or KCl as electrolyte there are a variety of agents used as thickening media. The extent to which these do or do not hydrate the skin surface has a marked effect on skin potential responses (SPRs). Fowles and Rosenberry (1973,) for instance, have shown that hydration produced by a standard electrolyte (0.5% KCl in agar jelly medium) virtually eliminated positive SPRs in com-

parison to KCl in a glycol medium which has the effect of absorbing water from the previously hydrated epidermis. The relevance of this to measurement of the recovery limb of the SCR is that positive SPRs are associated with fast recovery SCRs; hydration due to an aqueous electrolyte medium might therefore be expected to produce longer SCR recoveries than a medium such as UNIBASE (Lykken, 1968) which does not hydrate the skin surface to the same extent.

It is apparent, therefore, that absolute values of recovery from different laboratories cannot be compared unless identical recording measures are used.

An examination of recovery times

Bearing in mind the difficulty in making comparisons across laboratories some general similarities can be seen among the data available. Edelberg (1970) using 0.1 M NaCl in starch medium provides mean figures of 7.9 and 7.8 sec for $t/2$ of SCRs to neutral tones and flashes. Gruzelier and Venables (1972) using 0.5% KCl in agar medium provide a mean figure of 8.74 sec for $t/2$ of SCRs to neutral tones; while Gruzelier (1973a) for $t/2$ of SCRs to neutral tones provides data of 10.26 sec for the right hand and 8.29 sec for the left hand. These data are from normal subjects: under similar conditions $t/2$ of SCRs for non-institutionalised schizophrenics have a mean figure of 4.66 sec (right 4.53, left 4.98 sec) and for institutionalised schizophrenics mean half times are 6.77 sec (right 7.01, left 5.88 sec).

In a context where neutral and signal stimuli (stimuli to which a reaction is required) are presented randomly, half recovery times are approximately halved for schizophrenic and normal groups (Gruzelier and Venables, 1973; Rippon, personal communication). Edelberg (1970) also reports faster recovery in an RT situation $t/2 = 3.4$ sec. There is thus a suggestion of a shortening of recovery times in situations where there is task involvement. On the other hand, where stimuli are unpleasant e.g., the cold pressor test (Edelberg, 1972a) in spite of a higher general level of arousal recovery times are long. Similarly, Furedy (1972) reports longer recovery limbs with responses to stimuli which signal unpleasant shocks. Probably the most important report so far made in this still confused area is a report of a highly significant

subjects x task interaction by Edelberg (1972a). The data so far undoubtedly show marked individual differences and marked task differences and these interact. Edelberg (1972a) suggests that over the range of tasks he used fast recovery *S*s are consistently fast and slow-recovery *S*s are consistently slow. He used only normal subjects, however, and future work needs to examine how far overlap may occur when a wider range of subject groups is studied and in particular when groups of schizophrenics or pre-morbid children are brought within the ambit of the tested population.

Relation of the recovery limb to other SCR components

The extent to which the recovery limb of the skin conductance response measures something which is independent of other aspects of the response is an indication of its potential usefulness. Underlying the selection of a metric considered above, was the notion that at least measurement problems should not lead to an avoidable interaction between, say, amplitude and recovery rate. Nevertheless, even with the theoretically independent measurement of two independent processes there are occasions on which indices of the independent processes are related. Knowledge of when this is and is not so can lead to insights into the processes involved.

The earliest work on the recovery limb by Darrow (1932) used a measure of the angle of recovery (θ in figure 1) and showed that this was related to the peak resistance value of the response in such a way that the steepest angle was related to the lowest peak resistance. Darrow also showed that the steepest angle of recovery also was found when sweat was found to be present on the skin surface. While these data are not immediately relevant to others which will be reviewed they do suggest that there is a positive relation between fast recovery and tonic arousal indicated by resistance level. It should be noted that the stimuli used in this instance were clicks, mild shocks and sounds conditioned to the shocks. Edelberg (1970) tested the theoretical assumption of independence of recovery from amplitude. He reported correlations of 0.21, — 0.20, 0.28, 0.62, 0.74, and 0.19 between amplitude and $t/2$ based on 20 responses from 6 subjects. Independence of the two measures is thus not shown by all subjects.

One of the most extensive investigations of the interrelation between aspects of the SCR is that of Lockhart (1972). It is perhaps unfortunate, although we cannot be sure, that his measurements were taken using zinc electrodes and zinc sulphate electrolyte paste, the nature of the electrolyte medium is not reported. Data reported are from two experiments, the first on 129 subjects are for responses to standard intense shocks. The mean values for components of the responses are *latency* 2.11 sec, *rise time* 2.80 sec, $t/2$ 4.08 sec, *amplitude* 1.50, square root of conductance change. Correlations between these data show that amplitude is *not* related to any of the temporal measures (e.g., r amp. rec. $= -0.06$), however, the three temporal measures were significantly interrelated and the correlation between recovery and rise time was high $(+ 0.62)$.

Lockhart's second set of data are derived from a differential conditioning paradigm and is particularly concerned with "disparity" trials – "A disparity condition exists on a test trial when US is not presented as expected. Another type of disparity results when UCS is presented at some point during the CS – during without warning". It is the latter type of disparity which is used to provide the data in this instance. Disparity trials are compared to reference trials in which expected sequences are followed. Responses to the UCS are measured. For the reference trials, latency, rise time, recovery, and amplitude have values of 1.63 sec, 2.90 sec, 4.45 sec, and 1.61 $\sqrt{\triangle C}$; for disparity trials the figures are 1.92 sec, 3.05 sec, 5.36 sec, 1.47 $\sqrt{\triangle C}$. The $t/2$ figure for the disparity trials is significantly longer than that for the reference trials. What is, however, of particular interest are the interrelations between the measures which are shown under these conditions. For the reference condition the pattern of interrelations is no different from that shown with the shock data previously described. However, with disparity trials, with the exception of the non-significant relation between amplitude and latency, all other relations are significant, that between recovery and amplitude being $+ 0.44$ $(p < 0.01)$. Lockhart in summary states, "this is evidence that a correlation between amplitude and recovery is not solely an individual difference variable but may be determined in part by experimental conditions" (Lockhart, 1972). Another important aspect of the data which is pointed out by

Lockhart is that the consistently high correlation between rise time and recovery makes interpretation of recovery in terms of reabsorption processes (see below) somewhat less simple than it might otherwise be.

Other unpublished data from a recent experiment by a postgraduate student do not, however, confirm Lockhart's findings. Rippon (personal communication) measuring skin conductance with Ag/AgCl electrodes and 0.5% KCl in agar reports significant negative correlations between latency and amplitude and $t/2$ and amplitude in both "reference" and "disparity" conditions. The relation between $t/2$ and amplitude is, however, significant in both conditions only for SCRs measured from the right hand. For left hand SCRs neither condition produces significant relations. It is perhaps interesting that Lockhart's data were collected from the non-preferred hand. Data are available which show correlations between amplitude and recovery in one group of subjects but not in another in the same-behavioral situation. Gruzelier (1973b) examined SCRs to the presentation of 1000 Hz, 1 sec, 75 db in groups of schizophrenics and normals. SCRs were measured using Ag/AgCl electrodes and 0.5% KCl in agar as electrolyte. In control non-patient subjects amplitude and $t/2$ were uncorrelated ($r = -0.08$), conversely in the patients data, amplitude and $t/2$ were highly correlated ($r = -0.64$). (Note the opposite direction of correlation to that obtained in Lockhart's disparity trials but the same direction as that found by Rippon for both reference and disparity trials with normal subjects.)

Other data in which correlations between amplitude and $t/2$ are quoted are those from Ax and Bamford (1970). The correlations are not significant for schizophrenic or control subjects but as the half recovery times are abnormally long in this study, 20.4 sec and 13.0 sec for controls and schizophrenics respectively, for SCRs to conditioning stimuli, comparison with other data is difficult.

The outcome of this brief survey suggests that while there seem to be some consistent correlations between recovery and other temporal components of the SCR, there are variable relations between amplitude and recovery that depend upon both task and subject groupings; and that these occur in studies where the metrics used are theoretically independent.

Peripheral or central determinants of recovery

In the absence of any clear understanding of the determinants of the recovery limb it is only possible to review some of the candidates for the role of the mechanisms involved. A conservative position will emerge which suggests the possibility of a multifactor determination but one which hopefully will provide clues for the correct choice of task or situational variables which will maximize individual differences and the predictive capacity of the measure in high risk research.

An important point to bear in mind in the consideration of any proposals for mechanisms of recovery is that they must take into account not only the finding that the length of the recovery time reflects individual differences but also that "the recovery limb could indeed change markedly from one wave to the next, as a function of stimulus change, even though response amplitude, conductance level and potential level were the same" (Edelberg, 1973). While it is possible to suggest that consistency of individual differences might reflect something relatively permanent, such as consistent hormonal level which determines a peripheral sweat re-absorption process it must also be borne in mind that consistency of individual differences may reflect consistency of attentional, attitudinal or learned approach to a task. Thus, it is not by any means possible to equate individual differences with peripheral determinants and task differences with central determinants of recovery. With this in mind it is worthwhile attempting to review what is known about the physiological factors concerned in recovery; given this background what is known about the behavioral aspects will then be considered.

(a) Peripheral factors

It is not feasible to review here the material on the peripheral mechanisms involved in electrodermal activity which have been the subject of recent major reviews by Edelberg (1971, 1972b, 1973), Fowles (1973) and Venables and Christie (1973). However, some points of particular relevance can be drawn from this material which are necessary to gain a requisite understanding of aspects of the recovery function.

One fundamental piece of evidence is the relation of the recovery limb of the SCR to the presence of components of the SPR. Darrow

(1932, 1964) showed an association between rapid recovery SCRs, the presence of the positive component of the SPR, high initial SCL and surface sweating. Edelberg (1970) similarly showed that rapid recovery SCRs were accompanied by positive SPRs in contrast to slower recovery SCRs which accompanied monophasic negative SPRs. Edelberg (1966) showed that positive SPRs accompanied a reabsorption of surface moisture and (1970) that SCRs associated with a reabsorption reflex showed a more rapid recovery than those not accompanied by reabsorption. Fowles (1973) provides further evidence for the association of rapid recovery SCRs and the positive component of the SPR. Underlying these findings is a two component theory of phasic electrodermal activity, both Edelberg (1971, 1972b, 1973) and Fowles (1973) suggesting that the activity of duct filling and passage of current through an epidermal membrane may be involved in SCRs. In the slow recovery SCR we see evidence of the duct filling component, while in the rapid recovery SCR there is reflection of the activity of an epidermal membrane probably in the sweat duct wall at the level of the germinating layer. This does not rule out the idea of a similar membrane in the duct wall at dermal level. A possibility is that the dermal mechanism is concerned mainly with the selective reabsorption of NaCl from sweat and is not very permeable to water. However, at the epidermal level both water and NaCl are absorbed and the consequent greater conductivity of this epidermal mechanism makes it a more important candidate as an underlying mechanism for SCR.

Venables and Christie (1973) have presented a review of Edelberg's (1968) electrical model of the skin and Fowles' (1973) modification of it which indicates how at different levels of sudorific and electrical activity different electrodermal patterns may be produced. What is important at this point is to consider mechanisms which may be involved in the modulation of the epidermal ductal mechanism and hence the speed of recovery of the SCR. One initial factor is that the level of the sweat in the duct must reach the epidermal mechanism. Mild stimulation at resting levels of activity producing minimal SCRs with long recovery limbs at low SCLs would be expected, and are found when ducts do not fill and no surface sweat is visible. Once surface sweating takes place and sweat is at the level of the epidermal membrane in the duct wall where reabsorption may take place, then two factors may come into play. One would be the triggering of the

reabsorption mechanism; the second would be the capacity of that mechanism for reabsorption. Factors which can possibly trigger the reabsorption mechanism are (1) sodium concentration in sweat, (2) ductal hydrostatic pressure. Several possibilities are available to trigger reabsorption by this second mechanism, they are:

(a) increase in pressure due to increased sweating when there is poral restriction due to hydration of the skin surface;

(b) ductal myoepithelial contraction (Bligh, 1967) which has been suggested to be adrenergically innervated and hence provides the possibility of sympathetic innervation independent of the cholinergically mediated secretory activity;

(c) pressure on the sweat glands by underlying vasomotor activity; again offering the possibility of independent control.

The third possibility of a mechanism to trigger reabsorption is one of direct innervation; a possibility considered by Edelberg (1971) is that of a by-product of the arrival of efferent neural impulses serving to sensitize peripheral receptors.

Given that the reabsorption mechanism is triggered, then the extent of reabsorption of sodium is under the control of mineralocorticoids such as alodsterone, cortisol and cortisone. While it is possible that the extent of sodium reabsorption does effect speed of recovery of the SCR it should be pointed out that no direct experimental work appears to have been carried out to verify whether this is so.

A further possibility to be considered is the role of ADH in the control of water reabsorption; the evidence for the influence of ADH on eccrine ductal reabsorption of water is, however, contradictory.

In summary, at least three factors may influence control over the recovery function of the SCR at the periphery; the extent of secretory activity, the triggering of the epidermal ductal reabsorption mechanism and the momentary capacity of that mechanism dependent on on hormonal control. Such multifactorial determination allows for the momentary changes in recovery rate elicited by changes in task demands and also allows for longer term differences due to stressfull nature of a task situation while also permitting the possibility of more relatively long-term characteristics such as elevated levels of adrenal cortical steroids (as found in schizophrenic patients) having an influence in shortening recovery.

It should also be noted that the analysis presented leads to ex-

pectations about the relation between amplitude and $t/2$ of SCRs. As on the one hand small amplitude, non-duct filling SCRs have long recoveries we should not expect marked correlations between amplitude and $t/2$ when the subject is at a resting level and when using low intensities of stimulation. On the other hand, with highly arousing conditions and intense stimuli, we might equally expect minimal correlation between amplitude and $t/2$ as all responses would be of the high amplitude, short recovery type, Only where a range of SCR activity can be expected bridging secretory duct filling and membrane aspects of the SCR might a negative intra-individual correlation be expected. If, however, interindividual data are correlated then the extent of activity of the three types of factors outlined may lead to a variety of expectations.

(b) *Central physiological factors*

Very little is available in the form of direct evidence concerned with influence of central factors upon recovery of the SCR. This is hardly surprising when the peripheral aspects of the component are poorly understood. From the analysis in the previous section it might be expected that any central factor which is known to influence amplitude might also influence recovery, but what clearly is required is data where manipulation of central factors influences recovery independently of amplitude.

Two pieces of data may be presented, however, not because they completely show the required independence but because they are the only ones which seem to be available where work on central functions has been shown to have measured effect on recovery.

In 1965 Bagshaw et al. published a paper on the SRR orienting response in monkeys with ablation of the amygdala and hippocampus. The data were particularly relevant to the theoretical positions of Mednick (1970) and Venables (1973a, b; 1974) concerned with the involvement of the limbic system in schizophrenia and Bagshaw agreed to re-analyse the data with particular respect to the recovery limb of the SRR. Bagshaw divided responses into those between 1 and 2 kOhms and those between 2 and 4 kOhms. Stimuli were 1000 Hz, 2 sec, 77 db. For control animals $t/2$ values for small responses had a mean value of 2.45 sec and for large response 3.68 sec. For hippo-

campectomized animals $t/2$ values for small responses were 1.72 sec and for large responses 2.20 sec. The mean overall size of responses for the hippocampectomized animals was significantly larger than for the control animals. Thus, although as expected between groups of animals faster recovery was found with larger responses, nevertheless the recovery for the small responses in the hippocampectomized group was smaller than the recovery of the large responses for the control group. It would thus appear that hippocampectomy has an effect of shortening recovery time which may be independent of the size of response given. Of six amygdalectomized animals two were hyperresponsive and had very short values of $t/2$; the four other animals were under-responsive or gave no responses. If responses were given they had large values of $t/2$. Thus, ablation of parts of the limbic system known to have major effects on orienting, attentional and avoidance behavior produce changes in the recovery limb of the SRR. It was hypothesized (Mednick, 1970; Venables, 1973a, 1974) that aspects of schizophrenic behaviour were similar to those which might accompany disturbances in hippocampal function and the shortening of the SRR in hippocampectomized animals is in accord with this hypothesis. The under-responsiveness of the amygdalectomized animals (it is assumed that those who were hyperresponsive had discharging foci) also accords with findings (Gruzelier and Venables, 1972, 1973) showing zero responsiveness in a large number of adult schizophrenics.

A study by Grueninger et al. (1965) has possible relevance since SRRs of monkeys with lesions of the dorsolateral frontal cortex were examined. Frontal and normal animals did not differ with respect to their response amplitude to shock; however, frontal animals displayed a longer time "for skin resistance to return to pre-shock level". It seems most likely that what is measured here is tonic recovery; however, as stated earlier it is possible that long phasic recovery times cannot be distinguished from tonic changes. Other more indirect effects of CNS activity on the recovery limb via the intervention of hormone activity will be considered in the next section.

The recovery limb and behavior

In the absence of sufficient knowledge of the physiological mechanisms

responsible for the recovery limb, further insights into its function may be gained by consideration of behavioral concomitants of different types of recovery limb. Edelberg (1970) suggests although the length of recovery time may distinguish between a rest and a task state, and hence possibly could be considered as yet another measure of "arousal", that "fast recovery rates reflect a mobilisation for goal directed behavior." In 1972 he extended this hypothesis by examining a wider range of tasks and showed that, for instance, although levels of tonic arousal measured by SCL and frequency of spontaneous fluctuations were similar for a mirror tracing task and for a cold pressor test, tc was markedly different for responses in the two situations. In the mirror tracing task t was short and decreased with better performance and increasing task complexity. In the cold pressor test recovery was long and "suggests that enhanced electrodermal activity with retarded recovery may signal a defensive reaction". The interpretation of short recovery as an accompaniment of goal orientated performance is, according to Edelberg, difficult to fit with the finding of short recovery in schizophrenics. It is also not easy to envisage a dimension from "goal orientation to defensiveness" which can accompany a range of recovery from short to long.

One speculative possibility is to suggest that the behavior accompanying different lengths of recovery is akin to the notion of "openness or closedness" to the environments and is thus in some ways akin to the sort of dimension of activity that might be considered to accompany heart rate deceleration or acceleration (Lacey, 1967; Obrist et al, 1970). This point of view cannot be supported directly but requires the martialling of several pieces of disparate data. Data has already been cited showing that short recovery times are characteristic of schizophrenics. Venables (1973b) reviewing data in "input regulation" in schizophrenia has suggested that these patients characteristically exhibit as a primary part of the disease process an openness to the environment. Recent work by Lobstein (personal communication) has shown that under stimulus presentation conditions where startle is not produced, (e.g., by the use of auditory stimuli with controlled rise time) massive heart rate deceleration may be observed in schizophrenics even when very loud stimuli are presented; again this suggests an abnormal "openness to the environment".

Conversely Mednick (see page 142), Hare (1947) and Siddle (1973)

report an association of long SCR recovery limbs with tendencies to psychopathy. Hare (1972) reports a tendency to marked heart rate acceleration in psychopaths in response to simple stimuli. It could be suggested that one of the characteristics of psychopaths is that they are not open to the nuances of the environment which might otherwise lead to socially acceptable behaviour. These facts should be placed in conjunction with Edelberg's suggestion that "retarded recovery may signal a defensive reaction" and Furedy's (1972) finding that signals indicating the presence of noxious stimulation (hence requiring a defensive posture) give responses with long recovery limbs.

If these points are taken together it may be suggested that shortness – longness of recovery may accompany a dimension of openness – closedness of attentional stance. It is worthwhile recalling at this point that short recovery limbs are found in hippocampectomized animals and that the Douglas–Pribram (1966) model of attentional behavior postulates that it is the function of the hippocampus to "exclude patterns from attention through a process of efferent control of sensory reception known as gating". Hippocampectomy would thus lead to a breakdown in this "gating" and consequent openness to the environment.

It thus seems not unreasonable to paraphrase Edelberg's no tion of goal-orientation, which is the concomitant of short-recovery, by the term open attention; there is no doubt that the tasks which he used which demand goal orientation also demand openness of attention. Other speculations may be made concerning the relation of recovery limb to aspects of behavior, again via the involvement of the limbic system. It is known for instance (e.g., Olton and Isaacson, 1967) that rats with hippocampal lesions are superior at two-way active avoidance tasks, while animals with amygdalectomies (Goddard, 1964) show impaired active avoidance. On this basis, taking into account Bagshaw's results reviewed earlier, it might be expected that active avoidance would be an accompaniment of short recovery, while where any responses are shown at all in amygdalectomized animals whose active avoidance is impaired then these tend to have a long recovery limb. It is worth noting at this point that it has been suggested (e.g., Mednick, 1958; Mednick and Schulsinger, 1973) that schizophrenics exhibit superior avoidance behaviour.

Finally, work on the effect of amygdaloid or hippocampal lesions on

adrenal cortical steroids should be mentioned. While these experiments are primarily concerned with hormonal accompaniments of avoidance behavior it is possible insofar as the recovery limb may be a function of electrolyte reabsorption under adrenal cortical control that limbic control of the adrenal cortex may have this additional relevance.

Lesions of the hippocampus produce chronic increases in ACTH levels (e.g., Knigge, 1961) and hence elevated levels of adrenal cortical steroids leading to faster sodium reabsorption and possibly shorter SCR recovery. Conversely, lesions of the amygdala (e.g., Mason et al, 1961) lead to depression of steroid output and consequently a slower SCR recovery. While these speculations fit the data and produce a reasonably consistent picture, it is important that they are treated as speculations. Nevertheless, it is suggested that structure for future work has been provided by this review which hopefully will lead to a better understanding of the nature of the child at "high risk" for breakdown.

ELECTRODERMAL RECOVERY
AND PSYCHOPATHOLOGY

SARNOFF A. MEDNICK

In this article Mednick presents a discussion of the electrodermal recovery limb in relation to psychopathology. Particular reference is made to those studies which have dealt with schizophrenia and asocial behavior.

While the galvanic skin response and the electrodermal response (EDR) have interested psychologists and physiologists for some time, it is only relatively recently (and relatively infrequently) that they have attended systematically to the manner in which the function returns to its resting level. As Furedy (1972) indicates, electrodermal recovery (EDRec) is an "important but relatively ignored, characteristic of electrodermal behaviour" (p. 282). Darrow (1937) and Freeman and Katzoff (1942) published statements on recovery and, in 1958, Mednick gave this variable a central role in a theory of schizophrenia. In part to test this hypothesis, in 1962, Mednick and Schulsinger examined 207 children at high-risk for schizophrenia (the children have schizophrenic mothers) as well as 104 matched controls. The study was designed as a prospective investigation; when some of the high-risk children suffer psychiatric breakdown it is possible to return to their premorbid (1962) examination and determine what characteristics distinguish them from, e.g., high-risk children who resist breakdown.

In their attempts to measure EDRec, Mednick and Schulsinger (1964) were mainly interested in the early stages of the process. This was true for two reasons:

(1) Practically speaking, events such as subjects' thoughts, extra-laboratory noises or even the next stimulus trial frequently interfered with the relatively slow EDRec process.

(2) In the theory guiding the research, EDRec served as an index of the speed and amount of reduction of ANS activity level, following the peak of response amplitude.

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As will be discussed below, this reduction is seen as having rein-forcement value. Since the most important reinforcement effects are those occuring in the period immediately following the reinforced response, Mednick and Schulsinger concentrated on the early part of the recovery process. They measured the time for EDRec of half of the EDR. For example, if a response went from 2.5 to 3.1 micromhos the EDRec was scored as the number of seconds to return to 2.8 micromhos. This score was called half-recovery time (HRT). For a number of reasons they also devised another measure, recovery rate (RR). RR is calculated by dividing one-half of the size of the EDR by the number of seconds to recover one-half of the EDR. (In the example given above, assuming that HRT equals 5 sec, the RR would be 0.3 micromhos in 5 sec or 0.06 micromhos per sec).

Mednick and Schulsinger (1964) and Silber (1963) presented analyses of the EDRec data of the high-risk project which decisively disconfirmed Mednick's (1958) hypothesis relating slow EDRec to schizophrenia. The high-risk subjects were characterized by very *fast* EDRec: this finding was later supported when 20 of the high-risk subjects suffered psychiatric breakdown. Mednick and Schulsinger (1968) reported that the premorbid characteristic that best dis-tinguished these breakdown subjects from controls was fast EDRec. In 1963 and 1964 the original theory was revised in the light of the results of these empirical tests.

Role of recovery in two theories of deviance

Schizophrenia

In the 1963–1964 revision of the "learning theory" of schizophrenia EDRec played an even more central role than in the 1958 statement. As stated in a more clinical formulation of the theory (Mednick, 1962), schizophrenia, or at least some types of schizophrenia, is an evasion of life and this evasion is learned. The learning, it is suggested, takes place gradually over a period of years. It is this learning of evasion or avoid-ance, on the basis of physiological aptitude, which comprises an important part of the clinical syndrome.

To understand the importance of recovery to this theory we must

first clarify our view of avoidance learning. Consider the rat in the shuttle box. The rat is first placed in compartment A; a bell rings. Ten seconds later the floor of compartment A is electrified. The rat leaps up, runs around, defecates, urinates and eventually runs into B and safety. After perhaps 10 trials, the rat will learn to avoid the shock by running into B at the sound of the bell. It is important to ask the question – what factors are important in producing this avoidance learning in the rat? An obvious and critical factor is that he has a response of fear to the shock and bell. The more fear, the faster his learning to avoid. Another critical, but perhaps less obvious, factor is that when the rat runs into the safe compartment he is rewarded by fear reduction. To be more precise, his avoidance response is rewarded by fear reduction. The value of a reinforcement is directly related to its speed of delivery and magnitude. The faster and greater the reduction of fear, the greater the reinforcement value. The rate at which this fear is reduced depends in large parts on the rate at which the autonomic nervous system recovers from a fear state to a normal level. The faster the rate of recovery, the faster the delivery of the reinforcement and the greater the reinforcement. If the rat recovers very slowly the difference between the shock compartment and the safe compartment will be minimized as will be the reinforcement value of his avoidance response. If the rat has abnormally fast autonomic recovery his reinforcement will come abnormally quickly; he will learn the avoidance response abnormally quickly. Hyperresponsiveness (with poor habituation and quick latency) and fast autonomic recovery function as aptitudes for learning avoidance responses just as nimble fingers and absolute pitch provide aptitudes for learning to play the violin.

A human does not have to run to avoid an anxiety-producing stimulus. He can learn to avoid with situationally-irrelevant thoughts. These irrelevant thoughts will take him from an anxiety-producing stimulus. If he has fast recovery, the thoughts will be rewarded and will increase in their probability of being elicited in the presence of anxiety. Over years, the preschizophrenic will learn more and more of these avoidant thoughts. When his thinking is predominantly evasive, a clinician will be able to note the thought disorder and will diagnose schizophrenia. Note that this formulation requires not only the ANS deviance but also a noxious environment.

Our theory suggests that the combination of:

(1) an autonomic nervous system that responds too quickly and too much (and habituates poorly); *and*

(2) an abnormally fast rate of recovery,

provides an aptitude for learning avoidance responses. These ANS variables may be profitably classified into two categories, those that can produce ANS distress (fast latency, exaggerated response amplitude and lack of habituation) and the variable (fast recovery) which helps resolve the distress by providing an aptitude for learning to avoid distressing stimuli. If an individual is to become schizophrenic he must possess both types of ANS characteristics. If an individual is rapidly, exaggeratedly, and untiringly emotionally reactive he may become anxious or psychotic but will not tend to learn schizophrenia unless his rate of recovery tends to be very fast. It also seems likely that an extra-ordinarily reactive ANS will only require moderately fast recovery while an extraordinarily fast recovery will only require moderate reactivity. Both very high reactivity and very fast recovery will result in a very heavy predisposition for schizophrenia.

We have stressed the importance of the physiological predispositions. But the hypothesized ANS predispositions will only result in distress in *response* to unpleasant environments or noxious thoughts. An individual who is treated kindly is far less likely to evidence distressing ANS overexcitement and will have relatively little provocation to learn a massive pattern of avoidant responses. The development of schizophrenia depends then on an interaction of reactive, sensitive and quickly recovering autonomic nervous systems and unkind environments.

Asocial behavior

Trasler (1972) has described an approach to understanding law-abidance and non-abidance which suggests that, in addition to attempting to understand the origins of criminal behavior, it may also be of interest to direct our attention to understanding how the inhibition of unlawful expressions of these basic motives is learned and why some people fail adequately to learn this inhibition.

Let us consider how a child might learn to inhibit or avoid performing asocial acts. Mowrer (1960a, b) has presented a theory of learning which deals directly with this question. Particularly relevant is his

discussion of passive avoidance, a situation in which an individual avoids punishment or fear by *refraining* from engaging in a behavior which has been previously punished. A typical situation may have child A spanked each time he is aggressive to child B. Under normal circumstances the contingent punishment will eventually result in child A's aggression, or preparations for the aggression, evoking a fear response in child A. If anticipation of the aggression evokes a fear response of sufficient magnitude, child A's aggression will be inhibited. The same model may be used to explain how the inhibition of other asocial acts, such as stealing, may be learned.

This approach requires only two factors, the contingent punishment and child A's ability to learn a fear response. Hare (1968a) and Trasler (1972) have convincingly applied this two-factor approach to understanding criminal and psychopathic behavior. By study of peripheral measures of autonomic nervous system functioning, Lykken (1957), Quay (1965), Hare (1968a) and Schmauk (1970) have provided evidence supporting the hypothesis that psychopaths and criminals are characterized by a hyporeactive autonomic nervous system and that this may in fact be the grounds for their deficit in avoidance learning.

Mednick (1970) has suggested an explanation of avoidance learning which adds a third factor to the two-factor theory proposed. The original learned fear response is established by classical conditioning; this assertion is reasonable in view of the susceptibility of the ANS to contiguity training procedures. However, the inhibition of the asocial act is not an ANS response; it is a skeletal-motor response. The skeletal-motor system is also amenable to contiguity training but demonstrations of this amenability are, in practice, rather difficult to achieve. In contrast, when a skeletal-motor response is regularly followed by reinforcement, learning is accomplished with relative ease. Since avoidance learning can be so quickly and easily obtained, it may be of value to ponder what subtle reinforcement may be operating.

Consider child A who approaches another child with aggressive intent. As he anticipates his aggression, fear is aroused because of previous punishment by a parent or a larger peer. If the fear is great enough, the aggressive act will be inhibited. Now what reinforcement might be contingent on this inhibition? As soon as the aggressive act has been successfully inhibited and is no longer anticipated, the fear elicited by the anticipation will begin to dissipate or be reduced. Fear

reduction is, of course, one of the most powerful reinforcers psychology has encountered. The dissipation of the anticipatory fear could serve as a potent reinforcer for the inhibition of the asocial act. The fear-reduction reinforcement increases the probability that the inhibition of the asocial act will occur in the future. Each time the chain (asocial impulse-anticipatory fear-inhibition of the asocial act-dissipation of anticipatory fear) occurs, the inhibition of the asocial act will be reinforced and will increase in probability.

Thus, for a child to learn to inhibit asocial acts he must have:

(1) a censuring agent (such as family); *and*

(2) an adequate fear response; *and*

(3) the ability to learn to emit the anticipatory fear response so as to enhance the probability of his inhibiting the asocial act; *and*

(4) fast dissipation of the anticipatory fear so that the inhibitory response will be promptly rewarded with fear reduction.

Hare (1968a) and Trasler (1972) have elaborated theoretically and empirically the role of the first three requisites. The unique element in this explanation is the requirement of fast dissipation of anticipatory fear. The fear response is controlled chiefly by the ANS. We have suggested the measurement of a peripheral index of the rate of this ANS-fear dissipation by observation of the EDRec. This orientation would predict that (holding constant critical extraindividual variables such as social status, poverty level, etc.) those who commit asocial acts would be characterized by slow EDRec. The more serious and repetitive the asocial acts, the slower the EDRec.

Empirical evidence: recovery and deviance

a. Schizophrenia

In 1964, Mednick and Schulsinger reported that the EDRec of their high-risk subjects was substantially faster than that of controls. This finding was supported by a subsequent analysis indicating that EDRec for a subgroup of 20 of the high-risk subjects who suffered psychiatric breakdown was faster than the EDRec for matched controls. Indeed EDRec for just a single test trial served well to separate the breakdown subjects from the matched control groups. As a result of our most

recent assessment of the 1962 high-and low-risk groups, a group of definite schizophrenics has been diagnosed. Looking back 12 years, a preliminary analysis has disclosed that, in 1962, EDRec was significantly faster for those whom we now diagnose schizophrenic.

If EDRec is significantly related to the process of schizophrenia, and is not altered by the schizophrenic process or its consequents (e.g., hospitalization), then one would expect to observe fast EDRec in individuals already schizophrenic. Ax and Bamford (1970) reanalysing taped EDRec data, found faster EDRec in chronic schizophrenics than in controls. Gruzelier and Venables (1972) and Gruzelier (1973) also reported faster EDRec for schizophrenics than for controls.

In independent laboratories in three nations, evidence has been reported supporting the hypothesis that preschizophrenics and schizophrenics are characterized by fast EDRec. It would now seem useful to explore how this relationship covaries with parameters of stimuli (e.g., stress–non stress), subjects (e.g., subdiagnosis), situations, and methods of measuring EDRec.

Avoidance learning and schizophrenia.
Our theoretical orientation would predict faster avoidance conditioning for schizophrenics than non schizophrenics. An effective measure of avoidance conditioning with humans is eyelid conditioning. The task here is to learn to close an eyelid to a warning signal in order to avoid the noxious effects of a puff of air on the eyeball. Workers in this field can distinguish between a voluntary, involuntary and conditioned blink. Spain (1966) demonstrated that schizophrenics learn this avoidance response *faster than normals*! In addition those schizophrenics who evidenced the most withdrawn (avoidant) ward behavior manifested the fastest avoidance conditioning.

We would also expect relatively good performance from schizophrenics in situations where learning of an avoidance response is functional. In general, censure or punishment produces marked deterioration in schizophrenics' performance (Rodnick and Garmezy, 1957). If, however, the situation is constructed so that the schizophrenic can learn to avoid the censure, his performance improves disproportionately (Cavanaugh, 1958; Johannesen, 1964; Losen, 1961). Unlike normal subjects, schizophrenics learn faster when their response can avoid punishment than when their response merely produces reward (Atkinson and Robinson, 1961).

In our own high-risk sample we would predict that those with fast recovery will have learned more avoidant associates. In a test of this hypothesis in the 1967 breakdown subjects and their controls Lampasso has found a positive correlation between recovery rate and a score for avoidant word associations ($r = 0.48$, 25 *df*, $p < 0.05$).

b. Asocial behavior

In addition to psychiatric deviance, the high-risk subjects and their parents also evidenced considerable amounts of registered criminality (Kirkegaard-Sørensen and Mednick, unpublished paper). In conformance with previous EDR studies (Hare, 1968b), the criminals and psychopaths among our high-risk sample evidenced lower EDR lability than nondeviant controls or those with psychiatric deviance.

In view of our theoretical interest we analysed EDRec as a function of asocial behavior in the high-risk subjects themselves and as a function of registered criminality in their parents. The latter analysis was prompted by the results of a twin study in our laboratory (Bell, Gottesman, Mednick and Sergeant, unpublished study) indicating that of those indices analysed, EDRec was the only variable evidencing significant heritability (see table 1).

Registered criminality in the subject or the subject's parents tended to result in lowered EDR lability and slower EDRec. Among the 104 Controls for the high-risk subjects, there were seven who were registered for recidivistic criminality (some of these asocial acts were relatively minor violations). These seven evidenced slower EDRec than matched controls (Mednick and Loeb, unpublished study). In a new study of 11–13 years-old high-risk subjects, the finding relating parent's criminality to slower EDRec of their children was confirmed. These data lend some support to hypotheses suggesting that slow EDRec is a factor in the origins of asocial behavior. The finding on the heritability of EDRec and relating parents' criminality to slow EDRec in their children, certainly does not allow us to rule out the possibility that EDRec may be one of the genetically transmitted characteristics contributing to the heritability of psychopathy and criminality.

Siddle al. (1973) examined the EDR of 67 inmates of an English borstal. On the basis of 10 criteria, these inmates were divided into high, medium and low asociality. EDR amplitude varied inversely as

Table 1

Electrodermal intraclass correlations for monozygotic (MZ) and dizygotic (DZ) twins

Variable	R_{MZ}	R_{DZ}	H[a]	F[b]	p
Basal level (orienting)	− 0.24	0.61	0.00	0.29	ns
Basal level (conditioning)	0.00	0.49	0.00	0.25	ns
Number of Responses	0.53	0.11	0.20	1.25	ns
Onset latency	0.26	0.01	0.00	0.80	ns
Peak latency	0.76	0.73	0.33	1.50	ns
Peak amplitude	0.33	0.59	0.00	0.63	ns
Recovery time	0.89	0.46	0.89	8.94	< 0.01
Recovery rate	0.11	0.80	0.00	0.12	ns

[a]. Heritability estimated by: $H = (V_{DZ} - V_{MZ})/V_{DZ}$
[b]. F-ratio of within-pair: : $F = V_{DZ}/V_{MZ}$

a function of asociality. Venables suggested to Siddle et al. that they also measure EDRec in their sample. Siddle et al. scored EDRec and sent the data to Mednick for analysis. Speed of EDRec varied inversely as a function of asociality. EDRec on a single trial was surprisingly effective in differentiating the three groups (Mednick et al., unpublished paper).

Variables effecting electrodermal recovery

a. Stimuli

Edelberg (1970, 1972) has presented evidence suggesting that EDRec is slower under defense conditions and faster when the subject is goal oriented. Edelberg has also indicated that EDRec is an individual characteristic which is reliable across stimulus trials. Furedy (1972) has demonstrated that slow EDRec is an excellent indicator of a subject's anticipation of electric shock.

b. Genetics

Bell, Gottesman, Mednick and Sergeant (unpublished paper) measured EDR latency, amplitude, time to peak amplitude, basal

level and recovery. EDRec was the only one of those variables evidencing significant heritability (see table 1). It was interesting that the twins, as a whole, evidenced faster EDRec relative to controls.

c. Perinatal conditions

Mura and Mednick (in press) have observed faster EDRec as a function of perinatal difficulties. These data may help explain the faster EDRec of twins (whose pregnancy and delivery almost by definition is relatively difficult) mentioned immediately above. Mednick (1970) reports the strong relationship between perinatal difficulties and EDR factors among the 20 high-risk subjects who suffered psychiatric breakdown.

d. Limbic factors

Mednick (1970) and Venables (1973) have both presented arguments that the basis of the fast EDRec in schizophrenics may be found in non-optimal limbic system functioning, particularly hippocampal disfunction. Venables came to this position on the basis of neurophysiological data. Mednick found that among high-risk subjects who suffered psychiatric breakdown those with perinatal difficulties presented a pattern of behaviour in conditioning which was similar to the behaviour of hippocampectomized rats in conditioning tasks. Both Mednick and Venables discuss related biochemical and neurophysiological factors. Stimulated by Mednick's hypotheses suggesting that the etiology of the schizophrenic's difficulties (especially those with early onset) may lie partially in perinatally caused damage to the hippocampus, McLardy (1973) conducted neuropathological studies of early onset schizophrenic patients. In post mortem neuroanatomical studies of 17 early-onset schizophrenics, McLardy reports a greater paucity of dentate granule-cells than for controls. He points out "that perinatal anoxia ... could be responsible for premature cessation of mitosis, manifesting anatomically as paucity in granule cellularity".

Bagshaw et al. (1965) observed the effect of hippocampectomy on the EDR of monkeys. We encouraged Bagshaw to rescore their data for EDRec, hypothesizing that the hippocampectomized monkeys would evidence faster EDRec than amygdalectomized or non operated

controls. This hypothesis was strongly supported (Bagshaw and Kimble, 1972).

Measurement of electrodermal recovery

The material presented above suggests that it might not be completely fruitless to continue investigations on the variable of EDRec. Since some grounds exist for entertaining the hypothesis that EDRec is related to psychopathology, perhaps research attention could be directed to a better understanding of the psychological and physiological functions which influence EDRec; a related question is the meaning of the possible methods of scoring EDRec (see the preceding contribution by Venables).

In 1962, when we began measuring EDRec, we published data on the time to recover half of the response or half-recovery time (Mednick and Schulsinger, 1965; Silber, 1963). We discovered, however, that in the high-risk groups, half-recovery time correlated moderately with amplitude (—0.45). On the other hand when we expressed EDRec as a rate (1/2 amplitude/HRT) this correlation changed to 0.11. Consequently, in 1968, we began to publish material expressing EDRec as rate. The use of this score has recently been questioned by Edelberg (1972a) who recommends use of a measure equivalent to our 1962 measure, HRT. We have, since, tested EDRec in a variety of types of samples ranging in size from moderate ($N > 200$) to sufficient ($N > 1400$). In all of these samples we have routinely expressed EDRec both as HRT and recovery rate (RR). We are impressed by the variations in the correlation of amplitude with these two estimates of EDRec across types of samples. We can state an impression that the more the variation in the amplitude of response in a sample, the greater the correlation of amplitude with HRT and the smaller the correlation with RR. Intuitively, it seems reasonable that a *very* small response is not likely to take more absolute time to recover than a very large response. Thus in samples with a wide range of response amplitudes, we might expect HRT to correlate more highly with amplitude than in samples with a relatively restricted range of response amplitudes.

Our high-risk group is a sample which might be expected to exhibit an unusually wide range of amplitudes since it contains a number of

individuals who will eventually become schizophrenic as well as many who will eventually be recidivistic criminals. Perhaps this is the reason we observed a relatively high correlation in this group between HRT and amplitude. In any case, these observations have led us to tentatively conclude that sample characteristics might influence EDRec-amplitude correlations. We also have reason to suspect that these correlations will also vary as a function of stimulus conditions (Lockhart, 1972). Perhaps attention to the variations in relationships as a function of method of measurement, on the one hand, and sample characteristics and stimulus condition, on the other, will help us understand the significance of EDRec.

In closing this section, it may be noted that a recent (1973) analysis of the 1962 heart rate data by Therese M. Herrmann produced results substantially parallel to the GRS data previously obtained by Mednick and Schulsinger.

In 1972–1973 the Institute recalled the subjects tested in 1962–1973 for retesting and re-evaluation. Most of the original assessment techniques were repeated, often in a more sophisticated fashion; for example, the very active participation of Peter Venables and Turin Itil has greatly enhanced the scope and sensitivity of the neurophysiological procedures. In addition, with the assistance of Joseph Zubin and John Wing, the psychiatric interview has not only been expanded and refined but also has been coded for computer diagnosis. A number or new measures have been added to the battery to assess possible brain damage, cognitive controls, sensitivity to social censure, and early familial relationships.

At the time of writing, the analysis of data from the retest is in progress. Since the subjects are now approaching or are in early adulthood – with its attendant personal, social, and environmental demands – the results of this evaluation should prove particularly exciting.

Studies focusing on genetic factors

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This section deals with a group of studies conducted at the Institut which have contributed to the elucidation of genetic factors in psychopathology. The emphasis of these studies has been to employ the adoption methodology in relation to schizophrenia; studies of psychopathy criminality and alcoholism have subsequently been initiated.

The idea for the use of the adoption method in research in schizophrenia was conceived by Kety, Rosenthal and Wender. The file covers some 14,500 adoptees who had formally been given up for adoption between 1924 and 1947 in Denmark. Compilation of this invaluable data source was achieved by Kety, Rosenthal, Wender and Schulsinger with grant support from the United States Public Health Service. They have given their consent to other investigators to utilize this resource.

THE ADOPTED-AWAY OFFSPRING OF
SCHIZOPHRENICS*

DAVID ROSENTHAL, PAUL H. WENDER, SEYMOUR S. KETY,
JOSEPH WELNER AND FINI SCHULSINGER

The first paper in this section reports a study which employed the research strategy, described as design no. 2 in Rosenthal's contribution, wherein the functioning of adopted offspring of pathological parents is compared to that of controls.

Most investigators who have sought the root cause of schizophrenia have looked for it in the family. Two major hypotheses were put forth to account for the observations made. One had to do with familial behavior, the other with familial genes. Both variables are crude, and the studies that led to their inference have suffered from methodological weaknesses. The greatest weakness was the fact that the two implicated variables, the behavior and the genes, were always confounded in the same family, whether the familial relationship was parent-child or twin-cotwin. Other major weaknesses included faulty or biased sampling, the lack of adequate controls, the failure to control for diagnostic reliability, and the failure to keep the diagnostician blind with respect to whether the subject being examined was the relative of an index case or a control.

In our studies we have taken special precautions, insofar as we were able, to remedy these defects. We have unconfounded the two major variables through adoption. There are various ways to do this, each asking a different question. [...] The study we are reporting in this paper repeats the traditional research design that has used adoption

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to assess genetic and rearing factors with respect to normal or abnormal behavioral characteristics, such as intelligence or alcoholism. We call it the "Adoptees Study", since the focus of the study is the adoptees themselves, not their relatives.

The subjects

We started with subjects who had been given up for nonfamilial adoption at early ages and who had entered the age of risk for schizophrenia before the study began. We found slightly fewer than 5500 such adoptees. We then identified their biological parents through detailed, accurate records. Although there were slightly fewer than 11,000 such parents, we could not identify with sufficient certainty about one-fourth of the biological fathers. Thus we identified about 10,000 biological parents in all.

Through a central psychiatric register we determined who among these parents had been admitted at any time for mental illness. The hospital records of each such parent were reviewed by a psychiatrist, who filled out a form with the following information: the place, dates, and discharge diagnosis for each hospitalization; the behavior leading to the first admission; the major features of the life history and the premorbid personality; the precipitating factors; the major features noted at the first admission; additional major symptoms noted in later admissions; the clinical course and outcome; and the psychiatrist's own summary diagnosis. This completed form was then reviewed independently by two of us (D.R. and P.H.W.), and one of us (S.S.K.) reviewed some of the forms when he was still at NIMH. If we agreed that the parental disorder was schizophrenia, doubtful schizophrenia, or manic-depressive psychosis, the adopted-away child of that parent was chosen as an index case. From among the remaining adoptees, we chose as controls those whose both biological parents had no known psychiatric history – i.e., neither parent had a file in the psychiatric register. Controls were matched with the index cases for sex, age, age at transfer to the adopting family, and socio-economic status of the adopting family.

The index and control subjects were invited to participate in a study of the relationship between environment and health. Those who

refused are currently being assessed for psychopathology through the use of records, a personal interview by a psychiatrist at the subject's home, or through some minimal personal contact. The refusal rates were 21.1% and 21.4% for the index and control groups respectively. Thus, we were able to achieve almost 80% cooperation, an acceptable figure, and the two groups did not differ in this respect.

Although all cooperating subjects have now been examined, the data on some subjects have not yet been processed. At this time we are able to report on 76 index cases and 67 controls. Only a handful of the total cases are not accounted for in this summary. All subjects were given a psychiatric interview that lasted from about three to five hours. The interviews were all conducted by J. W., except for a brief period of illness, when F.S. carried on for him. Each subject also had one and a half days of psychological testing, but we are not able to present the test findings now. The examinations of all subjects spanned a period of four years.

The selection and processing of subjects were carried out in such a way that none of the examiners knew if the subject before him was an index or control case. Even the interviewing psychiatrist could be kept blind in this respect since the subject in most instances had no knowledge about his biological parents or the possibility that they had a mental illness. When the subject discussed his family, he was talking about his adoptive family, but his index or control status depended on his biological family. Thus, if the psychiatrist had a bias in favor of either the genetic or behavioral variable, he could not be influenced in his diagnosis so as to systematically favor one group or the other, wittingly or unwittingly.

Since age was one of the matching variables, the index and control groups had approximately the same mean age, 32.5 and 32.7 years for the two groups respectively. The age range for the entire sample was from 20 to 52. Thus the average subject had lived through more than half the age of risk, but an appreciable risk for schizophrenia still remained.

Age at transfer to the adopting family was another matching variable. The transfer age varied between five days and 48 months. The median transfer age was 5.9 months for the index cases and 5.8 months for the controls. We are able to compare the pretransfer histories of the two groups in several ways and will do so in the future.

Of the 76 index parents, 50 were mothers and 26 were fathers. The fact that more schizophrenic women than schizophrenic men have children is well known, and this finding is not surprising. Part of the reduced rate for fathers is accounted for by the loss that we had noted earlier of about one-fourth of all biological fathers.

The relation between the age at first admission for the index parent and the date of birth for the index child is important for two reasons:

(1) If the parent was already psychotic before the child was born, the child could have lived with that parent during the first weeks or months of his life, and this experience could have contributed to his developing schizophrenic illness later in life.

(2) If the index mother was actively schizophrenic while she was pregnant with the index child, abnormal gestational, prenatal, and perinatal factors could have contributed to subsequent instability and psychological disorganization in the child.

In our sample, we find that only nine of the 76 parents had their first psychiatric admission before the birth of the index child. Of the nine, five were mothers and four were fathers. The vast majority of parents, about 87%, did not require hospitalization until well after the child had been born – 10.8 years after, on the average, in the case of the fathers, and 12.1 years in the case of the mothers. Although this finding alone does not exclude the possibility that an appreciable number of the index parents may have been psychotic long before their first hospitalization, nevertheless such illness, if it existed, would probably have been milder than that of most hospitalized cases. Among all 50 index mothers, only two were in a mental hospital while pregnant with the index case. Thus, our study tends to be minimally complicated by such factors.

Diagnoses

In diagnosing the index parents, we used the following code designations: A = not schizophrenia; B_1 = chronic or process schizophrenia; B_2 = the more benign and acute schizophrenic-like conditions such as reactive schizophrenia, schizo-affective psychosis, or acute schizophrenic reaction; B_3 = borderline or pseudoneurotic schizophrenia; D = doubtful schizophrenia; M = manic-depressive

psychosis. In this report, we will group index parents according to their diagnosis and report for each group the diagnoses of the adopted-away children as made by J.W. We will not report all the diagnoses, since that would take too long. Rather, we will list those diagnoses that we are tentatively including in the "schizophrenia spectrum," that is, B_1, B_2, B_3, D, M, or some combination of these.

These disorders, except for manic-depressive psychosis, have long been thought by many clinicians to be different degrees of severity of the same basic disorder. At the present time, the "spectrum" concept represents a hypothesis to be tested. If these disorders tend to cluster in families whose members have been separated, this would provide one kind of evidence that the disorders have some common genetic basis. Manic-depressive parents were included in the study in order to have a contrasting mental disorder to compare with the schizophrenias. We include both types of subjects in the spectrum tentatively because some overlap of both disorders in families has been reported in the past, because in some cases judges could not decide definitely that the diagnosis was either a manic-depressive or schizophrenic disorder, and because this procedure provides a possible way of testing the hypothesis that these are in fact two different genetic disorders. Quite often, J.W.'s diagnoses were qualified and involved a lengthy statement regarding his diagnostic considerations. We cannot go into these in detail here. Instead, we will present the key words used by J.W. that lead us to include these cases in the schizophrenia spectrum.

In table 1 are listed the spectrum diagnoses of two groups of index adoptees: those who had a biological parent with a definite diagnosis of chronic schizophrenia, and those where at least one of the judges thought the parent could be a process schizophrenic. The first group, in which diagnostic agreement was complete, numbered 30 parents. Among their offspring we find seven spectrum cases. Among the 14 parents who at least one judge thought might be a process schizophrenic (shown as $B_1/$ in table 1), five of their offspring carried a spectrum diagnosis. Among these 12 spectrum diagnoses combined, three were called schizophrenic by J.W. These were the only subjects in the entire sample to whom he assigned this diagnosis. Only one of the three had ever been hospitalized.

Table 1 summarizes the spectrum diagnoses of all other index cases, according to the diagnosis of the sick parent. The numbers are too

Table 1

Diagnoses in the schizophrenia spectrum of index children and their biological parents

Diagnosis of index parent*	Children's diagnoses
B_1 (N = 30)	1 Schizophrenia (not hospitalized) 3 Borderline schizophrenia 2 Schizophreniform borderline 1 Significant paranoid tendencies: beginning paranoid schizophrenia?
$B_1/$ (N = 14)	1 Schizophrenia, chronic (hospitalized) 1 Schizophrenia, simple (not hospitalized) 1 Borderline paranoid 1 Probably borderline paranoid: schizoid 1 Schizoid: schizophreniform borderline?
B_2 (N = 4)	None
B_3 (N = 4)	1 Paranoid borderline 1 Paranoid character
M (N = 7)	1 Manic-depressive or schizophreniform psychosis (hospitalized) 1 Pseudoneurotic borderline
B_2/M (N = 6)	1 Psychotic or near psychotic 1 Schizophrenic borderline, well-compensated 1 Schizoid, prepsychotic 1 Schizoid character
B/D/M/A (N = 11)	1 Almost pseudoneurotic schizophrenic 1 Paranoid borderline? 1 Possible paranoid borderline 1 Schizoid personality

* Abbreviations: B_1 = process schizophrenia, diagnosed by all judges: $B_1/$ = process schizophrenia, diagnosed by at least one judge but not by all judges. B_2 = reactive schizophrenia: B_3 = borderline or pseudoneurotic schizophrenia: M = manic-depressive psychosis: B_2/M = judges could not agree which of these two diagnoses was correct: B/D/M/A = judges could not agree which of these diagnoses applied to a particular case (A = not in the schizophrenia spectrum; D = doubtful schizophrenia).

small for each group to be evaluated separately. However, among the 32 cases combined, 12 carry spectrum diagnoses. It is worth noting that the one case carrying a primary diagnosis of manic-depressive psychosis had a manic-depressive biological parent.

Table 2

Diagnoses in the schizophrenia spectrum of control subjects (N = 67)

1 Schizophrenic-like border case
2 Borderline schizophrenia
1 Paranoid borderline
1 Psychotic borderline
1 Close to borderline psychotic
1 Conceivably paranoid borderline
1 Pronounced preschizophrenic diathesis
1 Schizophrenic diathesis (with some doubt)
1 Pronounced prepsychotic features: suspicion of organic brain syndrome
1 Schizoid: beginning schizophrenia?
1 Moderately schizoid

In table 2 are listed the spectrum diagnoses for control subjects. There are 12 such diagnoses among all 67 controls. The rate of spectrum diagnosis is 31.6% for the entire index group combined, compared to 17.8% for the control group. A one tailed chi-square test indicates that the two groups differ significantly in this respect at the 0.05 level.

One might suspect that children who were transferred to their adoptive parents at later ages would be more likely, if they had a schizophrenic biological parent, to develop spectrum disorders than would those children who were transferred earlier. In checking this possibility, we found that the mean age at transfer was 6.8 months for the 24 index cases with spectrum diagnoses, compared to 9.6 months for the 52 index cases who did not have a spectrum diagnosis. The difference does not reach statistical significance, but its direction is opposite to what might have been predicted. Among the 67 control subjects, the mean age at transfer was 5.5 months for the 12 subjects with spectrum disorders and 10.1 months for the 55 subjects without such disorders. Again, the difference is not statistically significant. The findings show the same pattern even if we base the analysis only on index cases whose mentally ill biological parent was the mother.

Discussion

A few points regarding the implications of these findings need to be made:

(1) The evidence supports the theory that heredity plays a significant role in the etiology of schizophrenia spectrum disorders. This inference is based on the assumption that the families who adopted index or control subjects varied randomly across both groups and that there was no appreciable difference in their personality distributions or child rearing practices. Later, we will be able to present data that will help us to evaluate whether this inference is well founded or not.

(2) Among all 76 index cases, only one, or 1.3%, had ever been hospitalized for schizophrenia. Of course, a sizeable proportion of the risk period still remains for most subjects and this rate could increase. In traditional family studies, the risk for hospitalized schizophrenia in children of schizophrenics has varied between seven and 17% in different studies (Rosenthal, 1970). These rates tend to be appreciably higher than ours and suggest the possibility that adoptive rearing reduces the rate of hospitalized schizophrenia in children with a schizophrenic parent. One could argue that the sick parents in the other family studies were all process schizophrenics and that in our own sample we had only 30 such parents; therefore the rate could be higher in the other studies for genetic reasons alone. However, among our 30 offspring of process schizophrenics not one was hospitalized for schizophrenia and only one was called schizophrenic. A more direct and controlled comparison between home-reared and adoptively reared children of a schizophrenic parent needs to be made, and we will report such a study in the future.

(3) The 17.8% rate of spectrum disorders in the control group sounds high. Are we overdiagnosing our cases? Are parents who give their children up for adoption frequently in the spectrum themselves, even if they have never reached a psychiatric facility, and is that the reason for the high rate in the controls? Or is there really such a high rate of such disorders in the population at large? We are already carrying out and planning studies to answer these questions.

(4) We are still not satisfied with our criteria for some of the disorders currently included in the spectrum. Three of us (P.H.W., J.W. and D.R.) have been reviewing a number of cases while blind as to the

index or control status of the subjects, and we are attempting to specify syndromes in the spectrum in a more precise way. Later, we will test these syndromes while still blind to see if they are distributed differently in the index and control groups.

(5) Although only one of our adoptees was hospitalized for schizophrenia, in fact 18 in all have been admitted to a psychiatric facility at some time in their lives. Of these, 11 were index cases and seven were controls. The difference is not statistically significant, the hospitalizations have generally been brief, and the diagnoses not of major seriousness except in the case of the one chronic schizophrenic and the one manic-depressive or schizophreniform case. However, these hospitalizations at least suggest that we may expect more – and perhaps more severe – illnesses in our subjects in future years.

THE TYPES AND PREVALENCE OF MENTAL ILLNESS IN THE BIOLOGICAL AND ADOPTIVE FAMILIES OF ADOPTED SCHIZOPHRENICS*

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and FINI SCHULSINGER[†]

The relatively high incidence of schizophrenia that is consistently found in the parents, siblings, or children of schizophrenics (Slater, 1968) is compatible with both genetic and environmental transmissability of the disorder since close family members share both types of factors. Monozygotic twins, except for the relatively few who are separated at an early age, also share considerably more environmental components and psychological identification than do the dizygotic twins of the same sex (Kety, 1959). It was for these reasons that the suggestion was made in 1959 (Kety, 1959) that adopted children, who receive their genetic endowment from one family and their environmental interactions from another, consitute a uniquely useful population for disentangling these two groups of variables in the transmission of schizophrenia.

In 1963 we initiated a collaborative effort to carry out several studies utilizing adoption as a means of disentangling hereditary and environmental influences in schizophrenia (Kety et al., 1968; Rosenthal et al., 1968; Wender et al., 1968). This paper is based on the report of one of these studies, which examined the prevalence and nature of mental illness in the biological and adoptive parents, siblings, and half-

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siblings of individuals who were adopted at an early age by families not biologically related to them and who eventually became schizophrenic.

Methods

A detailed description of the methods employed was presented in the original report. In order to avoid selective bias it was important to begin with a total sample of adopted individuals. Through the cooperation of the State Department of Justice of Denmark, access to the complete file of adoption records was granted with appropriate safeguards regarding their confidentiality. From the total sample of legal adoptions a subsample was obtained that included all adoptions that met the following criteria:

(1) adoption granted by the City and Country of Copenhagen (the study is now being extended to all of Denmark),

(2) adoption granted between 1924 and 1948 inclusive, and

(3) adoption by persons not biologically related to the child. This yielded 5483 adoptions and constituted our sample of adoptees.

For the purpose of this study we agreed that we would include as "schizophrenic" those individuals whose psychiatric history was characteristic of "chronic schizophrenia", "acute schizophrenic reaction", or "borderline schizophrenia" as these terms are commonly used in the United States. The characteristics of each group were stipulated. It was then necessary to find a group of schizophrenic index cases among the total sample of 5483 adoptees.

Since 1920 the Psychiatric Register of the Institute of Human Genetics has recorded with little loss the names of those admitted to any psychiatric facility. A search of these records, supplemented by individual searches in specific hospitals, revealed that 507 adoptees had been admitted to a psychiatric facility for any reason. It was from this group that the index cases were selected. Because schizophrenia is more narrowly defined in Denmark and in Europe generally, English abstracts of the psychiatric histories of each of these 507 adoptees were prepared and independently examined by each of us. Where agreement could be reached on a diagnosis of schizophrenia, that adoptee became an index case. In this way, 33 index cases were agreed upon. For each of these a control was selected from the pool of adoptees with no

known psychiatric history and who matched the index case in sex, age, socioeconomic class of the adoptive parents, time spent with the biological family, and preadoption history.

These 66 names were then randomly pooled and used in a search through the adoption records and the very complete population register of Denmark in order to identify for each individual the biological and adoptive parents, siblings, and half-siblings. In this way 463 such relatives were identified.

The Psychiatric Register, the files of the 14 major psychiatric hospitals, records of the Mothers' Aid Organization, police records, and military records were then searched for the names of any of the 463 identified relatives of the index cases and their controls. This yielded 67 relatives to whom some mental or behavioral aberration could be attributed.

Since the diagnosis of mental illness in the biological and adoptive families of the probands was the crucial determination of the study, every effort was made to insure that this diagnosis was made independently by each of the four collaborators and in the absence of any knowledge that might bias his evaluation. For each of these relatives, the case records were obtained from the respective institutions and an English summary of each was prepared by a Danish psychiatrist who was not aware of the specific hypotheses being tested and not informed of the relationship of any relative to index or control probands. These summaries were transcribed and the transcriptions were edited to delete all personal names, diagnostic opinions, and any information that might suggest to a sophisticated reviewer that the subject in question was a biological or an adoptive relative of an index case or of a control.

Operating on the hypothesis that schizophrenia need not be transmitted as such but as a broader spectrum of disorders (Rosenthal, 1963), we postulated in advance that this "schizophrenia spectrum" would include clear-cut schizophrenia of the chronic, acute, or borderline type as well as cases where the diagnosis could not be as certain, which would be designated "possible schizophrenia" of one of the three subtypes. Our experience with the selection of index cases caused us to recognize the existence of a group similar in quality to the borderline schizophrenic but of considerably less intensity. This group is best described as "inadequate personality" in the standard nomenclature

and it was included as the mildest of the disorders of the schizophrenia spectrum. After independent evaluation by each of the collaborators, a consensus was arrived at in all but four of the cases and these four were excluded from the subsequent analysis.

Results

The adoptive relatives differed from the biological ones in age, in the number of siblings, and especially in the number of half-siblings. In addition, the adoption agency would have employed some type of screening, which might have tended to reduce psychopathology among them, while it would be expected that emotional instability and psychopathology would be higher in the sample of biological parents, who were usually unmarried, than in the population at large. On the other hand, such differences would not be expected to exist between the families of index cases and their controls, whether biological or adoptive. Thus, the prevalence of particular types of mental illness in each group of relatives of the index cases can appropriately be compared with that in the corresponding relatives of the controls, permitting the separate testing of hypotheses based on genetic or environmental factors in the transmission of schizophrenia.

Table 1

Incidence of schizophrenia spectrum disorders among the biological and adoptive relatives of schizophrenic index cases and controls

Sample	Biological relatives	Adoptive relatives
Total sample		
Index cases ($N = 33$)	13 out of 150	2 out of 74
Controls ($N = 33$)	3 out of 156	3 out of 83
Significance[a]	$p = 0.0072$	n.s.
Subsample: separated within one month of birth		
Index cases ($N = 19$)	9 out of 93	2 out of 45
Controls ($N = 20$)	0 out of 92	1 out of 51
Significance[a]	$p = 0.0018$	n.s.

[a] p is one-sided, from exact distribution.

Mental illness other than that in the schizophrenia spectrum showed a random distribution among the biological and adoptive relatives of index cases and controls. On the other hand (see table 1) there was a highly significant concentration of disorders in the schizophrenia spectrum in the biological relatives of the index cases as compared with the similar relatives of the controls. When the examination was confined to those index cases and controls who spent the shortest period of time with their biological relatives (less than one month), the difference became even more significant, probably by virtue of eliminating some among the controls where mental illness in the biological family may have been a factor in putting the child out for adoption. Of the 13 biological relatives of index cases who were found to have disorders in the schizophrenia spectrum, seven were paternally related half-siblings with whom the index cases would have had in common not even an *in utero* environment but only some degree of genetic overlap.

The conclusion appears warranted that genetic factors operate significantly in the transmission of schizophrenia, and that the higher than expected prevalence of schizophrenia in the families of naturally reared schizophrenics is a manifestation of such transmission.

The prevalence of disorders in the schizophrenia spectrum in the adoptive relatives of the index cases is low and it is not significantly different from the prevalence that exists in the adoptive relatives of the controls. Although this does not support hypotheses that depend on the acquisition of schizophrenic behavior by learning from or imitation of other members of the family, it should be pointed out that our findings do not argue against the importance of environmental factors in the etiology of these disorders. Besides the presence in the household of an individual who exhibits some of the features of schizophrenia, there are many other aspects of life experience – including subtle personality characteristics, child rearing practices, nutritional habits, or even exposure to toxic or infectious agents – that may serve to evoke and elaborate one or another type of disorder in the schizophrenia spectrum in a genetically vulnerable individual. In an effort to obtain more information that may help to define such environmental variables, systematic interviews are being conducted with these biological and adoptives relatives. From the numerous questions relating to early life experience, education, peer relationships, parental qualities, and

history of physical and emotional illness, it may be possible to derive some hypotheses regarding environmental factors that differentiate from the rest those adoptive families in which a schizophrenic illness has occurred.

Examination of the types of schizophrenia spectrum disorder discovered in the biological relatives of the index cases (table 2) indicates a broad distribution over the whole spectrum with no tendency for the type of schizophrenia in the index case to be reflected in the type or intensity of illness in the relatives. This appears to be more compatible with a polygenic form of inheritance rather than with any simple monogenic mode. A parsimonious explanation of the findings, and the one that we prefer, since it helps to account for many of the observations of other workers, is that schizophrenia is not transmitted genetically as such but as a vulnerability or predisposition that requires the operation of other factors, probably environmental. The presence or absence of schizophrenia, the position on the schizophrenia spectrum, or the extent to which the individual is eccentric or even creative may be determined by an interaction between these genetic and environmental variables.

The data on the distribution of disorders in the schizophrenia spectrum among the biological relatives of the index cases also permits inferences regarding the nosology of schizophrenia. None of the biological relatives of the index cases diagnosed as "acute schizophrenic reaction" were found to have schizophrenia spectrum disorders, nor did any of the relatives of any index cases receive that diagnosis themselves. This serves to call into question the appropriateness of classsifying all such acute psychotic reactions as schizophrenic disorders without further evidence from premorbid personality characteristics or the later course of the illness. On the other hand, it is noteworthy that the biological relatives of the index subjects whom we had diagnosed as having "borderline schizophrenia" showed a pattern of schizophrenia spectrum disorders that was not significantly different from that of the biological relatives of the chronic schizophrenic index cases. We suggest that this constitutes compelling evidence for continuing to regard such borderline states as forms of schizophrenia.

It is interesting that although there is a roughly ten percent prevalence of disorders in the schizophrenia spectrum among the biological relatives of the index cases, there is a much lower prevalence of chronic

schizophrenia than one would have been led to expect from the pre-valence reported for that disorder in the families of naturally reared schizophrenics (Slater, 1968). Thus, among the 82 identified biological relatives of the chronic schizophrenic index cases only one could be diagnosed as having chronic schizophrenia, a prevalence of a little over one per cent. Six others whom we classified in our deliberately broad schizophrenia spectrum would probably not have fulfilled the tra-ditional criteria for schizophrenia. One possible explanation may be that the presence of a dignosed schizophrenic in a family that is living together makes more intensive the search for an more likely the dis-covery of mental disorders or abnormal traits in other members and their diagnosis as schizophrenic. In our sample, on the other hand, the transfer of information regarding the existence of mental illness be-tween the adoptee and the biological family was extremely unlikely by virtue of his early transfer from the biological family, by the fact that most of the schizophrenia spectrum disorders occurred in half-siblings, and because most of the mental illness in the biological family occurred after the separation of the index cases. In our study of adoptees, it was found that 87% of the schizophrenic biological parents had their first admissions to a psychiatric facility some time after the birth of the child.

Table 2

Distribution of schizophrenia spectrum disorders in the biological relatives of 33 schizophrenic index cases

Index cases	Total number of relatives	Schizophrenia			Possible schizophrenia			Inadequate personality
		chronic	acute	border-line	chronic	acute	border-line	
Chronic schizophrenia (N = 16)	82	1		3			2	1
Acute schizophrenic reaction (N = 7)	30							
Borderline schizophrenia (N = 10)	38			3		1	1	1

If it can be shown that the higher incidence of more severe types of schizophrenia in the families of naturally reared schizophrenics is not an artifact of ascertainment or diagnosis, another explanation could be entertained for the relatively low intensity of schizophrenia in the biological relatives of the index cases. If schizophrenia does in fact depend upon an interaction of environmental and genetic factors, the risk of their combination should be highest in the families of naturally

reared schizophrenics, while adoption, by placing a predisposed individual in an environment with only a chance distribution of schizophrenogenic factors, should tend to decrease the risk of occurrence and the severity of schizophrenia. We are now engaged in collecting a sample of nonadopted individuals who can be matched with the 5483 adoptees in age, sex, and social class as the basis for a comparison group of naturally reared schizophrenics in whose relatives we shall seek to determine the prevalence and type of schizophrenia spectrum disorders using the same diagnostic criteria we have used in the sample of adoptees.

Acknowledgement

THE CONCEPT OF SUBSCHIZOPHRENIC DISORDERS*

DAVID ROSENTHAL

In this article the author discusses the concept of a spectrum of schizophrenic disorders. Following a brief description of one contemporary Soviet approach, Rosenthal presents data obtained from the Adoptees Study carried out in Denmark.

When Dr. Kety, Dr. Wender and I decided to explore and utilize the concept of a spectrum of schizophrenic disorders, we were not unaware that we might be opening another Pandora's Box, of which there are already so many in studies of mental illness. Nevertheless, there was historical precedent for what we planned to do, and the literature on the genetics of schizophrenia suggested that not all cases that might reflect a manifestation of a schizophrenia genotype were being counted.

The concept of subschizophrenic syndromes has attracted a lot of attention and stimulated much reexamination of this old problem. Not only has this issue aroused interest in the United States, but it has even become a major focus of concern in the Soviet Union. Professor A. V. Snezhnevsky (1972), who is head of the Institute of Psychiatry in Moscow, an Institute which is dedicated entirely to research on schizophrenia, is making research on the spectrum concept a central focus. He has coined the terms "*nosos*" and "*pathos*". He describes nosos as a morbid process, a dynamically developing formation, whereas pathos involves stable changes which are the result of the pathological process. Thus, the schizophrenic state is nosos while some of the suggestive manifestations seen in the relatives of a schizophrenic, which have been described as the schizophrenic constitution, the schizoid, latent schizophrenia, and residual schizophrenia are called pathos. Thus, pathos

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contains the possibility of a pathological process (nosos) on one hand, and residual signs on the other. Dr. Snezhnevsky's Institute will cary out its research in accord with this conceptual framework.

In our studies we are trying to decide on whether or not our schizophrenia spectrum disorders really are what we label them. In one study which we call the Family Study, the findings strongly favor the view that diagnostic categories such as uncertain schizophrenia and borderline schizophrenia are genetically related to classical process schizophrenia, but schizoid personality is not. Thus, we now talk about a hard spectrum and a soft spectrum which, when you think of it, may be taking us down the path of Snezhnevsky's nosos and pathos.

Undaunted, I want to show you why I think that the soft spectrum, which includes a number of syndromes that we call schizoid, is indeed genetically related to process schizophrenia.

First, however, I must point out that most recent studies that have captured the scientific community's imagination, e.g., Heston's (1966), Mednick and Schulsinger's (1968), and our own (Rosenthal et al., 1968), began with a proband schizophrenic who was also a parent. No effort was made to determine the diagnostic status of the second parent. Such a research strategy may be useful, but from a genetic standpoint, it is equivalent to Gregor Mendel beginning his investigation with one selected type of sweet pea plant in the F_1 generation, crossing it with other plants whose characteristics he knew nothing about, and then trying to relate all the characteristics he finds in the F_2 generation to those of the F_1 parent whose special characteristics were known to him. Imagine the confusion and folly of this procedure. A proper genetic study must be based on who mates with whom. In fact, although genetics has been defined in various ways, the simplest and perhaps best definition of genetics is: *the science of matings*. This definition is especially appropriate for human genetics, since we do not have control of such mating and we tend to seek other research strategies to circumvent the problem of not having selected matings available to us in the ways or numbers we would like.

For these reasons, we decided to obtain psychiatric interviews of the second parent who had mated with the schizophrenic or manic-depressive index parent to produce the index child who was adopted away. We call this the Co-parent Study, which is just one aspect of the Adoptees Study. Full details of the methodology employed in this investigation are given in the opening chapter of this section.

Dr. Bjorn Jacobsen conducted psychiatric interviews of the co-parents. The co-parent names were interspersed with the names of subjects who were part of two other studies we were carrying out at the same time, and so he could not be certain that any particular subject belonged to the co-parent study. Even if he could, he had no clear hypothesis about what the co-parent diagnoses should be, and he could not therefore be biased in this respect. After we received the report that accounted the interview in detail, Dr. Wender and I independently and then consensually made our own diagnoses of the co-parent, at the same time remaining blind as to the diagnosis of the index parent and the index child.

Our diagnostic coding system follows that of the American Psychiatric Association Diagnostic Manual II. However, we have added to it our own conception of the schizophrenia spectrum disorders. These include: questionable and definite acute schizophrenic episode; schizophrenic personalities such as undifferentiated inadequate and subparanoid, and schizoid personalities, all of which we refer to as the soft spectrum; and the hard spectrum which includes borderline and chronic schizophrenia, questionable or definite. We have also assigned an identifying number to each diagnosis to facilitate recording of diagnoses, and we have numbered the diagnoses so that, in the main, the higher the number – the worse the diagnosis. The schizophrenia spectrum begins with 62, which is "*questionable acute schizophrenicepisode*", and ends with 99, which is "*chronic schizophrenia, hebephrenic*". Numbers below 62 indicate that the diagnosis is not in the schizophrenia spectrum.

At this point in our work, we have not defined all the spectrum disorders as clearly or in as detailed a way as we would like, but we do seem to share a common conception of the respective disorders in the spectrum. We hope, of course, to provide the desired definitions in the future, and we have made a beginning in this respect. However, it should be pointed out that any degree of unclarity in our definitions of the spectrum disorders serves to work against us, in the sense that it leads to unreliability of diagnosis and increased disagreement among ourselves.

In the Co-parent Study, there were 79 co-parents. Some had died or were not available for study. However, we obtained an intensive psychiatric interview and or additional information on 54 co-parents to

whom we could assign a diagnosis, a participation rate of almost 70%
which is appreciable, considering the relatively advanced ages of the
co-parents. Table 1 shows the diagnoses of the index parents and ad-
dresses itself to the question: *with whom do schizophrenics mate?*

Table 1

Schizophrenia spectrum and psychopathic personality disorders in co-parents of
index adoptees

Diagnosis of index parent	Co-parent male			Co-parent female		
	Number	Spectrum disorders	Psychopathic disorders	Number	Spectrum disorders	Psychopathic disorders
S_1*	15	5	5	9	4	0
S_2	3	0	1	1	1	0
S_3	2	0	1	2	1	0
S_1/ or S_3/	6	0	2	2	2	0
D_1/	1	1	0	1	0	0
S_4	2	1	0	1	0	1
M	3	2	0	6	2	0
Total	32	9	9	22	10	1

* S_1 = chronic schizophrenia; S_2 = acute schizophrenia; S_3 = borderline schizo-
phrenia; S_1/ or S_3 = possible or probable chronic or borderline schizophrenia;
D_1/ = doubtful schizophrenia; S_4 = mixed symptoms of schizophrenia and manic-
depressive illness; and M = manic-depressive illness.

It can be seen that when the index parent is female, the co-parent is
diagnosed as having either a spectrum or psychopathic disorder in
56% of the matings, the two disorders represented equally in the male
co-parents. When the index parent is male, however, almost half of the
female co-parents (45%) have a spectrum diagnosis, and only one has a
diagnosis of psychopathic disorder.

Thus, at least two salient points are brought out in table 1 which
are relevant to our present discussion.

1. If we define a mating between two persons, each of whom has a
spectrum disorder, as an assortative mating, then it appears that such
assortative matings are probably occurring at an appreciable rate.

2. A study such as Heston's (1966), which begins with a proband

schizophrenic mother and finds an elevated rate of psychopathic disorders in the offspring, cannot conclude that the psychopathy is genetically associated with schizophrenia, unless he can show that the male co-parents were not psychopaths themselves.

Table 2

Diagnosis of offspring of schizophrenics according to whether the co-parent has a schizophrenia spectrum disorder or not

#	♀ index	×	♂ co-parent	Sex	Diagnosis
1265	S_1*	×	78	♀	Psychoinfantile anxiety-neurotic, hysteriform woman.
3055	S_1	×	70/64	♂	Sz** borderline or perverse (homosexual?, transvestite). Could break down with Sz episode.
2243	S_1	×	65	♀	S is a very extroverted and self-assertive hysteric, childishly self-centered but completely without prepsychotic or schizoid characteristics.
4021	S_1	×	65/40 + 48	♀	A beginning paranoid schizophrenic; unusually poor contact, vague, autistic-like life.
4643	S_1	×	65	♂	Pronouncedly antiaggressive; taciturn, shy.

#	♂ index	×	♀ co-parent	Sex	Diagnosis
1145	S_1	×	80	♂	Unusually introverted and shy; disturbed thinking.
1236	S_1	×	80/70	♀	schizophreniform borderline? Micropsychotic-like episodes.
1617	S_1	×	67/78	♂	Mildly character neurotic. No schizoidy or psychosis. Salesman personality.
5332	S_1	×	67/21	♂	Schizophreniform borderline case; primary process-like thinking.
26	S_1	×	62/65	♀	Schizophrenic borderline, or even more serious than that.

* S_1 = chronic schizophrenia
** Sz = schizophrenia

Table 2 (continued)

#	♀ index	×	♂ co-parent	Sex	Diagnosis
1034	S$_1$	×	51 + 13/77	♂	A normal person without any nervous symptoms worth mentioning. No prepsychotic characteristics ascertained.
3298	S$_1$	×	51 + 13	♀	Neurotic personality (anxiety and hysterical). No prepsychotic features.
3796	S$_1$	×	51/13	♀	Mentally defective. Personality can not be described with exactness, but no suspicion of psychosis or prepsychotic characteristics.
2093	S$_1$	×	51/42	♀	Hysterical personality.
5295	S$_1$	×	51 mild	♀	Neurotic personality with depressive, anxious and hysterical characteristics. No schizoid or prepsychotic phenomena.
100	S$_1$	×	13/42	♂	Though not schizoid or pre Sz, rather vulnerable. Orally dependent. Depressive reactions.

#	♀ index	×	♂ co-parent	Sex	Diagnosis
360	S$_1$	×	43/30	♂	An above average mentally healthy person.
5245	S$_1$	×	20	♀	Phobic anxious neurosis, with anti-aggressive character structure.
2154	S$_1$	×	01	♂	Healthy. A psychosomatic case without neurotic symptoms or structure.
2177	S$_1$	×	01	♂	Sz in a narrow sense. Sz thinking, primitive impulse breakthrough, pale contact.

Table 2 (continued)

#	Mating pattern ♂ index	×	♀ co-parent	Offspring Sex	Diagnosis
521	S₁	×	43/48	♀	Affective disorder. Secretiveness and reserve. Vacillating psychopathic personality?
2127	S₁	×	39	♂	Complicated character neurosis.
4618	S₁	×	40/32	♂	Sensitive, self-insecure; vague schizoid tendencies.
2250	S₁	×	36	♀	Psychoinfantile personality with anxiety and hysterical symptoms. Thought process Sz-like, with regression. Acute Sz reaction? Oneroid state?

Table 2 presents tentative evidence to the effect that the soft spectrum disorders are indeed genetically related to process schizophrenia, and it does this in the most direct way possible, utilizing a proper genetic study in which both F_1 parent phenotypical characteristics are identified and the F_2 phenotypical characteristics described qualitatively and quantitatively.

In table 2 all index parents have a consensus diagnosis of chronic schizophrenia. The diagnoses of the co-parents are represented by our numerical code. All numbers between 65, which represents "questionable schizophrenic or schizoid personality," and 79, which represents "paranoid personality" are in the soft spectrum. Numbers 80 and above represent the hard spectrum. Numbers 01 to 61 represent normality, organic, neurotic, affective, and personality disorders. Numbers 62 and 63 represent questionable and definitite acute schizophrenic reaction, respectively. Frequently, the co-parent diagnosis involves two diagnoses separated by a slash mark. This was done because symptoms were often diverse and multiple, representing more than one diagnostic category, and we thought that both should be represented. The first diagnosis is the one we thought of as most salient, or primary, and the other was secondary. Anyone with a diagnosis of 65 or higher, whether primary or secondary, is included as an assort-

atively mating co-parent. Almost all assortative matings in table 2 involve co-parents with a *soft* spectrum diagnosis.

On the right hand side of the table are Dr. Welner's most relevant diagnostic statements about the index adoptee. These diagnostic formulations can be classified as representing spectrum disorders or not, and the reader may make his own judgments about them. At this point, we raise the crucial question: *Will we find more spectrum disorders among the offspring of assortative matings than of non-assortative matings, even when almost all the assortative matings involve a co-parent with diagnosis in the soft spectrum?* If so, such a finding would suggest that the genetic input from the soft spectrum coparent adds to the genetic input from the chronic schizophrenic index parent to foster increased schizophrenic manifestation in the offspring. Two judges, Dr. Wender and I, independently sorted the offspring diagnoses as either "spectrum" or "not spectrum." With respect to four subjects, one of the judges could not make a decision with confidence and called the diagnosis "doubtful." The results are shown in table 3.

Table 3

Offspring diagnosis as spectrum or not spectrum according to the diagnosis of the co-parent when all index parents are chronic schizophrenic

	Diagnosis of Offspring	
Co-parent diagnosis	Spectrum	Not spectrum
Spectrum	5 (6)*	3 (4)
Not spectrum	1	10 (11)

* Figures in parentheses include subjects whose diagnosis was called "doubtful" by one judge but "spectrum" or "not spectrum" by the other. One subject was called "doubtful" by both judges, and cannot be shown in the table.

Fisher Exact Probability Test: $p = 0.024$ (Ss called "doubtful" by one judge excluded); $p = 0.015$ (Ss called "doubtful" by one judge included)

It can be seen in table 3 that the frequency of spectrum disorders in the offspring is about 3 to 5 times as frequent when the co-parent has a spectrum diagnosis than when he does not. Similarly, the offspring are about 3 times more likely not to have a spectrum diagnosis if the co-parent has no spectrum diagnosis. Unfortunately, the numbers are small, but a Fisher exact probability test indicates that the differences are significant at the 0.025 level, whether the doubtful cases are

included or not. Dr. Kety and Dr. William G. Lawlor also sorted the offspring diagnoses independently, and they too obtained statistically significant differences.

Thus, the findings favor the view that the spectrum disorders are indeed genetically related to process schizophrenia. We have additional data on the remaining matings, but we are not ready to present them at the moment. In fact, we are planning to review Dr. Welner's interview summaries in detail and to make diagnostic assessments based not only on his diagnostic formulations, but upon his entire summary.

However, the immediate question before us involves an apparent disagreement between the Family Study findings outlined above and the findings from the Adoptees Study with regard to the soft spectrum. *Why should a difference occur at all?* Probably the best explanation can be found in the data shown in table 4.

Table 4

Median risk rates for schizophrenia in first and second degree relatives of schizophrenics. (According to E. Zerbin Rüdin (1972) Morbitidy Risk, %)

First degree relatives		Second degree relatives	
Parents	6.3	Grandparents	1.6
Children	13.7	Grandchildren	3.5
Siblings	10.4	Half-sibs	3.5

The large majority of subjects in the Family Study were halfsibs of the probands. The index cases in the Adoptees Study are offspring of schizophrenics. In table 4, risk rates for first degree relatives of schizo-phrenics are shown on the left, and for second degree relatives on the right. Note how the rates fall off, sometimes precipitously, as we move from first to second degree relatives. For sibs a median rate among various studies is about 10.4%, but for halfsibs, the rate is about one third that. The risk rates for children tend to be higher than the rates for sibs. The rates most relevant to a comparison of the Family Study and the Adoptees Study are the rate for halfsibs and the rate for children, the rate for the latter being about four times larger. Thus, the degree of manifestation should be about four times as great in the Adoptees Study than in the Family Study. This difference probably

applies to the soft spectrum as well, in which case the decreased manifestation in the half-sibs would be sufficient to make the identification of spectrum cases in the half-sibs appreciably more difficult, and many cases may be obscured or lost. The fact is that, even in the Family Study, one of the three judges did successfully discriminate the index and control relatives with regard to the soft spectrum. If the spectrum disorders were not related to schizophrenia, but functioned like other personality disorders, the probability of one judge in three making such a discrimination would be miniscule. Thus, I believe that the concept of a schizophrenia spectrum of disorders is valid throughout its length, and that we will have to reckon with it not only in assessing the genetics of schizophrenia, but in achieving a better understanding of general mental health problems as well.

PSYCHOPATHY: HEREDITY AND ENVIRONMENT*

FINI SCHULSINGER

This study also used the adoptee design to separate genetic and environmental factors in psychopathic behavior.

Nothing indicates that the disease or condition we today call "psychopathy" has not been prevalent as far back in the history of mankind as have psychosis, mental retardation, and neurosis. Once psychosis and mental deficiency had been delimited, psychiatrists became interested in describing and classifying those conditions that could not be ascribed to either psychosis, mental deficiency, or gross neurological damage.

The real pioneer of today's psychiatry, Philippe Pinel (1801), contributed to the concept of psychopathy, which he described as *manie sans délire* – insanity without symptoms of delirium or delusions. Pinel wrote: "I was much astonished to observe several insane persons who never presented any lesion of their intellect and who were dominated by a sort of instinctual rage, as if the affective abilities alone were damaged."

Esquirol and other French psychiatrists developed Pinel's concept further. The culmination was Morel's 1859 treatise in which he outlined a hierarchy of hereditary degeneration: If the first generation of ill people showed even a simple increase of their parents' nervous temperament, then the following generations would be worse and worse. The fourth generation would include the most defective individuals, idiots and cretins. Psychopathy, as defined today, would probably appear in the second generation.

Pritchard (1835), in his treatise on insanity, described a special form, "moral insanity", a term that has continued to be synonymous with psychopathy far into the twentieth century. Pritchard's concept was rather broad and included a collection of disparate conditions that should be ascribed to a variety of psychoses, as borderline or latent forms.

The modern use of the term "psychopathy" was coined by the German psychiatrist Koch (1891) in his book *Die psychopatische Minderwertigkeiten* (*The psychopathic inferiorities*). Under this heading he included "all, be they inborn or acquired, mental abnormalities that influence the life of a human being but that, even in severe cases, do not provoke psychosis and in the affected persons, even in the best cases, do not let them appear as being in complete possession of mental normality and capacity." Thus, Koch's concept was also rather broad, and many of his cases would today be included among neuroses and organic brain syndromes.

Kraepelin (1915) conceived of the psychopathic conditions as circumscribed infantilism or circumscribed development inhibitions. He described and subclassified the psychopathic conditions into seven groups and presented their sex distribution and prevalence on the basis of a hospital population.

Kahn (1931) and Kretschmer (cited in Schneider, 1934) both tried to correlate psychopathy with other aspects of personality. Kahn described 16 types of psychopathy, which he then assigned to either a drive, a temperament or a characterological aspect of the personality. But these aspects of the personality were further elaborated, which again had the sad effect of enabling very few patients to be assigned more easily to one of Kahn's subclasses than to several of the others. Kretschmer's typology was more dynamic; it was based on four psychological stages: "the uptake", "the retention", "the working through", and "the release". A person's way of experiencing something could vary from sthenic to asthenic, which made three forms of reaction possible: the primitive reaction, the expansive reaction, and the sensitive reaction. Each of these three forms of reaction were characterized by a different constellation of the above-mentioned four psychological stages.

Obviously, the classification of psychopathy is an intricate problem. Inasmuch as we have been unable to classify psychopathic disorders

according to well-known etiologies, the most useful compromise has been to classify them purely on the basis of clinical description. This is what Kraepelin did, and it is what Schneider (1934) called a "system-free typology". Schneider improved Kraepelin's typology to some extent because he added to Kraepelin's mainly transgressive psychopaths some groups of personality deviations that did not necessarily lead to antisocial behavior. Schneider aimed at a concept and classification free of moral values. He conceived of psychopaths as deviants from average norms. The deviations caused the affected individual and/or his environment to suffer. Since the only behavioral norms clearly outlined are those that can be deducted from the penal code, it is difficult to imagine how Schneider could settle on norms without making a choice based on his own moralistic equipment (Vanggaard, 1968). Apart from this philosophical weakness, Schneider's typology has been relatively easy to apply; and it has, to a large extent, pervaded European and other schools of psychiatry.

Up until 1939, British psychiatry favored a concept of psychopathy mainly as a moral disease. Since then, Henderson (1939), Curran and Mallinson (1944), and Craft (1966) have made classifications of psychopathy on a purely descriptive basis, but in a much less elaborate way than their German colleagues. None of the British authors specified more than three classes. In England the urge for systematic classification has been much less intense than in Continental Europe; and the forensic aspects of psychopathy have been in the foreground, partly because of the existence, until recently, of the death penalty. For this reason, and because of the strong position of social psychiatry, British psychiatrists have focused more on the treatment aspects of this disorder than has been usual in most of Continental Europe.

In the United States, Benjamin Rush (cited in Craft, 1966) wrote:

> There are many instances of persons with sound understanding and some of uncommon talent who are affected with this disease in the world. It differs from exculpative, fraudulent and malicious lying in being influenced by none of the motives of any of them. Persons with this disease cannot speak the truth on any subject.

Rush thought of psychopaths as having an originally defective organization "in those parts of the body which are occupied by the moral faculties of the mind." He called the condition "moral derangement", and he considered it a valid entity for treatment by physicians.

In the twentieth century, American interest in psychopathy has taken a course that differs in some ways from the European traditions. First, the application of research methods has been more common, perhaps because psychologists and sociologists have had greater academic prestige in the United States than is common in Europe. Second, psychoanalytic theory and practice were integrated into mental health practice much earlier in the United States than in Europe, where it was delayed partly as a consequence of the opposition of the German Nazis to psychoanalysis. The result has been a vast body of more or less sociologically oriented surveys in America on large populations of delinquents and criminals many of whom were psychopaths. Another result has been several, very different attempts at unifying psychoanalytic and descriptive principles in relation to the concept of psychopathy (Greenacre, 1945; Karpman, 1947; and others). Partridge (1930) proposed the term "sociopathic personality", which has become the official American term for psychopathy – a term possibly adopted for operational reasons, but with an unavoidable moralistic content, which does not make it easier for modern criminologists to fight the spirit of retaliation in the penal systems.

Alexander (1930) supplied a comprehensive description and explanation of the "neurotic character", which was the old-time analysts' term for psychopathy. His psychodynamic interpretations of case records are not easy to evaluate from a scientific viewpoint, but his clinical descriptions add much to the otherwise usable, system-free, descriptive classifications of Kraepelin and Schneider. Alexander's description of the "neurotic character" makes the concept of psychopathy a coherent one. Its focus is on personality traits that are also common, to a large extent, to Kraepelin's and Schneider's subgroups, which then become more meaningful. The essence of Alexander's description is that "neurotic characters" show a consistent pattern of acting out and that this acting-out is mainly of an alloplastic nature (except, perhaps, for some alcoholics and a few others).

This very sketchy and condensed review of such a huge topic as the concept of psychopathy does not pretend to do justice to all facets of the subject and all the authors who have written about it. I find a relatively simple, descriptively based concept of psychopathy the most useful tool in research; and as will be evident later, Alexander's description has proved most tempting and also operationally useful to me.

Etiology

Genetics

The very special eugenic ideas of the Third Reich involved some German psychiatric geneticists in the classical type of family studies on relatives of psychopathic probands (Berlit, 1931; Riedel, 1937; Stumpfl, 1936). Their work was carried out in the same neat way as other, respectably intended, genetic work from the famous Munich school. The results of these studies unanimously indicated that heredity plays a role in the etiology of psychopathy.

The nature-nurture problem has always been particularly pronounced with regard to psychopathy, because therapists of all kinds have always been struck by the terrible environments to which many of their delinquent and/or psychopathic patients have been exposed. Newkirk (1957) stated: "As adopted delinquents permit research on the constitutional separate from the environmental element, thorough statistics on adoption and adopted persons including their ancestry should be devised and collected" (p. 54). Reiter (1930) tried to utilize this technique in a prospective design; but, for unknown reasons. nothing but a first presentation of the study has been published. Perhaps he feared German eugenics of the 1930s!

Brain pathology

A number of electroencephalographic (EEG) studies on psychopaths, in different countries, have shown an excess of abnormal EEGs in psychopaths compared with the general population. The more violent or impulsive the psychopaths are, the greater is the number of their EEG abnormalities. The deviations have been shown to be of an unspecific nature, neither focal nor epileptic. Generally, these mild dysrhythmias are viewed as signs of immaturity. Otherwise it is difficult to interpret certain findings. How much of the abnormality is inherited, and how much comes from insufficient obstetrical care, or from series of minor cerebral concussions among the wildest of boys?

This physiological correlate of psychopathy cannot yet, in any case, be ruled out as a possible etiological factor.

Cytogenetics

Among tall, violent lawbreakers, the prevalence of the XYY syndrome
is greater than among other offenders and the general population
(Court Brown, 1968; Nielsen et al., 1969). Such findings are fascinating
and encouraging. However, as only about 1% of severe criminal psy-
chopaths in two psychopathic prisons showed this chromosome abnor-
mality, a cytogenetic solution to the etiology of psychopathy is not to
be expected in the near future.

Deprivation in infancy

Broken homes, loss of parents, hospitalization, lack of proper physical
and emotional care, and institutionalization are all factors believed
by many psychologists and psychiatrists to be of etiological significance
in psychopathy, retardation of development, and other mental abnor-
malities occurring in childhood and later. This belief, or conviction,
has been utilized in many countries to convince politicians and admin-
istrators of the value of humane and well-staffed children's institutions.
Unfortunately, it is often difficult to provide proper care for children
simply because they deserve it.

Writers such as Spitz (1945) and Bowlby (1951) have been influ-
ential in a positive way. From a scientific viewpoint, however, most
of the classics on early experience and its later effects are more dubious,
as has been shown in the more recent works of Clarke (1968), Heston
(1966), and Pinneau (1955). A basic methodological error in the
classical studies of institutionalization effects was that they were per-
formed without proper genetic control. Heston's study has shown with
reasonable certainty that the genetic variable is far more important
than institution versus family rearing with regard to the later devel-
opment of psychosis, personality deviations, and other manifest mental
disturbances.

Current investigations in Denmark

Inasmuch as any pathological condition is a result of an interaction
between genetic and environmental factors, the ideal research should

aim at clarification of this interaction. The greater the knowledge about one of the two factors, the greater are the possibilities of planning investigations on the impact of the other factor.

The usual genealogical studies in psychiatry show that the closer the relationship between a family member and a mentally ill proband, the greater is the risk of mental illness for the family member. As already indicated, the relatives in the usual studies share with the probands not only genes but also environment. A realistic way to "isolate" the genetic factor is to conduct studies of probands who have been reared apart from their biological relatives and to analyze the prevalence of mental disorders among their biological and their foster relatives. This idea is not new, but the practical implications of this technique have generally discouraged possible investigators from making serious attempts.

In an investigation initiated by Kety et al. (1968) seven years ago, we explored the possibilities in Denmark of conducting such a study on schizophrenia. It turned out that studies of the desired nature were feasible in Denmark, for the following reasons:

(1) Denmark has a central register of all adoptions, under the supervision of the State Department of Justice. This department, understanding and appreciating our scientific goals, gave us permission to use its registers. (Of course, permission was granted only subject to several discretionary conditions.)

(2) Denmark has a central register of psychiatric hospital admissions – meant for research purposes. This register goes back to 1916.

(3) Denmark has maintained, since 1924, municipal population registers that make it possible to trace a person if one address from 1924 or later is known. By use of old census lists, it is possible even to trace people farther back – in some instances, as far back as the year 1800. In addition, the Danish population is relatively homogeneous, and there are few emigrants.

The schizophrenic probands in the first adoption study were found among 507 adoptees with psychiatric hospital records from a total pool of 5483 adoptees, encompassing all the nonfamily adoptions in the city and county of Copenhagen between 1924 and 1947. All the case record material for these 507 adoptees with a record of mental illness was screened and reviewed by two Danish psychiatrists, the writer being one.

During this work I was amazed to find a relatively large number of adoptees who had been in contact with psychiatrists because of personality disturbances. Therefore, I planned to do a family study of psychopathy using this adoptive sample, for which it was possible to separate hereditary from environmental factors. The study began in June 1967, and the collection of data ended in September 1969.

Procedures

The first step was to establish an operational and reliable definition of psychopathy. The following criteria were subjected to reliability testing:

(1) A consistent pattern, lasting a reasonable period beyond adolescence, of impulse-ridden or acting-out behavior must be evident. This behavior can be (*a*) mainly active, expansive, or manipulating, or (*b*) mainly passive-asthenic. (Alcohol and/or drug abuse can be an expression of either *a* or *b*.)

(2) The abreactions are inadequate in relation to the precipitating factors (of course, on the basis of very vaguely defined Danish behavioral norms).

(3) The abreactions are frequently of an alloplastic nature. These criteria are all positive.

The negative criteria are the following:

(4) Character neurosis must be excluded, i.e., a consistent pattern of neurotic restriction of activity and gratification.

(5) Borderline psychosis must be excluded.

(6) Cases in which acting-out is found in an otherwise psychotic person are excluded.

I think most psychiatrists would consider this definition of psychopathy adequate for most cases.

Twenty cases were picked from the 507 mentally ill adoptees whom I had originally given a diagnosis of psychopathy in 1964, before the present study was planned and before the above definition of psychopathy was formulated. Twenty other cases with other diagnoses, but with the same amount of case record material and of the same sex and age as the 20 psychopaths, were selected from the same pool.

All the available sets of records for the two groups were then mixed into a common group and evaluated again blindly by two other experienced psychiatrists and me, following a discussion of the criteria.

Each of the criteria was rated on a four-point rating scale. I now found 21 persons of the 40 who could be classified as psychopaths. The other psychiatrists considered 17 and 16 of these 21 cases, respectively, to be psychopathic. In 14 cases all three of us agreed upon the diagnosis of psychopathy; and as the raters had classified, respectively, 21, 22, and 20 persons as psychopaths, the over-all agreement among the three raters was 67%. However, one of the criteria, i.e., that the acting-out behavior should have lasted a reasonable time beyond adolescence, was applied differently by the three raters. An exclusion of the cases below 20 years of age from the screening raised the over-all agreement to 74% among the three raters. If agreement about absence of psychopathy were included, the over-all agreement would increase to 82%.

It turned out that the scoring system discriminated very well between psychopaths and character neurotics. Eight of the 40 persons were characterized by one or two raters as possibly borderline psychotics. The total scores of these eight persons were rather varied with regard to psychopathy, but none of them was high. As a result of the reliability testing procedure, the original definition was changed on one point: it was now required that the psychopathic symptoms should have lasted beyond the age of 19 years.

On the basis of the definition thus established, it was possible to select 57 psychopathic probands from the 507 adoptees with known mental disorders. Then, from the pool of nearly 5000 adoptees who were not mentally ill, a control was selected for each of the 57 index probands. For every adoptee in this pool there was a form in the central register showing sex, age, and age at first transfer to the adoptive family; names and birthdates of the adoptive parents; occupation of the adoptive father, his stated annual income and financial status, and his address at the time of the adoption: and the names, birthdates, occupations, and addresses of the biological parents. Starting with the form on the index proband, an alternating forward and backward search was made until four possible controls had been found. A control had to be of the same sex and born during the same period, to avoid the different influences of changing society. They were also matched for the age at transfer to the adoptive home and for the social class of the adoptive parents, on the basis of a Danish classification by Svalastoga (1959).

A pretransfer history was prepared for every index proband and

his or her four possible controls – that is, a report of how long, with whom, and where each stayed until the transfer to the adoptive parents. In almost every one of the 57 cases it was possible to find a perfect control, with exactly the same age, social background, length of institutionalization, length of stay with biological relatives, and number of environmental shifts before the transfer. It was easy to match for social class, and in many cases to match even for the same section of the city of Copenhagen. The comparability of the two groups is evident in the following summary:

	Index probands	Controls
Number of females	17	17
Average age of females	35.8 years	35.8 years
Number of males	40	40
Average age of males	36.7 years	35.8 years
Number of environmental shifts	1.18	1.21
Months of institutionalization	5.63	5.62

The total number of biological and adoptive relatives age 20 or above was 854. Their distribution in terms of relationship was fairly similar for the two groups, as the following figures* indicate:

	Index probands		Controls	
Relationship	Biological	Adoptive	Biological	Adoptive
Half-sibs	169	12	156	8
Full sibs	25	8	16	11
Fathers	54	54	56	57
Mothers	57	57	57	57
Totals	305	131	285	133

Findings

Mental illness among the relatives was found through a search for the

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* Three biological fathers of index probands and one biological father of a control could not be identified. Three adoptive mothers of probands were unmarried at the time of adoption. Adoptive full sibs are offspring of both adoptive parents; adoptive half-sibs are offspring of only one of the adoptive parents.

names of all 854 relatives in the archives of all the psychiatric institutions in Denmark. A research assistant traveled throughout the country and spent several days at each institution searching the files (with greatly appreciated assistance from the local secretaries). I reviewed and summarized all the available case record material and did a diagnostic classification blindly, i.e., without knowing whether the person was related biologically or by adoption to an index proband or to a control. The findings on mental illness in the various categories of relatives are summarized in table 1.

Table 1

Distribution of mental illnesses in relatives of the Index Probands (I) and Controls (C)

					Half-siblings				
			Siblings		Maternal		Paternal		
	Father	Mother	Sister	Brother	Sister	Brother	Sister	Brother	Totals
Biological	I C	I C	I C	I C	I C	I C	I C	I C	I C
Total number	54 56	57 57	13 11	12 5	35 33	35 33	46 51	53 39	305 285
Mentally ill	15 5	16 12	2 1	3 2	4 5	6 4	7 4	5 4	58 37
Spectrum disorders	15 5	7 2	2 0	3 0	3 2	5 3	6 3	4 4	44 19
Core psychopathy	5 1	0 0	0 0	1 0	1 0	2 1	1 1	2 1	12 4
Adoptive									
Total number	54 57	57 57	3 6	5 5	4 2	3 1	5 3	0 2	131 133
Mentally ill	7 3	9 7	0 0	1 3	0 1	0 1	1 0	0 1	18 16
Spectrum disorders	5 1	4 3	0 0	1 0	0 1	0 1	0 0	0 1	10 7
Core psychopathy	1 0	0 0	0 0	0 0	0 1	0 1	0 0	0 0	1 2

The distribution of mental illnesses of all types was as follows (total number of ill relatives, 129):

	Biological	Adoptive
Index	$\dfrac{58}{305} = 19.0 \pm 2.3\%$	$\dfrac{18}{131} = 13.7 \pm 3.0\%$
Control	$\dfrac{37}{285} = 13.0 \pm 2.0\%$	$\dfrac{16}{133} = 12.0 \pm 2.8\%$

It may be noted that the rates of illness are approximately the same in both groups of adoptive relatives and in the biological relatives of the controls. The overall rate of illness for the biological relatives of the index probands, however, is considerably higher than the rates for the other three subgroups of relatives.

The quality of the case record material, of course, varied according to the institution, the tradition of the time, and, especially, the length of institutionalization. It therefore seemed most useful to operate with a *spectrum* (Rosenthal, 1972) of personality disorders, in which psychopathy was the "nuclear" disease. In some cases a diagnosis of psychopathy was rather likely, but the case record material did not permit application of all the criteria from the definition of psychopathy. These cases were classified as "observation for psychopathy" (probable psychopathy). Some cases were too mild or too inconsistent to be classified psychopathic according to the definition, and they were just classified as "character deviations". If the case record material was relatively sparse in such cases, they were classified as "observation for character deviation". A number of cases had to be classified as evidencing either criminality, alcoholism, or drug abuse, with no other clarifying diagnosis. (In my view, they probably belong to the spectrum of personality disorders more or less related to psychopathy.) A few cases had to be diagnosed as hysterical character deviation (but not conversion hysteria). These cases were counted within the psychopathy spectrum. A single case of an obsessive-compulsive character was not included in the psychopathy spectrum; nor were cases of completed suicide for whom there was no psychiatric information.

The figures that follow show the distribution of psychopathic spectrum disorders among the relatives:

	Biological	Adoptive
Index	$\dfrac{44}{305} = 14.4 \pm 2.0\%$	$\dfrac{10}{131} = 7.6 \pm 2.3\%$
Control	$\dfrac{19}{285} = 6.7 \pm 1.5\%$	$\dfrac{7}{133} = 5.3 \pm 1.9\%$

It is immediately evident that there is a great surplus of such disorders among the biological relatives of the index probands, more than 14% of whom have a psychopathic spectrum disorder compared with 5.8% among the other three relative groups. Among the biological relatives of the index probands, 76% of "mental illnesses of all types" belong to the psychopathy spectrum, compared with 44.56% in the other relative groups. The differences between the biological relatives of the index probands and the other relative groups would have been even greater if the diagnosis of hysterical character deviation had been omitted from the psychopathy spectrum.

Base rate figures for the expectancy of psychopathic spectrum disorders as classified here are not available for the Danish population. It may be seen, however, that the rates of disorder are again about the same in all of the relative groups except the biological relatives of the index probands.

The prevalence of the core disease, psychopathy, among the relatives is shown below:

	Biological	Adoptive
Index	$\dfrac{12}{305} = 3.9 \pm 1.1\%$	$\dfrac{1}{131} = 0.8 \pm 0.8\%$
Control	$\dfrac{4}{285} = 1.4 \pm 0.7\%$	$\dfrac{2}{133} = 1.5 \pm 1.0\%$

Psychopathy is certainly overrepresented among the biological relatives of the index probands.

This difference is even more marked when the distribution of psycho-
pathy is compared in the four parent groups only.

	Parents	
	Biological	Adoptive
Index	$\dfrac{5}{111} = 4.5 \pm 2.0\%$	$\dfrac{1}{111} = 0.9 \pm 0.9\%$
Control	$\dfrac{1}{113} = 0.9 \pm 0.9\%$	$\dfrac{0}{114} = 0\%$

In fact, as none of the mothers in any group received the diagnosis
of core psychopathy, the comparisons may be confined to the fathers
only. Psychopathy occurs more than five times as frequently among
the index probands' biological fathers as among their adoptive fathers
or the biological fathers of the controls, as may be seen here:

	Fathers	
	Biological	Adoptive
Index	$\dfrac{5}{54} = 9.3 \pm 4.0\%$	$\dfrac{1}{54} = 1.9 \pm 1.9\%$
Control	$\dfrac{1}{56} = 1.8 \pm 1.8\%$	$\dfrac{0}{57} = 0\%$

Referring back to table 1, it will be noted that there is an over-all
tendency for the psychopathic spectrum disorders, and for core psycho-
pathy in particular, to appear more frequently among the male than
among the female relatives. The sex differences, however, are not as
marked and consistent in the sibling and half-sibling subgroups as
in the parent subgroups. The table also shows that the differences
between the biological relatives of the index probands and the controls
do not increase consistently as one moves from the comparisons of
rates of mental illness in toto to rates of psychopathic spectrum dis-
orders to core psychopathy. The differences between the index and
control relatives increase substantially, for example, as one goes from
the psychopathic spectrum disorders to core psychopathy in the bio-

logical fathers, while in the biological mothers the increase occurs between the all-mental-disorders category and the spectrum-disorders category. It is not entirely clear from these preliminary analyses, therefore, whether the psychopathic spectrum as classified here is meaningfully related to the definition of core psychopathy. The difference in the patterns of the mothers and fathers may reflect the generally agreed upon fact that males are more likely than females to be classified as core psychopaths in Denmark. The symptomatology involved in the author's definition of psychopathy is more easily recognized in males who have to go to a hospital.

Assuming, however, that the psychopathy spectrum *is* appropriately classified, it is of further interest to examine the distribution of spectrum disorders on a family basis. The figures below indicate the distribution of the psychopathic spectrum disorders in the affected families, the presence of such a disorder in a biological or adoptive family being indicated by +, and its absence by —:

	Number of families		
	Index	Control	Total
Group 1: biological +, adoptive —	27	11	38
Group 2: biological —, adoptive —	22	39	61
Group 3: biological +, adoptive +	5	4	9
Group 4: biological —, adoptive +	3	3	6
Totals	57	57	114

A chi-square test for this distribution (with groups 2 and 3 combined) results in $p < 0.005$.

Discussion

The conclusion to be drawn from these findings is that genetic factors play an important role in the etiology of psychopathy. The definition of psychopathy that we used is purely descriptive, and, applied to case record material, it requires only a minimum of interpretation of the data. The definition has proven reliable, and it probably has face validity as well.

The selection of controls was made with due respect to possible etiological factors. Social background in the adoptive homes was

matched, as was the period of birth. Even the possibility of deprivation during infancy was partially taken into consideration, as the controls and the index probands had been subject to the same number of environmental shifts, had spent the same amount of time in institutions, and had been with their biological relatives the same length of time before placement in their adoptive homes.

The assistant who visited all the psychiatric institutions to find the mentally ill relatives processed all the relatives as one group, without knowing whether they were index or control cases or adoptive or biological relatives.

I selected the index probands and the controls during 1967 and did not, at that time, make any notes about them. When I reviewed the case record material of the mentally ill relatives about two years later, I was unable to tell whether the relative belonged to an adoptive or biological family or to an index proband or a control, with few exceptions. In three cases I felt, because of very peculiar last names, that I could identify a relative as belonging to the biological family of an index proband. In a few cases I could identify relatives as adoptive relatives of probands, but did not know if these probands were controls or index cases. In each such instance, a note to this effect was made in the case summary. It turned out that these few cases of recognition had no influence on the results of the study.

Although the design of this study aims especially at demonstrating possible genetic factors in the etiology of psychopathy, this does not at all mean that the findings exclude environmental factors. However, the above figures indicate that the frequency of psychopathy and related disorders in the adoptive families can be excluded as an important etiological factor in this sample. Only three of the index probands had a unilateral prevalence on the adoptive side, and three of the controls also had this environmental load. Only five index probands and four controls had a bilateral load of psychopathic spectrum disorders.

Another possible environmental factor is deprivation during early infancy, as expressed in number of environmental shifts and lengths of institutionalization in early childhood. If this factor were to be tested in the study, it would have to be a test of, for example, the hypothesis that psychopathic spectrum disorders would be less frequent among the biological relatives of the index probands who were transferred late to

their adoptive homes than among those thransferred at an early age.

In order to make a statistical analysis of these data, it is necessary to take into account the great difference in the number of relatives between the biological families and the adoptive families. It is also necessary to take into account that fathers, mothers, and full siblings are first-degree relatives whereas the half-siblings are second-degree relatives. The following scoring system was used for our provisional analysis:

No disorder	0
Disorders other than psychopathy spectrum	1
Criminality, alcoholism, drug abuse	2
Character deviations and observations for psychopathy	3
Psychopathy	4

Each disease score was multiplied by one if the disorder appeared in a half-sib and by two if it appeared in a first-degree relative. Then the disease scores were totaled separately for each of the proband's two families (biological and adoptive), and the total score for each was divided by the number of relatives in the family group. In order to avoid 0 in the numerator, a score of 1 was added to the total disease score of each family before dividing.

$$\text{Family score} = \frac{\Sigma \text{ (disease score} \times \text{relationship score)} + 1}{\text{Number of relatives}}$$

Fifteen index probands were one month old or less at the time of transfer to their adoptive home; 42 were older than this at the time of transfer. No significant difference in the frequency of psychopathic spectrum disorders among biological family members of the two subgroups was found when the biological family scores were compared by a *t*-test ($p > 0.15$). In this study, therefore, early deprivation could not be held responsible for psychopathy in the index probands. Further, a repetition of this analysis, but with one year of age as the time of transfer as the separation factor, also revealed no significant difference ($p > 0.15$).

One of the possible etiological factors in psychopathy is brain damage. The case record material available for the relatives does not permit an evaluation of this factor, which would require a personal

examination of all the relatives. However, a relevant factor could be pregnancy and birth complications. A search for the official midwife reports about the childbirths of the 114 probands and controls yielded 107 reports. Information on the births of 50 matched pairs of probands and controls was thus available.

The content of older Danish midwife reports is difficult to evaluate. There is some agreement in Denmark that not every complication is registered in these reports. On the other hand, if something is registered, one can feel sure that it really happened. In other words, the midwife reports yield minimum information. Every midwife report was rated according to a five-point rating scale devised in collaboration with Professor F. Fuchs, Chairman of Gynecology and Obstetrics at Cornell Medical School, New York. This scale, based on the relatively primitive type of information in the midwife reports, ranged from 0 (no complications) to 4 points (for severe complications); the total score could be 5 or more points.

The figures below compare the pregnancy/birth complications of the index probands and the controls:

	Index probands	Controls
Number with birth records	53	54
Total scores	94	102
Average score	1.8	1.9
Number with birth records for both groups	50	50
Total scores	80	97
Average score	1.6	1.9
Number with score of 0	24	19
Number with 1–4 points	21	19
Number with 5 + points	5	9
Number with single scores of 3 and/or 4	8	5
Number with single scores of 4	6	3

This analysis does not establish a brain damage etiology of psychopathy, at least insofar as brain damage from birth complications is concerned. If there were such brain damage etiology, we could expect the index probands without obstetrical complications to have a more severe genetic load of psychopathic spectrum abnormalities than the index probands with complications. Twenty-four index probands had not suffered any pregnancy/birth complications (score 0), and 14 had a total score of 3 or above. To obtain a score of 3+, they had to have

experienced one or more serious complications, or a combination of minor complications. Comparing the biological family scores for psychopathic spectrum disorders for the two groups, using the t-test, we found no significant difference in the genetic load in the two groups ($p > 0.20$). Therefore, this analysis, too, failed to yield support for an etiological role of pregnancy/birth complications in psychopathy per se.

ALCOHOL PROBLEMS IN ADOPTEES RAISED APART FROM ALCOHOLIC BIOLOGICAL PARENTS*

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This study makes use of the same research design as outlined in the first contribution to this section: it compares the adopted children of alcoholics with controls whose biological parents were not alcoholics.

For years, studies have indicated that alcoholism is a familial disorder. By most estimates, at least one quarter of the fathers and brothers of alcoholics are likewise alcoholic. (Amark, 1951; Boss, 1929; Brugger, 1934; Gregory, 1960; Winokur, 1970). The lifelong expectancy rate for alcoholism among men in the general population is believed to be about 3% to 5%. (Bleuler, 1932; Fremming, 1947; Luxenburger, 1928; Stögren, 1948; Slater, 1935).

"Familial" is not synonymous with "genetic". Usually the biological parents of individuals are also important persons in their environment. One approach to separating "nature" from "nurture" is to study individuals separated from their biological relatives soon after birth and raised by nonrelative foster parents. Adoption studies, however, pose many problems. Obtaining access to adoption agency records may be difficult. Most agencies have little information about the drinking habits of parents whose children are placed for adoption. Among highly mobile people such as Americans, locating subjects is a formidable undertaking.

For these reasons a collaborative adoption study has been conducted in Denmark, a country where few of these difficulties exist. There is

little immigration in or out of the country, and centralized national registries about adoptions, psychiatric hospitalizations, and criminal records can be made available for scientific purposes on sound discretionary conditions. The purpose of this study was to determine whether men raised apart from their biological parents were more likely to have drinking problems or other psychiatric difficulties if one of their biological parents was alcoholic than if there was no recorded alcoholism among their biological parents.

Method

The sample was obtained from a pool of 5483 nonfamily adoption cases, namely, all such cases which took place in the city and county of Copenhagen, from 1924 through 1947. This pool of adoption cases was originally established as part of a family study of schizophrenia. As part of the same study, all available psychiatric records from the adoptees and their biological and adoptive parents were screened. The sample consisted of an index group of probands who had a biological parent who had been hospitalized primarily for alcoholism. Having such a parent was a cardinal criterion for inclusion in the study as a proband. In addition, the proband group consisted entirely of males who had been separated from their biological parents before the first six weeks of life, were adopted by nonrelatives, and had no known subsequent contact with their biological relatives. By applying these criteria, 67 proband adoptees were selected for study. Only male adoptees were studied, since men are known to be at higher risk for alcoholism than are women. Eighty-five percent of the alcoholic parents were fathers.

In choosing a control group of adoptees, the above criteria were all applied with one exception: none of the controls had a biological parent with a hospital record indicating alcoholism or alcohol abuse. Otherwise, they were matched with the probands by age, sex, and time of adoption. Two control groups were established. In one group, none of the controls had a biological parent with a record of psychiatric hospitalization. In the second control group, the adoptees had a biological parent at one time hospitalized for a psychiatric condition *other* than alcoholism. In this manner, 70 controls were chosen for the

first group and 37 for the second. The controls consisted of adoptees closest in age to the probands who met the other selection criteria. The first control group was somewhat larger than the proband group in anticipation of possible deaths and other reasons for inability to study the individuals. Of the 37 controls who had a biological parent hospitalized for a psychiatric condition other than alcoholism, most had a diagnosis of depression or character disorder; schizophrenics were excluded.

A psychiatrist interviewed the subjects with no knowledge of whether they were probands or controls except in four instances where he correctly guessed the category because of knowledge that four controls

Table 1
Demographic characteristics of adoptees (%)

	Probands[a] (N = 55)	Controls[b] (N = 78)
Age		
20–24	9[c]	10
25–29	51	53
30–34	14	19
35–39	14	10
> 40	11	8
Marital history		
Ever married (never divorced)	62	74
Ever divorced[d]	27	9
Never married	11	17
Academic education		
< 9 yr	67	69
9–11 yr	24	23
12–15 yr	7	8
> 15 yr	2	0
Socioeconomic class		
Low	53	46
High	47	54
Served in military	67	72

[a] Refers in this and other tables to adoptees of alcoholic parentage.
[b] Refers to adoptees of presumed nonalcoholic parentage.
[c] Figures rounded off to nearest whole number for ease of perusal. Sums may therefore not equal 100%.
[d] $p < 0.02$.

Table 2

Foster home experience (%)

Adoptive home characteristics	Probands (N = 55)	Controls (N = 78)
Home intact	87	86
Parental economic status		
Below average	15	19
Average	58	55
Above average	27	26
Parental psychopathology, any	42	50
Father[a] "depressed"		
Possible	2	8
Definite	7	4
Father "alcoholic"		
Possible	5	10
Definite	7	12
Father "antisocial"		
Possible	0	3
Definite	0	0
Father, any psychopathology	24	36
Mother "depressed"		
Possible	4	5
Definite	16	9
Mother, any psychopathology	28	29

[a] "Diagnoses" are based on the adoptees' observations and do not represent first-hand psychiatric observations.

were being added at the end of the study. The interviews were in Danish but recorded in English. They lasted two to four hours and followed a lengthy schedule eliciting information about demographic factors, the adoptive parents, psychopathology in the adoptees, drinking practices and problems, and a wide range of other life experiences. The study was not identified as an "adoption" study and subjects rarely volunteered information about their biological parents; no subject mentioned that he had a biological parent with a drinking problem. Law enforcement records also were reviewed for information about the adoptees and their biological parents.

The interviews and records were sent to Washington University in St. Louis where coding, card punching, and computer analysis was

performed, again without knowledge of the subjects' category. The study was "blind" from beginning to end.

Statistical tests were χ^2 (two-tailed, Yates' correction) and "Student's" t for uncorrelated means (two-tailed).

Results

From the original sample of 174 men compiled from adoption records, 41 subjects were not located or refused to be interviewed. Of these, 14 were probands and 27 were controls. The proportion of unlocatable individuals and refusals was essentially the same in the proband and two control groups. One other subject was dropped from the study because it was impossible to establish which of two possible biological fathers was the real one. This left 133 subjects who were located and cooperated fully in the study. They consisted of 55 adoptees with an alcoholic biological parent (the proband group), 50 control adoptees with no recorded psychiatric hospitalizations among their biological parents, and 28 controls who had a biological parent psychiatrically hospitalized with a diagnosis other than alcoholism.

Analysis of the data revealed no significant differences between the two control groups. Therefore, the two groups were combined to provide a total control group of 78.

Table 1 compares demographic variables in the proband and control groups. As noted above, all subjects were men. The mean age in both groups was 30 with a range of 23–45 years at time of interview.

Divorce was the only demographic variable that distinguished the two groups. The probands had a divorce rate three times greater than that of the control group ($p < 0.02$).

The data pertaining to education can be misleading, given the educational system in Denmark. "Academic" schooling is often followed by various forms of "vocational" or other training which are equivalent to high school or college education in the United States. The data presented conforms closely to academic education levels in the population from which the sample was drawn. Social class estimates were based on a rating scale adapted from Svalastoga (1959) used in other Danish adoption studies.

Table 2 presents information about the adoptive parents. The home

was "intact" when the subject lived with both adoptive parents from adoption until at least 16. Estimates of psychopathology in the adoptive parents were based on information provided by their adopted children and cannot be considered definitive. In general, the parents were considered depressed, alcoholic, or suffering from some form of psychopathology when they reportedly sought medical treatment for the condition.

In general, the two groups of adoptive parents were very similar. The adoptive parents of the probands tended to have somewhat more depression than did the adoptive parents of the controls, but the differences were not significant. The presumptive alcoholism rate actually was higher in the adoptive parents of the control group, but the difference again was not significant.

Table 3 compares psychopathology, exclusive of alcoholism, in the adoptees themselves. Diagnoses of anxiety neuroses, depression, and sociopathy were based on the criteria of Feighner et al. (1972). The controls had somewhat more anxiety neurosis and depression than did the probands, but the differences were not significant. Nor were they significant with regard to sociopathy and drug abuse. Various character diagnoses commonly used in Denmark are combined under the heading of "personality disturbance." Total psychopathology rates, exclusive of alcoholism, were almost identical in both groups.

With regard, however, to psychiatric treatment and hospitalization, the two groups differed significantly. (Psychiatric treatment refers to any type of treatment – verbal or pharmacological – administered by any health professional for a mental or emotional problem.) Nearly half of the probands had received psychiatric treatment as compared to one quarter of the controls. The probands had five times the rate of psychiatric hospitalization compared to the controls. Of the eight probands who had been hospitalized, six were alcoholic by criteria presented in table 5. Of the two controls who had been hospitalized, neither was alcoholic.

Four of the six hospitalized alcoholics were definitely, according to their hospital records, admitted for alcohol-related problems; records were not available for the other two. Thus, alcoholism, as defined in table 5, contributed to the disproportionately high rate of hospitalization in the proband group. This also may be true with regard to psychiatric treatment in general. Of the 55 probands, 22 had received

psychiatric treatment, nine of whom were alcoholic by these criteria. In the control group 19 had received psychiatric treatment, two of whom were alcoholic. The difference between the alcoholics in the two groups who received treatment was significant at the 0.02 level.

Since outpatient records were not available, it was impossible to determine how many of the alcoholics who received outpatient treatment were treated primarily for alcohol-related problems. Nevertheless, the strong correlation of alcoholism and psychiatric treatment suggests the two may be related.

Table 3

Pyschopathology in adoptees (%)

	Probands (N = 55)	Controls (N = 78)
Anxiety neurosis		
Possible	16	18
Definite	2	10
Depression		
Possible	13	17
Definite	2	3
Sociopathy		
Possible	2	3
Definite	5	3
Drug abuse		
Possible	4	1
Definite	5	1
Personality disturbances, other (excluding above)[a]	51	53
Psychopathology, any (excluding alcoholism)	56	53
Psychiatric treatment, any[b]	40	24
Psychiatric hospitalization[c]	15	3

[a] Refers to a variety of character diagnoses commonly used in Denmark, eg, anti-aggressive personality, compulsive personality, sensitive-insecure personality. Most of these are not synonymous with "psychiatric illness" as the term is commonly used.
[b] $p < 0.01$.
[c] $p < 0.05$.

Table 4 lists problems associated with drinking reported by the adoptees. Almost without exception, the proband group had more drinking problems than did the control group. With regard to five

Table 4

Comparison of drinking problems and patterns in two adoptive groups (%)

	Probands (N = 55)	Controls (N = 78)
Hallucinations[a]	6	0
Lost control[b]	35	17
Amnesia	53	41
Tremor	24	22
Morning drinking[b]	29	11
Delirium tremens	6	1
Rum fits	2	0
Social disapproval	6	8
Marital trouble	18	9
Job trouble	7	3
Drunken driving arrests	7	4
Police trouble, other	15	8
Treated for drinking, any[a]	9	1
Hospitalized for drinking	7	0
Drinking pattern		
Moderate drinker	51	45
Heavy drinker, ever	22	36
Problem drinker, ever	9	14
Alcoholic, ever[b]	18	5

[a] $p < 0.05$.
[b] $p < 0.02$.

variables, the differences between the two groups were statistically significant. "Hallucinations" in table 4 refers to auditory or visual perceptual distortions associated with withdrawal from alcohol. "Lost control" refers to the experience of wanting to stop drinking on a particular drinking occasion but being unable to do so. "Morning drinking" refers to repeated morning drinking, not just one or two before-breakfast drinking experiences.

The proband group had an average of 2.05 alcohol-related problems. The control group had an average of 1.23 alcohol-related problems. Subjects in both groups were ranked according to number of alcohol symptoms reported. The difference between the two groups was significant at the 0.02 level ($t = 2.49$).

Table 4 also compares the two groups with regard to how many subjects in each received treatment specifically for alcoholism and how

many were hospitalized with a known diagnosis of alcoholism or alcohol abuse. Five probands reported receiving treatment for a drinking problem; all received disulfiram (Antabuse). This compared to one subject in the control group who had received treatment for a drinking problem; he had never received disulfiram. Four probands had been hospitalized for a problem known to be alcoholic in nature; as noted above, two other probands may have been hospitalized for this reason, but records were not available. No subject in the control group had been hospitalized for an alcohol problem.

The last item in table 4 represents a composite picture of drinking patterns based on quantity and frequency of drinking as well as problems with drinking. Criteria for the four drinking categories are shown in table 5. Using these criteria, ten of the 55 probands were described as "alcoholic" as compared to four of the controls. In other words, the probands had nearly four times the alcoholism rate as did the control group. Comparing alcoholics with other drinkers results in a statistical difference between the two groups at the 0.02 level ($\chi^2 = 5.835$). No one in the study was a teetotaler. Heavy and problem drinking, as defined in table 5, occurred somewhat more frequently in the control group than in the proband group but the differences were not significant. Only alcoholism, as defined in table 5, significantly distinguished the two groups. The mean age of subjects in all four drinking categories was the same – about 30.

To be categorized as "heavy drinker," "problem drinker," or "alcoholic," the subject must have drunk in a manner to meet the criteria for at least a year's period *at some time in his life*. Information was also obtained to determine whether the period of maximal drinking was "current" or had occurred at least a year prior to the interview. Eight of the probands and three of the controls were currently alcoholic, as defined in table 5. The difference between the two groups was significant at the 0.05 level ($\chi^2 = 4.867$).

In addition to the criteria for alcoholism presented in table 5, the Danish psychiatrist (L.H.) who performed the interviews ranked the subjects on a 4-point scale ranging from the mildest drinkers with the fewest problems to the heaviest with the most. The heaviest group comprised individuals who, according to the *World Health Organization International Classification of Diseases*, 8th edition, would be diagnosed in a group of alcoholic psychoses together with cases of excessive, episodical

Table 5

Criteria for drinking categories

Moderate drinker – neither a teetotaler nor heavy drinker.

Heavy drinker – for at least one year drank daily and had six or more drinks at least two or three times a month; or drank six or more drinks at least one time a week for over one year, but reported no problems.

Problem drinker – (a) Meets criteria for heavy drinker.
　　　　　　　　 (b) Had problems from drinking but insufficient in number to meet alcoholism criteria.

Alcoholic – (a) Meets criteria for heavy drinker.
　　　　　 (b) Must have had alcohol problems in at least three of the following four groups:
　　　　　　　 Group 1: Social disapproval of drinking by friends, parents
　　　　　　　　　　　 Marital problem from drinking
　　　　　　　 Group 2: Job trouble from drinking
　　　　　　　　　　　 Traffic arrests from drinking
　　　　　　　　　　　 Other police trouble from drinking
　　　　　　　 Group 3: Frequent blackouts
　　　　　　　　　　　 Tremor
　　　　　　　　　　　 Withdrawal hallucinations
　　　　　　　　　　　 Withdrawal convulsions
　　　　　　　　　　　 Delirium tremens
　　　　　　　 Group 4: Loss of control
　　　　　　　　　　　 Morning drinking

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drinking [303.0], excessive habitual drinking [303.1], and alcohol addiction [303.2]. Using this scale, the proband group had twice the number of "heaviest" drinkers than did the control group. By rejecting cases where there was disagreement between the diagnosis based on criteria presented in table 5 and the "heaviest" drinker category, there were eight subjects in the proband group having the most severe form of alcohol problem, compared to three in the control group. The difference was significant at the 0.05 level ($\chi^2 = 4.867$). Where specific "problems" were the basis for diagnosis, therefore, there was no disagreement and the difference between the proband and control group was statistically significant, with the proband group having a disproportionately higher number of alcoholics.

Table 6 presents variables that could be construed as reflecting "orality" as well as judgments by the interviewer regarding whether

Table 6

Comparison of two adoptive groups, miscellaneous (%)

	Probands (N = 55)	Controls (N = 78)
Heavy smoker	49	37
Marked oral traits, global	11	22
"Great" liking for food	20	23
Artistic-creative[a]	66	82
Religious-philosophical	15	18
Sports-minded	53	46
Marked self-esteem problems	4	3
Psychopathology by diagnosis, any (including alcoholism)	22	18
Psychopathology by diagnosis[b] and/or impression: any (including alcoholism)	62	69

[a] $p < 0.05$.

[b] For explanation of high figures, refer to table 3. In other Danish adoption studies, control samples have also demonstrated a rather high prevalence of psychopathology. Information about rates of psychopathology in a comparable group of *non*adoptees is currently being obtained.

the subjects were unusually creative, interested in philosophy and religion, was sports minded, or had severe "self-esteem" problems. Only one comparison was significant. The controls tended to be somewhat more "artistic-creative" than did the probands. There was no evidence of greater "orality" in either group.

The two groups were also compared with regard to whether they had *any* form of psychopathology, including alcoholism, various character diagnoses, and those psychiatric conditions defined by specific criteria referred to above (Feighner, 1972). In the proband group, 62% had some form of psychopathology, based either on specific diagnostic criteria or implicit criteria based on the judgment of the interviewer. This compared with 69% in the control group. Limiting the term "psychopathology" to conditions where specific criteria were used, 22% of the probands and 18% of the controls were suffering from one or more of these psychiatric conditions. In short, differences between the two groups with regard to total psychopathology were negligible. Only alcoholism, particularly when defined by criteria

based on problems from drinking, significantly distinguished the two groups.

Since four controls received a diagnosis of alcoholism, conceivably one or more might have had an alcoholic biological parent who had not been hospitalized and therefore had no medical record of alcoholism. Police files also were available. None had a parent with a police record.

Sixteen of the 55 biological parents of probands had been arrested for alcohol intoxication, compared to ten of the 78 control parents ($\chi^2 = 4.441$, $p < 0.02$). This provided additional evidence of the validity of the hospital diagnosis of alcoholism in the parents of the probands.

Law enforcement records also were screened to learn how many of the adoptees had a police record. In both groups, 44% had some police record, almost always for minor offenses. Twenty percent of probands had been arrested for intoxication compared to 10% in the control group. The difference, however, was not statistically significant. The only significant difference between the two groups pertained to subjects who received "treatment" instead of being jailed or fined for their offense. Eleven % of the probands had received treatment compared to 1% of the controls, a difference at the 0.01 level. What "treatment" consisted of, or how often it may have directly or indirectly been related to alcohol abuse, could not be determined from the records.

As shown in table 2, about 13% of the probands had an adoptive father designated by the interviewed adoptee as a "possible" or "definite" alcoholic, compared to about 22% in the control group. Of the ten alcoholic probands, two had an adoptive parent considered alcoholic. Among the four alcoholic controls, one had an alcoholic adoptive father. There was no significant correlation between the drinking pattern of the adoptees and the presence or absence of alcoholism in the adoptive parents.

Comment

The data indicate that children of alcoholics are more likely to have alcohol problems than are children of nonalcoholics, despite being separated from their alcoholic parents early in life. All individuals in

the study were separated from their biological parents before the first six weeks of life and raised by nonrelatives without known subsequent contact with their natural parents. Nevertheless, by their late 20's or earlier, offspring of alcoholics had nearly two times the number of alcohol problems as did children of individuals without a record of hospitalization for alcoholism.

Judgment regarding the presence or absence of a "problem" was made by a trained psychiatrist with no knowledge of the parentage of the subjects being interviewed. This "blindness" was rigidly maintained from the beginning of the study until data analysis was completed.

The primary focus of the study was on alcohol problems and not on "alcoholism." The latter term lends itself to such a divergent range of definitions that whatever definition is used can be challenged by those who disagree with it. It should be emphasized, therefore, that "alcoholism" as used in this paper involves applying criteria which are arbitrary; a certain minimum number of problems are required before the diagnosis is made and no single problem is considered diagnostic. Nor is the diagnosis based on quantity and frequency of drinking, although generally problems are directly correlated with amount of alcohol consumed.

However, the criteria used in this study have been used in previous studies and been validated against official records indicating a serious drinking problem. (Guze and Cantwell, 1965; Guze and Goodwin, 1972). In any case, alcoholism, as defined here, did distinguish the two groups, with the offspring of alcoholics receiving the diagnosis nearly four times more often than the offspring of presumed nonalcoholics. (Presumed means there was no hospital record of alcoholism among the biological parents of the control group; it is possible that some of the parents of the controls were alcoholic but had not been hospitalized).

Perhaps the most objective measure of increased alcohol problems in the proband group was the extent of psychiatric treatment in the group. Eight of the 55 probands had been psychiatrically hospitalized as compared to two of the 78 controls. Moreover, six of the eight probands hospitalized were diagnosed as alcoholic by criteria in table 5. None of the four controls with a diagnosis of alcoholism had been hospitalized. Nine of the ten alcoholic probands had received psy-

chiatric treatment, compared to one of the four alcoholic controls. Finally, when *current* alcoholism was the dependent variable, the probands were significantly more likely to be considered current alcoholics than were the controls, suggesting their problems were possibly more severe and intractable.

In ranking the subjects on a 4-point scale, there were some discrepancies between the judgment of the interviewing psychiatrist, where quantity of alcohol consumed was a factor, and the diagnosis based on purely problem-type criteria. Even so, the probands were significantly more alcoholic than the controls when the comparison was restricted to those cases where there was agreement between the two approaches.

Apart from alcoholism, the two groups were virtually indistinguishable with regard to other types of psychiatric illness and life experiences, with one exception: divorce. The probands were three times more likely to be divorced than were the controls. Drinking did not appear to be related to the higher divorce rate. Moderate drinkers in the proband group were as likely to be divorced as heavy drinkers and alcoholics. Divorce and alcoholism have often been associated, but the former has generally been attributed to disruptive effects of the latter. Our data suggest that divorce and alcoholism may perhaps be covariants of a single or related genetic predisposition.

Concerning both alcoholism and divorce, it is important to note that most of the subjects have by no means transversed the age of risk for either of these problems. More than 60% of the subjects were still in their 20's at time of interview. It might have been expected that the alcoholics in the present study would have been older on the average than the nonalcoholics. Subjects, however, had a mean age of 30 regardless of their drinking history. Studies by Amark (1951) and others indicate that the age of risk for alcoholism is roughly from 20 through 45. Therefore, it is possible that the alcoholism rates, as well as divorce rates, will continue to increase over the next two decades, although whether the difference between the proband and control groups will continue to widen cannot be predicted.

The finding that, apart from divorce, *only* alcoholism significantly distinguished the two groups suggests there may be a specificity in the transmission of the disorder heretofore underestimated. The rates of diagnosable depression, anxiety neurosis, sociopathy, and drug addic-

tion were fairly low in both groups and neither group had a significantly higher rate of one of these conditions than did the other. Also, it is interesting that heavy and even problem drinking, as defined in this paper, fail to distinguish the two groups. If anything, there was somewhat more heavy and problem drinking in the control group than in the proband group, although the differences were not significant. This suggests that severe forms of alcohol abuse may have a genetic predisposition but that heavy drinking itself, even when responsible for occasional problems, reflects predominantly nongenetic factors.

It should be emphasized that "genetic predisposition" remains more probable than proven, and certainly may not apply to *all* alcoholics. The adoptees, after all, as a rule spent the first few weeks of life in the care of at least their biological mothers. Wives of alcoholics may well differ from wives of nonalcoholics and conceivably the mothers of the probands in some cases were themselves alcoholic or had other forms of psychopathology, leading to neglect or other kinds of pathogenetic influence on their children. Although this possibility cannot be ruled out, it would seem somewhat farfetched with regard to explaining the findings as a whole.

Another nongenetic factor that may have biased the results was selectivity in the process of adoption. Possibly, those infants having a known alcoholic parent at time of adoption may have been matched with less "desirable" parents than were children of presumed normal parentage. Adoption practices in Denmark 20 to 50 years ago are difficult to assess. From an adoption study of criminality also conducted in Denmark, it appears that a bias did occur in the adoption process, but only at the extreme ends of the social spectrum. In other words, upper-class adoptive parents tended to receive upper class biological children, and low-class adoptive parents received low-class adoptive children. However, in the very large medium group there was no evidence of bias. Moreover, since the adoptive parents of the two groups did not differ with respect to economic status or other demographic variables, including divorce, it would appear that a selective bias in adoption was minimal at most.

Other evidence for and against a genetic predisposition to alcoholism was recently reviewed by Goodwin (1971). The nature-nurture problem in alcoholism has been approached in various ways, but two studies are particularly relevant to the present one. In the early 1940s Roe and

Burks (1945) obtained information about 49 foster children in the 20 to 40 year age group, 22 of normal parentage and 27 with a biological parent described as a "heavy drinker." Among children with heavy drinking parents, 70% were users of alcohol, compared to 64% in the control parentage group. In adolescence, two children of "alcohol-parentage" got into trouble because of drinking too much as compared to one in the "normal-parentage" group. The authors found that adopted children of heavy drinkers had more adjustment problems in adolescence and adulthood than did adopted children of nonalcoholics, but the differences were not significant, and neither group had adult drinking problems. They concluded there was no evidence of hereditary influences on drinking.

This conclusion, however, can be questioned on several grounds. First, the sample was small. There were only 21 men of "alcoholic" parentage and 11 of normal parentage. Since women, particularly at the time of the study, were at very low risk for alcoholism, discovering they had no problem with alcohol was not unexpected. Second, although the biological parents of the proband group were described as "heavy drinkers," it is unclear how many would justify a diagnosis of alcoholism. Most had a history of antisocial behavior and apparently none had been treated for a drinking problem. By contrast all of the biological parents of the proband group in the present study received a hospital diagnosis of alcoholism, and at a time when this diagnosis was rarely employed in the country where the study took place.

Probands in the Roe and Burks study also differed from controls in other respects. They were older at time of placement and a much higher percentage was placed in rural areas or small towns where alcoholism rates are considerably lower than in urban areas (Cahalen et al., 1969). In view of the finding in the present study of a high divorce rate among the children of alcoholics, it is interesting that Roe and Burks report that 35% of their probands were "unhappily married" compared to 20% of the controls. The difference was not significant, however, and further study is needed to confirm our findings.

More recently, Schuckit et al. (1972) also studied a group of individuals reared apart from their biological parents where either a biological parent or a "surrogate" parent had a drinking problem. The subjects were significantly more likely to have a drinking problem if their biological parent was considered alcoholic than if their surro-

gate parent was alcoholic. Studying 32 alcoholics and 132 non-alcoholics, most of whom came from broken homes, it was found that 62% of the alcoholics had an alcoholic biological parent compared to 20% of the nonalcoholics. This association occurred irrespective of personal contact with the alcoholic biological parent. Simply living with an alcoholic parent appeared to have no relationship to the development of alcoholism. Although the sample was relatively small, the results were significant at the 0.0005 level, and tend to support the findings of the present study.

REGISTERED CRIMINALITY IN THE ADOPTIVE AND BIOLOGICAL PARENTS OF REGISTERED MALE ADOPTEES*

BARRY HUTCHINGS and SARNOFF A. MEDNICK

In this paper, delivered to the 1973 meeting of the American Psychopathological Association, the authors address the problem of criminality. Again, they rely upon naturally occurring adoptions in order to investigate the possible components attributable to hereditary or environmental factors.

The recent renewed interest in biological etiologies for criminal behavior (e.g. Hare, 1968) stimulated a re-evaluation of the genetic basis for criminality. The existing evidence is based almost wholly on twin studies, cf. a recent summary in Slater et al. (1971).

The present study is a preliminary report of a retrospective investigation using archive material of registered criminality amongst adoptees and their adoptive and biological relatives. Adoption is regarded as an *ex post facto* experiment in which the hereditary influences represented by the biological parents and the environmental influences as indicated by the adoptive parents can be separated. If there is a genetic basis for criminality then there should be an attendant correlation between the criminality of the biological parents and that of the adoptees. Furthermore, this correlation should be independent of the criminality of the adoptive parents.

The opportunity was available in Copenhagen of working with adoptee material of unusually fine sampling characteristics. Kety, Rosenthal, Wender and Schulsinger, with the support of contracts

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* This article is also scheduled to appear in *Genetics and Psychopathy* (edited by D.A. Zubin).

between Copenhagen's Psykologisk Institut and USPHS, established a file of 5483 adoptees encompassing all nonfamilial adoptions in the City and County of Copenhagen between 1924 and 1947. The creation of this file is described more fully in Kety et al. (1968). The study reported in the present paper centered on the 1145 male adoptees in this file who were born between January 1st, 1927 and December 31st, 1941. Thus, the adoptees were between 30 and 44 years of age at the time their criminality was ascertained in 1971. This would mean that the sample has passed through the greater part of the risk period for criminality, especially for registration of a first offense. It also has the advantage for epidemiological purposes of being a complete series, at least in the sense that it is unselected for criminality. Denmark provides excellent demographic facilities for such a study with a small population having low rates of emigration and immigration; a national population register; centralized police and psychiatric registers.

Initial study of 1145 male adoptees

For comparison purposes the 1145 adoptees were matched individually with a group of non-adoptees for sex, age, occupational status of their father and residence (using old census lists).

The police records for Denmark are housed centrally in the Police Record Office (*Rigsregistraturen*). A chronological index after birth-data gives access to the main alphabetically arranged files on all persons "known to the police" (*Hovedkartotek*). In itself this file is unsuitable for criminological research as it includes very minor offenses and some things which are not offenses at all. Traffic offenses are included although parking infringements, cycling without lights and jaywalking are not. On the other hand certain administrative matters are registered such as admission to hospital in a concussed state and psychiatric patients who discharge themselves from hospital. Inclusion in this file cannot by itself be taken as an indication of antisocial behavior.

A separate criminal record (*Personaliablad*) is kept on all persons who have at any time been convicted of offenses treated as *stats-advokatsager*. These correspond very closely to indictable offenses in British Justice and can be contrasted with *politisager* (summary offenses). Generally speaking, indictable offenses are those against the Danish

Penal Code (*Straffeloven*) plus a few of the Special Laws (*Særlove*) such as narcotics offenses; cruelty to animals and serious customs and excise offenses. On the other hand some offenses against the penal code such as begging and disorderly conduct are normally dealt with as summary offenses. The distinction corresponds very roughly with the difference between felonies and misdemeanors in the U.S.

It is the "criminal record" which is used as the primary source of information for this study. The lifetime risk for registration of a male in Denmark for criminality so defined is about 9%.

The 1145 adoptees and their matched non-adopted controls were checked for registration in the police files. The distribution of these two groups in the files is shown in table 1. It should be remembered that in this and succeeding tables the category "minor offenders" also includes some non-offenders who are known to the police for one reason or another. As can be seen 185 (16.2 %) of the adoptees have criminal records, markedly more than either the controls or the corresponding population figure.

Table 1

Distribution of the initial sample of adoptees and their matched non-adopted controls in the police files

	Adoptees	Non-adoptees
Unidentifiable		1
Not known to the police	566	721
Minor offenses only	394	322
With criminal record	185	101
	1145	1145

The adoptive and biological fathers of the adoptees and the fathers of the non-adopted controls were now checked through the police files. The distribution of the fathers is given in table 2. The rates of criminality of the adoptive fathers and the fathers of the non-adopted controls are very similar. The biological fathers of the adoptees, however, evidence almost three times these rates of criminality.

Table 2

Distribution in the police files of the adoptive and biological fathers on the initial sample of adoptees and of the fathers of the matched non-adopted controls

	Adoptive fathers	Biological fathers	Fathers of controls
Unknown or unidentifiable	26	174	27
Not known to the police	755	464	779
Minor offenses only	220	154	212
With criminal record	144	353	127
	1145	1145	1145

The association between the registered criminality in the adoptees and their adoptive fathers is given in table 3a. The percentage of adoptees with a criminal adoptive father increases from 9.2 % of the unregistered adoptees to 21.7 % of the criminal adoptees ($\chi^2 = 19.52$, 2 df, $p < 0.001$).

The criminal status of the 971 adoptees whose biological fathers could be indentified is tabulated in table 3b in relation to their biological fathers' criminality. Taking into account the increased criminality among the biological fathers themselves, the same pattern can be seen as with the adoptive fathers ($\chi^2 = 16.91$, 2 df, $p < 0.001$).

The results shown in table 3c for the non-adopted control are very similar to those of the adoptees and their adoptive fathers when expressed as percentages.

These results suggest an association between the criminality of the sons and their fathers. This association appears to approximately the same degree amongst both adoptees and non-adoptees. With the adoptees it appears on both the biological and adoptive fathers' sides.

Proband study of 143 criminal adoptees and matched non-criminal controls

The proband study was made in order to make a closer examination of the relatives of a criminal group and to compare them with the relatives of a non-criminal group. The design is discussed in Rosenthal

Table 3a

Distribution of adopted Danish males aged 30–44 years by registered offenses and by criminality of their adoptive fathers

Criminal record of adoptee	N	Criminal adoptive fathers %	Non-criminal adoptive fathers %
Not registered	554	9.2	90.8
Registered for minor offense only	385	14.0	86.0
Registered for criminal offense	180	21.7	78.3
Total	1119		

$\chi^2 = 19.52$, $p < 0.001$.

Table 3b

Distribution of adopted Danish males aged 30–44 years by registered offenses and by criminality of their biological fathers

Criminal record of adoptee	N	Criminal biological fathers %	Non-criminal biological fathers %
Not registered	473	31.1	68.9
Registered for minor offense only	334	37.7	62.3
Registered for criminal offense	164	48.8	51.2
Total	971		

$\chi^2 = 16.91$, $p < 0.001$.

Table 3c

Distribution of non-adopted Danish males aged 30–44 years by registered offenses and by criminality of their fathers

Criminal record of non-adopted control	N	Criminal fathers %	Non-criminal fathers %
Not registered	706	9.5	90.5
Registered for minor offense only	314	12.4	87.6
Registered for criminal offense	100	21.0	79.0
Total	1120		

$\chi^2 = 12.05$, $p < 0.001$.

(1970) and has been used by Kety et al. (1968) in their adoption study of schizophrenia (see the second article in this section).

A group was selected from the 185 criminal adoptees to include all those cases where the biological fathers were identifiable and whose adoptive and biological fathers were born from 1890 onwards. This latter criterion was to maximize the reliability of the police records. These 143 criminal adoptees became the index probands. They were matched individually with 143 adoptees who were not known to the police and who became the control probands. Matching was made on the basis of age and occupational status of the adoptive father. Table 4 presents identifying information on these two groups. As can be seen from the ages of first transfer to the adoptive homes, the amount of possible contact between the adoptee and his biological father was minimal. Actually in almost all cases it was nonexistent since the transfer to the adoptive home took place from a children's home rather than from the biological home.

Thirty-three (23%) of the adoptive fathers of the criminal probands

Table 4

Mean characteristics of index adoptees (criminal probands) and their matched control adoptees (non-criminal probands)

	Index adoptees (Criminal probands) ($N = 143$)	Control adoptees (Non-criminal probands) ($N = 143$)
Occupational status of adoptive father	2.3	2.4
Occupational status of biological father	1.7	2.1
Age on 1st January 1971	35.3 yr	35.3 yr
Age at birth of the child of		
Adoptive mother	30.8 yr	31.6 yr
Adoptive father	32.5 yr	33.6 yr
Biological mother	23.3 yr	23.6 yr
Biological father	26.1 yr	27.9 yr
Age at 1st transfer to adoptive home (median)	6 mth	7 mth
Age at legal adoption (median)	19 mth	16 mth
Income of adoptive father	DKr. 4290	DKr. 4387
Fortune of adoptive father	DKr. 2065	DKr. 1848

had received criminal records as against only 14 (9.8%) of the control adoptive fathers. ($\chi^2 = 9.17$, 1 *df*, *p* < 0.01). This difference was also reflected in various indices of criminality such as number of recorded cases and total length of sentence.

Amongst the biological fathers of the index cases there are 70 (49%) who have criminal records as against 40 (28%) of the biological fathers of the non-criminals ($\chi^2 = 14.43$, 1 *df*, *p* < 0.001). Again the difference was found with all measures of criminality considered. Not only were the index biological fathers more often criminal than the controls but they were worse criminals, with an average of 7.1 cases recorded against each of the criminals amongst the index fathers compared with 4.7 cases against the control fathers who were criminals. On both the adoptive and biological sides the differences were more marked with respect to property offenses than to crimes of violence, but due to the overwhelmingly greater incidence of property offenses and the difficulty of classifying individuals according to dominant offenses it is difficult to draw a hard conclusion here.

When the criminal adoptees are graded in terms of the severity of their criminality by classifying them as recidivists, prisoners etc., there was some tendency for concordance rates to be positively associated with increasing severity. These differences were not statistically significant but were more marked on the adoptive side.

Whilst there are relatively fewer adoptive or biological mothers registered as criminals, their data are, proportionately, in agreement with those of the fathers.

There was considerably more mental illness recorded for the index probands than for the controls with 56 of the former being known to the Psychiatric Register as against only 7 of the latter. Psychopathy was predominant but it should be remembered that the presenting symptom is often the criminal act. More interesting in this context are the psychiatric records of the parents on the adoptive and biological sides. Here there was no difference between the psychiatric histories of the index and control adoptive parents. The adoptive parents had been quite thoroughly screened for mental illness and there was a notable absence of psychosis. 47 of the index probands and 32 of the control probands had at least one *biological* parent who was recorded in the Psychiatric Register. This difference was statistically significant at a low level ($\chi^2 = 3.97$, 1 *df*, *p* < 0.05). The differences were

mainly on the side of the mothers and were due to increased psychopathy and neurosis rather than psychosis. This data is given in table 5.

Table 5
Incidence of psychiatric illness in the biological parents of criminal index probands and non-criminal control probands

	Index cases		Control cases	
	Biological mother	Biological father	Biological mother	Biological father
With psychiatric history	22	32	10	23
Primary diagnosis				
A1 Non-genetically predisposed psychoses		1		3
A2 Genetically predisposed psychoses				
a. psychoses of aging				
b. manic-depressive psychoses		1		1
c. schizophrenia	1	4		2
d. epilepsy				
A3 Psychogenic psychoses	1		4	1
B Neuroses	8			4
C Psychopathies	3	6		6
D + E Oligophrenia and other defects of ability		1	1	
F Abnormal reactions	5	3	2	3
Total persons given diagnoses	18	16	7	20
Alcoholism	1	5		8
Suicide (completed)	1	3		
Suicide (attempted)	3	5	2	5

Midwives' reports were obtained on 92 of the index cases and 93 controls. The two groups did not differ in respect to the course of the pregnancy or delivery nor to the nature and extent of the ensuing complications. Such slight differences that were noticed were in the

direction of the controls having slightly more favorable obstetric histories.

Up to this point a number of variables thought to be of relevance in the determination of criminal behavior have been examined independently. Two questions stimulated the analyses reported in the following section: (1) What is the *combined* effect of the several predictors believed to be of relevance? and (2) Are different aspects of criminality differently determined?

The traditional way of attacking the first of these questions would be to combine several variables in "*n*-way" contingency tables. This is somewhat unsatisfactory. In the first place examination of more than 2 or 3 predictors in such a manner requires prohibitive numbers of cases: certainly more than are available in the present design. But basically the problem is that of spuriousness. To what extent does the effect of A on X disappear when the effect of B on X is taken into consideration? This of course can be extended to variables not being examined when it becomes a question of how much of the variance are we explaining? Such questions are best answered by the use of linear statistical techniques, in particular multiple regression. These analyses enable one to measure the relation of the various predictors *inter se* and to avoid the risk of explaining the same variance several times and of giving the exaggerated impression of relationships which can arise from tabular analyses.

The independent variables were coded as contrasts with a value of 1 signifying the presence of a particular factor, such as a criminal or psychiatric diagnosis, and 0 as its absence. The following variables were included to predict the criminality of the adoptee:

Criminal record and psychiatric hospitalization in biological or adoptive mother or father, social class, severe birth complication, and several of the more promising interactions.

The data for the 143 noncriminal probands and 143 criminal probands were subjected to a stepwise multiple regression analysis.

The three factors which contributed significantly to the regression analysis were (and chosen in this order):

(1) Criminality in at least one *biological* parent
$F = 16.31$, 1 df, 284, $p < 0.001$.

(2) Criminality in at least one *adoptive* parent
$F = 8.04$, 1 df, 283, $p < 0.01$.

(3) Psychiatric diagnosis for the biological mother $F = 5.88$, 1 df, 282, $p < 0.05$.

It is realized that there are problems with stepwise procedures and one cannot from such an analysis conclude that any one predictor is more important than another, or compare their relative importance. What one can do is to conclude that the predictors which make significant contributions to the regression equation do exert their effects independently of each other. In the present analysis the conclusion can be stated that the criminality of the biological parents and of the adoptive parents together with the mental illness of the biological mother make contributions to the criminality of the child even when the partial correlations of these variables amongst themselves have been taken into consideration. Taken together these three predictors reach a multiple R of 0.315 with the criminality of the adoptee, indicating that altogether about 10% of the variance has been accounted for. When interpreting this figure one should recall that variables were coded as values of either 1 or 0 which would tend to underestimate the multiple R but also that the independent variable (criminality in the adoptee) represents two extreme groups from the population namely, criminals and persons not known to the police, which would tend to overestimate the R.

When 12 indices of criminality (such as type of crime and severity of sentence) amongst the criminal probands were subjected to a factor analysis, two factors were extracted which together accounted for about 70% of the variance, Factor 1 which is much the larger, is loaded heavily on theft, property damage, multiple offenses, number of offenses and a relatively early start to the criminal career. It would seem to be a fairly general factor describing typical nonviolent criminality. Factor 2 is clearly a factor correlated with offenses against the person. The high loading on injuries to the victim contrasts with the low loading on thefts and property damage. The high positive loadings on ages at first and last offenses indicate that these are crimes occurring fairly late in life.

When the regression analysis and the factor analysis were subjected to a split-half replication they both turned out to be reasonably stable.

The two factors obtained in the factor analysis were each separately regressed on the predictors of the regression analysis in order to pose the question whether the different aspects of criminality were dif-

ferently determined. This latter analysis was unclear in result and proved totally unstable when subjected to a split-half replication.

Cross-foster analysis

The cross-fostering method, well known in genetic studies with animals, has been described in the context of studies such as the present one by Rosenthal (1970).

Returning to the total sample of 1145 adoptees we find that the sample is just large enough to examine the cross-fostering situation. 52 adoptees were born to biological fathers who were not known to the police but with criminal adoptive fathers. A larger group of 219 adoptees had criminal biological fathers but were adopted by fathers who were not known to the police. The distribution of these 271 adoptees in the police files is shown in table 6. The expected frequencies in each cell are given in parentheses.

Table 6

Cross-foster analysis

	N	Status of Adoptee		
		not known to the police	minor offender	criminal
Adoptive father criminal but biological father not known to the police	52	26 (23.2)	20 (18.8)	6 (10.0)
Biological father criminal but adoptive father not known to the police	219	95 (97.8)	78 (79.2)	46 (42.0)
Total	271			

$\chi^2 = 2.50$ ns.

This can be taken as a direct test of whether having a criminal biological father is more important than having a criminal adoptive father with respect to predicting criminality in the adoptee. It can be seen that the data is in the direction of the hereditary effect being more important than the environmental effect when indexed in this way though the analysis is not statistically significant.

When neither the biological father nor the adoptive father is known to the police ($N = 333$), 35 or 10.4% of the adoptees are criminals. When both fathers are criminals ($N = 58$), then 21 or 36.2% of the adoptees are criminal. The percentages for the two cross-fostered groups above are respectively 11.2% and 21.0%.

Discussion

Within the limits of the adoption methodology there appears to be a correlation between criminality in adoptees and criminality in their biological parents. The most important limit of the adoption method is the possibility that the adoption procedure results in selective placement, promoting correspondence between the adoptive home and the characteristics of the biological parents. Indeed, in this study we noted a significant correspondence in the social classes of the biological and adoptive fathers ($r = 0.22$, 880 df, $p < 0.001$). The Danish organization which arranged many of the adoptions examined in this study states clearly that they do aim at matching in certain respects. Since the hallmark of the adoptive method is the separation of genetic and environmental influences this matching is a serious problem for the researcher.

From the incidence of criminality amongst adoptive fathers and amongst biological fathers one can calculate the expected number of cases where both fathers are criminal if only chance factors have operated in the matching at adoption. For the present sample of 1145, allowing for the unidentifiable fathers, this expected figure is 55. The actual number of adoptees in the 1145, both of whose fathers are criminal, is 58. Thus it can be concluded that whatever effect the matching of the adoption agency might have, it does not express itself directly in registration for crime of the fathers.

It is worth restating that the operational definition of criminal

behavior used here is that of detected, apprehended and registered acts defined by the Danish society as worthy of police and judicial action. It is thus primarily an administrative definition. The extent to which it is also a sociological definition is debatable; the extent to which it is a biological definition is even more doubtful.

In considering whether or how these results obtained in Copenhagen, Denmark can be extrapolated to other national settings, one consideration should be borne in mind. The laboratory experimenter in behavior genetics reduces the variance ascribable to environmental influences when he wishes to explore the effects of strain differences. As environmental variance increases, the strain difference effects become more and more masked. While operating in a narrower range than is available to the laboratory researcher, the extent of variability of a natural, human research environment (in our case, Denmark) will also influence the strength which genetic factors will exhibit. We would suggest that the amount of variability in a culturally and racially homogeneous population such as Denmark for almost any dimension will be less than that of a country like the United States. There is also the problem of extrapolation from an adopted sample to non-adoptees; criminality amongst adoptees may not be typical in certain respects. It follows, then, that in practical terms extrapolation of our Danish findings to other national situations must be conducted with great caution. Stated simply these findings should not be used to explain crime in the United States.

Studies focusing on environmental factors

The papers included in this final section present a complementary picture to those included earlier. They encompass a number of environmental variables which range from *in utero* development to social class.

PERINATAL CONDITIONS AND INFANT DEVELOPMENT IN CHILDREN WITH SCHIZOPHRENIC PARENTS*

SARNOFF A. MEDNICK, ELAINE MURA, FINI SCHULSINGER
and BIRGITTE MEDNICK

The first opportunity which genetic endowment has to interact with the environment is *in utero*. The following study analyzes the effects of pregnancy and delivery complications upon the children of pathological and nonpathological parents.

In 1962, in Denmark, Mednick and Schulsinger (1965, 1968) began the examination of 207 children with a high risk for schizophrenia; these children have chronically and severely schizophrenic mothers. We also examined 104 control children. We estimate that approximately one hundred of these children will manifest serious deviance while approximately thirty will become schizophrenic. We plan to follow these children for some twenty years until they have gone through the major risk period for schizophrenia. When sufficient numbers of these individuals have suffered psychiatric breakdown, we intend to look back at the 1962 assessment procedures to see how the breakdown subjects differ from those who do not breakdown. We hope thereby to develop measures that can be used in the early detection of high-risk samples. We also hope to gain an understanding of factors predisposing to mental illness. Our ultimate goal is to use this knowledge in research on prevention.

In 1968, when the project reached its sixth year, twenty of the children of schizophrenic mothers had suffered severe psychiatric breakdown. An analysis of the data from our 1962 assessment revealed

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a number of premorbid characteristics which markedly distinguished these subjects from controls (Mednick and Schulsinger, 1968). Two of the most successful discriminating characteristics were (1) the presence of a poorly controlled hyperresponsive ANS, and (2) a history of severe perinatal distress. In the light of these perinatal data it is interesting that at the time of the pregnancy of these breakdown individuals, 69% of their mothers were undergoing very severe environmental stress (e.g., jailing of a husband). This was true for only 24% of the controls who had schizophrenic mothers.

Further analysis revealed that the individuals in the breakdown group who had manifested the ANS findings were, almost to a man, the same individuals who had suffered the perinatal distress. In brief, we tentatively interpreted those findings as suggesting that the pregnancy and birth complications (PBCs) had produced neurological damage to inhibitory brain centers which then failed to adequately control or modulate autonomic nervous system responsiveness.

Interestingly enough, while this PBCs-ANS relationship was marked in the children with schizophrenic mothers, no such relationship was observed in children from families with no history of psychiatric hospitalization. We tentatively interpreted this finding to suggest that the PBCs trigger or exacerbate a genetically predisposed vulnerability of the ANS. These findings are reminiscent of the findings of Fraser (1955), who by subjecting pregnant mice to a heavy dose of cortisone during pregnancy could radically increase (up to 100%) the frequency of cleft palates in a genetically vulnerable strain. Ingalls et al. (Stern, 1960) reduced atmospheric pressure in the environment of mice 9 days pregnant and caused an increase in sternum malformations. The frequency of these malformations was especially increased in genetically predisposed groups. We will return to the discussion of these interactive effects.

As is well known, this finding of a relationship between PBCs and mental illness is not at all unique in the literature. Pasamanick and coworkers have, in repeated studies, demonstrated such a relationship (e.g., 1956). Pollack and Woerner (1966) and Tait and Goldfarb (1964) have implicated PBCs in the etiology of childhood schizophrenia. Pollin and Stabenau (1968) found in twins discordant for schizophrenia that the schizophrenic twin had suffered more asphyxia during delivery and was smaller and lighter at birth. Many investi-

gators have found low birth weight to have widespread and marked effects on child development and on psychiatric disorders (Caputo and Mandell, 1970). This listing of studies is merely illustrative.

In view of our interest in the possible differential effects of PBCs in groups varying in genetic vulnerability, and in view of the rather high rate of schizophrenia in individuals with schizophrenic parents, we instituted a new longitudinal study of a group of children with schizophrenic parents for whom excellent perinatal data existed. As controls we took children with "normal" parents and children with parents who have suffered nonschizophrenic psychiatric disorders. We call this new longitudinal study the "OB" project. It will be the subject of this report.

We hypothesized that PBCs could trigger or exacerbate a genetically predisposed vulnerability involving the ANS and could in this manner be a pivotal factor in the development of schizophrenia. We began to bring these children in for intensive study in the summer of 1971. In this report we will describe their pregnancy, delivery, and infant development.

The pregnancies and births of these children had been the subject of intensive study at the University Hospital in Copenhagen as part of a larger perinatal research project on 9006 consecutive pregnancies. These births occurred in 1959–1961 so that the children are now 9–11 years old. This large perinatal project was initiated and concluded by Professors Fritz Fuchs, Dyre Trolle, and Preben Plum, and Drs. Zachau-Christiansen and Aage Villumsen. Our examination of this pool of data was made possible by the courtesy of Preben Plum, Professor of Pediatrics at the University Hospital of Copenhagen.

By reference to central registers existing in Denmark we were able to locate all of the fathers and mothers of the entire sample who had ever been to a mental hospital. From these, we culled those with a definite diagnosis of schizophrenia and matched them with a group of psychiatric controls and a group of normal controls. We were then able to go back to the rich data gathered on the births of these individuals; this presentation contains a report of the complications which distinguish the pregnancies and births of children with schizophrenic parents. As a part of the original study all children were given a physical and neurological examination at birth and at the age of one year. We will also report differences among our groups on these

examinations. The data analyses to be presented are preliminary and tentative. Some of the results are based on unproven scales devised for measuring pregnancy complications and delivery complications. Lastly we have not yet really digested and integrated these rather complex data. We present them to illustrate the methodology and to give an inkling of the direction of some of the more impressive early findings.

Method

A total of 9006 pregnant woman who delivered at the University Hospital in Copenhagen between September 21, 1959 and December 21, 1961 were almost all observed by a single senior obstetrician. The data recorded concerned earlier pregnancies and maternal diseases, and the pregnancy and delivery under investigation. The child was examined during the neonatal period and at one year of age. Almost all of the pediatric examinations were conducted by a single senior physician. All of the data have been recorded on magnetic tape for ready access.

In order to determine which of the 9006 mothers, 9006 fathers, and 9182 children (multiple births) had been admitted to mental hospitals, the names of the parents were ascertained and checked through the Danish Central Psychiatric Register of all admissions to psychiatric hospitals in the kingdom of Denmark. This check was supplemented by a check of the records of Bispebjerg Hospital in Copenhagen which did not report to the national register for a period of years. Of the 18,012 parents, 554 had a record of psychiatric hospitalization. These records were screened independently by two senior psychiatrists who selected 83 cases with a diagnosis of schizophrenia using the same criteria used in previous investigations from this institute (Kety et al., 1968). We found 183 cases of parents with a variety of diagnoses which were clearly not schizophrenic and could be included under the rubric of character disorders (CD). Their hospital diagnoses covered a range including psychopathy, character disorder, inadequate personality, alcoholism, drug abuse, situational neuroses, suicidal attempts, and short term depressive reactions. None of these diagnoses were modified by the terms schizoid, paranoid, manic-

depressive, or sensitive. Subjects who had no record of hospitalization for mental illness were considered to make up the "normal" pool of subjects. From both the CD group and the Normal pool of subjects, individuals were selected by computer as controls to match the 83 schizophrenics. These controls were selected individual for individual on the basis of the following criteria (in order of importance): (1) sex of ill parent; (2) sex of child; (3) race; (4) multiple birth status (twins, triplets, etc.); (5) pregnancy number; (6) social class; (7) mother's age; (8) mother's height; (9) father's age.

The information on the matching criteria is given in table 1 which also includes means for the entire sample of 9182 births. Note that the fertility of the schizophrenic mothers is slightly below that of the total sample. This is due to the relatively small number of schizophrenic women for whom this is more than pregnancy number three. This difference in fertility does not quite reach statistical significance. Table 2 presents the means for the matching criteria as a function of sex of parents. As might be expected there were about twice as many schizophrenic women who were mothers as there were schizophrenic men who were fathers. Table 3 presents the means for the matching criteria as a function of the sex of the child.

Pregnancy and delivery scales

In order to facilitate statistical analysis, a scale of pregnancy and delivery complications was constructed on the basis of the data coded in the larger perinatal project. Table 4 presents an example of assignment of complications with their various weighting to the categories studied in the project. The weightings assigned for each complication were determined in consultation with Danish and American obstetricians and pediatricians.

Two scores were obtained from these weightings, a sum weighted scale score and the highest severity scale score. The sum weighted score simply adds the weights for each observed complication or deviance. With this score it is possible for a large number of minor difficulties to sum to a relatively high score. The highest severity score is the weight of the single most severe complication in that category in the woman's record.

Thus, we obtain a sum weighted scale score and a highest severity

Table 1

Identifying characteristics for entire sample: schizophrenics, character disorders, and normals

Group	Sex		Number of twins	Mean pregnancy number	Mean pregnancy social class*	Mean mother's age	Mean mother's height in cm	Mean father's age
	Males	Females						
Entire sample (N = 9006)	4696	4486	170	1.96	3.45	26.0	163.9	28.4
Schizophrenic parents (N = 83)	42	41	3	1.86	3.58	26.6	163.8	30.8
Character disorder parents (N = 83)	42	41	3	1.90	3.54	26.7	164.5	31.2
Normal parents (N = 83)	42	41	3	1.87	3.53	26.6	164.0	30.6

* General register office, 1951, p. 313. Scale range: 1 (high) to 5 (low).

Table 2

Identifying characteristics for schizophrenics, character disorders, and normals by sex of parent (all Caucasian)

Group	Sex		Twins	Pregnancy No		Social class*		Mother's age		Mother's Ht.		Father's age	
	Male	Fem.		Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
Schizophrenic mothers (N = 57) .	29	28	2	1.74	0.96	3.71	1.10	26.37	6.71	163.79	6.89	30.93	7.59
Character disorder mothers (N = 57) .	29	28	2	1.75	0.96	3.52	1.03	26.53	7.13	164.86	5.74	29.80	8.67
Normal mothers (N = 57)	29	28	2	1.75	0.99	3.61	1.09	26.40	6.69	164.12	6.37	30.75	7.13
Schizophrenic fathers (N = 26) . . .	13	13	1	2.12	1.37	3.31	0.86	26.96	5.99	163.92	6.21	30.40	7.17
Character disorder fathers (N = 26) . .	13	13	1	2.23	1.53	3.58	0.73	27.15	5.71	163.73	7.33	34.25	9.55
Normal fathers (N = 26)	13	13	1	2.12	1.25	3.36	0.88	27.04	6.12	163.73	6.04	30.40	7.17

* General Register Office, 1951.

Table 3

Identifying characteristics for schizophrenics, character disorders, and normals by sex of child

Group	Mean pregnancy number		Mean social class*		Mean mother's age		Mean mother's height		Mean father's age	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Schizophrenic parents (male = 29, female = 28)	1.88	1.83	3.55	3.61	26.24	26.88	162.85	164.83	31.08	30.44
Character disorder parents (male = 29, female = 28)	1.90	1.91	3.63	3.58	26.64	26.80	165.17	163.83	30.86	31.57
Normal parents (male = 29, female = 28)	1.90	1.83	3.51	3.56	26.29	26.93	163.54	164.42	30.83	30.44

* General Register Office.

score for Pregnancy, for Delivery, for "Other" (mainly low birth weight) and a Total Score which combines these categories. These scales have not as yet been factored or item analyzed. We intend to take this opportunity to devise improved scales.

Table 4

Examples of items and their weights from the pregnancy scale, delivery scale, and "other" scale

Pregnancy scale	Weight
Staining during the 4th–9th month of pregnancy.	1
Hypertension	3
Severe eclampsia	5
Delivery scale	
Weak labor; labor stimulated	1
Forceps or vacuum extraction	3
Duration of labor more than three days.	5
"Other" scale	
Birth weight 2500–3000 grams.	1
Birth weight 1500–2000 grams.	3
Birth weight less than 1000 grams	5
Rh positive with moderate sensitization.	3

Child's examination scales

As pointed out above, the children were examined during the first five days of life and at the age of one year. A group of pediatricians delimited the range of examination outcomes that could be considered "not normal". A count was made for each of these scales of the number of instances of "not normal" notations. For the Neonatal Examination these were placed in the categories of *Physical* and *Neurological* anomalies; for the One-year Examination they were grouped as *Medical, Neurological,* and *Developmental* anomalies. Most of the Developmental items in the One-year exam, and some items in the Physical scale in the One-year exam were based on mother's reports. All the other items were based on observations by an experienced pediatrician.

Table 5

Examples of items considered anomalies in neonatal and one-year examinations*

	Anomalies
Neonatal	
Physical	tachypnea (rapid, shallow breathing)
Neurological	sign of brain damage: pain with touching of head
One-year	
Physical	any illness in any month during the first year of life
Neurological	abnormal or no patellar reflex
Developmental	inability to stand by one year of age

* Each anomaly received one point.

Results

The PBCs, Neonatal, and One-year exam scales were scored for all subjects. The data analysis comparing the three groups was carried out in three stages. First, the pregnancy and delivery data were compared across the diagnostic groups. Then the Neonatal and One-year examinations were compared. Finally, the effect of the PBCs on the Neonatal and One-year child examinations was studied. In addition to analyses of scores on the constructed PBC, Neonatal, and One-year exam scales, analyses were conducted of the individual items going into these scales.

Now we can present the most salient results of our preliminary data analyses. Inasmuch as we traced these subjects some 9 to 11 years after the birth, we found that many of the parents in the disturbed groups became mentally ill some time after the birth. This was true of approximately two-thirds of the disturbed parents.

Pregnancy and delivery complications

The condition and progression of the pregnancies and deliveries of the Schizophrenic, Character Disorder, and Normal groups were highly comparable, except for one variable, "Other Complications." (The Other Complications Scale score is predominantly determined by low-birth-weight anomalies.) The children with schizophrenic parents

evidenced higher Other Complications scores than the other two groups. The differences, however, are not dramatic (table 6).*

Table 6

"Other" complications scores for schizophrenic, character disorder, and normal parents*

"Other" complications scores	Schizophrenic parents	Character disorder parents	Normal parents
0	39	41	46
001–020	8	17	15
021+	36	25	22

* Chi-square = 7.87, 4 *df*, *p* < 0.10.

Two factors were found to contribute to this finding in Other Complications. First, for the schizophrenic mothers, the Other Complications scores resulted from lower birth weights contributed disproportionately by those who broke down during their pregnancy or within a year after delivery. Second, a relatively large number of children of schizophrenic fathers (46%) had low normal birth weights (2550-3000 grams). Low normal birth weight for the Character Disorder fathers and Normal fathers were 23% and 19% respectively. Consonant with this finding of lower birth weight, in the neonatal examination the pediatrician judged the children with schizophrenic parents to have a relatively thin layer of subcutaneous fat.

Certain specific items in the pregnancy distinguished the schizophrenic mothers (see table 7). They had suffered more central nervous system disorders before the beginning of pregnancy. In addition, the obstetrician overseeing the pregnancies seemed to question the progress of the fetus far more in the case of the schizophrenic women in that a significantly greater proportion of this group experienced x-ray exam-

* In this connection, the reader's attention is directed to a subsequent paper by the authors (Social Biology, 1973, 20, 111–112). Here, it is pointed out that a significant difference in birth weights results between the children of the Schizophrenic Parent Group (mean = 3053.5 g) and those of the Control Parent Group (mean = 3263.2 g) when the Parent Groups are matched for marital status.

inations in the last month of pregnancy. Of interest in view of the reports of increasing fertility of schizophrenic women is the fact that they testify to engaging in coitus during pregnancy with greater frequency than do the CD or normal women. This finding is in keeping with our observation of rather high levels of promiscuity in the schizophrenic mothers of our old longitudinal sample.

Table 7

Frequency of occurrence of specific anomalies in items contributing to the PBC scales in the three mother groups

Item	Schizophrenic		CD		Normal		χ^{2*}	p
	Yes	No	Yes	No	Yes	No		
CNS disorder observed before pregnancy	14	43	1	56	3	54	18.24	0.01
X-ray in last month	10	46	5	51	2	54	6.41	0.05
Coitus in last month	16	36	7	48	3	51	12.89	0.01

* These chi-squares have 2 *df.*

Typically, male infants suffer as much or considerably more pregnancy and delivery difficulty than do female infants. This pattern was observed for the children of the CD and Normal groups. However, as can be seen in figure 1, in the schizophrenic-parent group, the females experienced considerably more pregnancy difficulties than did the male infants. These included such items as staining, hypertension, and infections. In view of Rosenthal's finding (1962) of greater concordance for like-sexed relatives of schizophrenics, these results for the daughters of schizophrenic mothers might have a ready integration with existing literature. This may very well be so, but unfortunately the pregnancy of the daughters of schizophrenic men proved to be even more difficult. A finding which is somewhat related was reported by Taft and Goldfarb (1964). In their examination of the births of schizophrenic children and controls, they report (as is the rule) a greater frequency of pregnancy and delivery complications for the male control children. For both the schizophrenics and their siblings, however, the girls suffered the greater number of pregnancy disorders.
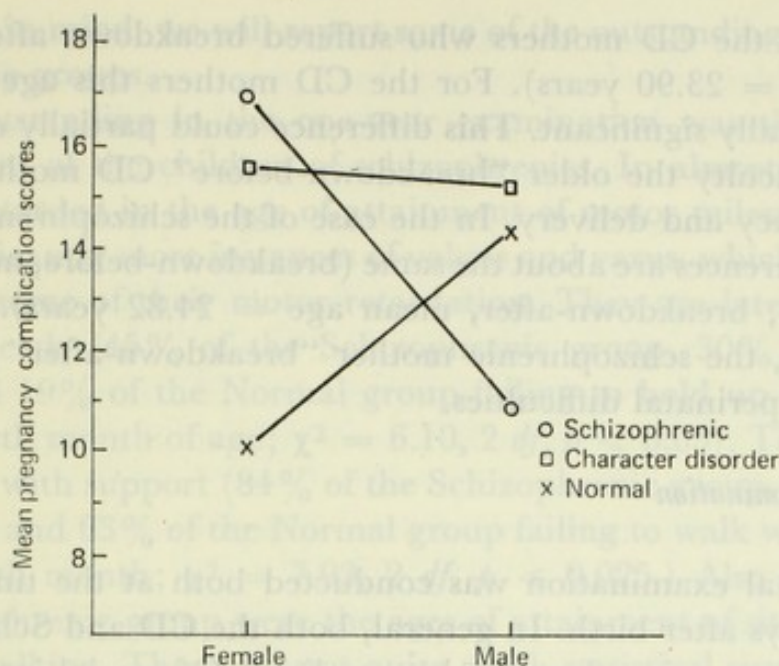
Fig. 1. Mean pregnancy complication scores for schizophrenic, character disorder, and normal parents by sex of child. The interaction of diagnosis and sex of child was significant ($F = 4.25$, $2/246$ *df*, $p < 0.05$).

Onset of mental illness before or after the delivery

If the CD mothers were already mentally ill, the course of the pregnancy and delivery proved more difficult than if they became mentally ill more than one year after the delivery. Surprisingly enough, for the mothers of the Schizophrenic group the pregnancy went more smoothly if she were already mentally ill when the pregnancy began. If they were destined to become schizophrenic some time in the future but were not yet diagnosed, the pregnancy had more complications.

This finding is rather puzzling. One begins to recall from clinical experience, schizophrenic women who reported marked well-being when pregnant. Interpretations involving diminished sexual identity conflicts suggest themselves as do biochemical explanations. Another possible explanation might be the age *at time of delivery* of the "breakdown-before" and "breakdown-after" groups. The CD mothers who suffered breakdown before the delivery were older (mean age = 29.44

years) than the CD mothers who suffered breakdown after delivery (mean age = 23.90 years). For the CD mothers this age difference was statistically significant. This difference could partially explain the greater difficulty the older "breakdown-before" CD mothers had in the pregnancy and delivery. In the case of the schizophrenic mothers the age differences are about the same (breakdown-before, mean age = 29.47 years; breakdown-after, mean age = 24.82 years). However, despite this, the schizophrenic mother "breakdown-after" group suffered more perinatal difficulties.

Neonatal examination

The neonatal examination was conducted both at the time of birth and five days after birth. In general, both the CD and Schizophrenic group children evinced more abnormalities. Of special interest is the fact that when the N or CD subject evidenced an abnormality at birth the difficulty usually cleared up by the fifth day. This was not the case for the children of schizophrenics. They tended to retain their symptoms. However, this tendency did not reach statistical significance. The abnormalities for the children of schizophrenics tended to come in the absence or weakness of their motor reflexes.

Character disorder children showed a pattern quite opposed to that of the schizophrenic group. While the children of schizophrenics were generally retarded in their motor reflexes, the children of character disorders exhibited highly reliable motor reflex responses. The finding presages their very superior performance in motor development at the age of one year.

One-year examination

A grave problem in interpreting the results of the one-year examination concerns the large quantity of missing data for certain of the scoring categories. In general, the schizophrenic mothers and the character disorder fathers evidenced between 30–40% missing data on large segments of this examination. In addition, developmental information and information concerning illnesses of the children in the course of the first year of life were based on retrospective maternal reports whose validity is somewhat suspect (Hefner and Mednick, 1969). With these

limitations in mind, we will report some of the outstanding differences between the groups.

Most outstanding in the one-year examination was the retarded development of the children of schizophrenics. In almost every item they are retarded in the age of attainment of motor milestones. They show significantly more instances of valgus and varus, which is perhaps related to some of their motor retardation. They are late in holding up their heads (45% of the Schizophrenic group, 30% of the CD group, and 19% of the Normal group failing to hold up their heads by the fourth month of age; $\chi^2 = 6.10$, 2 *df, p* < 0.05). They are late in walking with support (84% of the Schizophrenic group, 64% of the CD group, and 63% of the Normal group failing to walk with support by the tenth month; $\chi^2 = 7.93$, 2 *df, p* < 0.025.) Also delayed for the Schizophrenic group were the ages of attainment of sitting, standing, and walking. These did not quite reach statistical significance.

The children of character disorder fathers were, on the other hand, impressively superior in their rate of motor development; these children evidenced no area of retardation and were quite advanced in most areas of motor development. They contrasted sharply with the children of schizophrenic fathers who in almost all items showed greater frequency of retardation in attainment of motor milestones.

Immediate and longterm effects of pregnancy and delivery complications

The relationship between the pregnancy and delivery complications and the Neonatal and One-year examination scale scores was explored by intercorrelating these scores. In this manner, high scale scores on the birth factors indicating complications and high scale scores on the postnatal examinations indicating abnormalities should tend to go together and yield positive correlations. As expected, almost all correlations were positive. Note that all of these findings relate to correlations within each of the diagnostic groups.

Neonatal examinations and birth scores

In almost all groups a low birth weight was correlated with an increased number of anomalies in the neonatal examination. Difficulties in pregnancy and delivery, however, showed no significant correlations

with neonatal status for any of the groups except for the schizophrenics. For the children of schizophrenics, both pregnancy and delivery scales correlated positively and significantly with the child's appearance at the time of the neonatal examination. There seem to be two likely interpretations for these findings:

(1) Our scale scores are relatively insensitive and undetected high levels of damage are being done selectively to the children in the Schizophrenic group

(2) Identical pregnancy and delivery complications inflicted on the children of schizophrenics strike a more vulnerable group and produce a greater neonatal effect.

It is also possible that both of these interpretations are true.

One-year examination

Low birth weight was highly related to difficulties in the Neonatal examination. For all groups but the schizophrenics it proved to be unrelated to the status of the child at the One-year exam. Exclusively in the case of the schizophrenics, and especially so in the case where the mother was schizophrenic, birth weights below 3000 grams were associated with retarded development during the first year.

Pregnancy complications, while relatively insignificant in producing anomalies in the Neonatal examination, were quite effective in all groups in being associated with abnormalities in the One-year examination. An interesting pattern emerged in the type of effect that the pregnancy complication produced in the mother group. For the children of schizophrenic mothers the pregnancy complication scale score tended to be related positively to the one-year exam scores for physical condition, illnesses, and accidents. For the child of the CD mothers pregnancy difficulties are related to neurological symptoms, for the children of N mothers, to developmental retardation. This differential pattern between these three mother groups may be related to latent-genetic differences which are triggered by the pregnancy disturbances.

In view of the great profusion of groups, measures and findings, let us review our results:

(1) The children born to schizophrenics evidenced a higher incidence of mildly low birth weight. It is interesting also that such low birth weight in the Schizophrenic group is associated with developmental

abnormalities in their one-year examination. Children with identically low birth weights in the other two groups show no evidence of such effects at one year, despite the fact that all had shown effects at the neonatal examination. This finding suggests the possibility of a genetic predisposition being precipitated by the perinatal stress.

(2) In the nonschizophrenic groups (as in previous research) infant males had a more difficult time in pregnancy than did infant females, or there was little difference between them. In the Schizophrenic group this finding was reversed; female infants suffered more from pregnancy complications. This was especially true in the case where the schizophrenic parent was the father. One interpretation of all these results may be that with the schizophrenics, boys who suffered very severe pregnancy difficulties aborted very early in the pregnancy. Girls with the same level of pregnancy difficulties may have survived. A similar argument has been made by Birch (1964) in the case of mongolism.

(3) There are a large number of positive results which involve the schizophrenic fathers. These may be ascribed to genetic effects, but could also be due to environmental influences. It is perhaps something of a burden to a woman who is pregnant to be living with a schizophrenic man. In this sample a large number of the mothers were unmarried and not living with the child's father. This may make it possible for us to assess the relative weights of the environmental and genetic influences.

One final point. In the study by Ingalls et al. (Stern, 1960) it was found that strains of mice differ in the probability of litters suffering a genetically determined sternum fetal malformation. Strain DBA/1 has a probability of 5%, while strain C57BR/cd has a probability of 30% of developing malformations. If the pregnancy of the mother mouse is disturbed by subjecting her to five hours of low atmospheric pressure on the ninth day of pregnancy we see an increase in per cent of the litter affected by this malformation. The DBA/1 strain has an increase of 70%; the C57BR/cd strain has an increase of 15%. Note that as a consequence of this low atmospheric treatment, the per cent of malformed fetuses has reached a much higher level in the DBA/1 strain which is usually less genetically vulnerable. This dramatic response of the DBA/1 strain to the low atmospheric pressure must

represent a special genetic susceptibility to this specific pregnancy complication.

Thus, in considering the etiology of a target disorder we must, of course, take into account basic genetic vulnerability. However, quite as much as in the case of the DBA/1 strain of mice, we must also consider the possibility that individuals will have an independent genetic vulnerability to specific types of perinatal stresses.

BREAKDOWN IN HIGH-RISK SUBJECTS: FAMILIAL AND EARLY ENVIRONMENTAL FACTORS*

BIRGITTE R. MEDNICK

The author assesses the impact of early environmental factors, both pre and post-natal, upon the offspring of schizophrenic mothers.

The aim of this study is to compare aspects of the premorbid histories of two groups of adolescents, who are part of a larger longitudinal study (Mednick and Schulsinger, 1968).

One group (the breakdown group) has recently suffered severe mental breakdown. The other group (the improved group) has improved in mental health over the course of the longitudinal investigation (seven years' duration). Both groups have severely schizophrenic mothers; they are matched individual to individual for age, sex and socioeconomic status. In addition, they are matched for their levels of adjustment at the inception of the longitudinal study, on the basis of a clinical psychiatric examination. The current study was stimulated by several recently reported findings:

(a) the clear demonstration by Kety, Rosenthal, Wender, and Schulsinger (1968) and Heston (1966) of a genetic etiological factor in schizophrenia;

(b) evidence involving *pregnancy* disturbances in the etiology of schizophrenia (Mednick, 1970; Mednick and Schulsinger, 1968; Stott, 1958); and

(c) evidence implicating early separation from the parent in the etiology of schizophrenia (Goldfarb, 1945, 1947; Mednick and Schulsinger, 1968).

It was decided to attempt to determine what role these three factors

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(familial disposition, pregnancy factors, and parental separation) may have played in the psychological breakdown suffered by the break-down group. (This breakdown group is equivalent to the group desig-nated as the sick group in Mednick and Schulsinger, 1968). Preliminary study had revealed that data relevant to these three factors could be obtained from three sources: the copious hospital case records for the schizophrenic mothers which routinely contained information relating to the first two of these three factors; the National Psychiatric Register in Denmark where all psychiatric hospitalizations during the last 40 years are registered, which yields information relevant to the first factor, familial disposition; and the interviews with the children and their parents or guardian at the time of the inception of the longitudinal study. The interview data could be used along with the hospital records of the mothers to illuminate the third factor (parental separation) as well as to provide supplementary information on the second factor (pregnancy).

The information obtained from the hospital records, the National Psychiatric Register, and the interviews consists of the following three classes of data:

(1) Data on the mental illness in the subject's family, which can be subdivided into data on the amount of mental illness in the mother's family, data on the mother's premorbid psychological adjustment, and data on the mother's illness such as total length of hospitalization and age of onset.

It was hoped that these data would *in part* reflect the loading of mental illness in the familial background of the children and relate to possible genetic predisposition in the children.

(2) Data on the mother's emotional status at the time of pregnancy and birth of the subject: Emotional disturbances during pregnancy have been shown to relate to pregnancy and delivery difficulties and to later deviances in the resultant children (Joffe, 1969; Stott, 1958).

(3) Data on presence or absence of mother or mothering figure during the subject's childhood. An earlier study on the same children (Mednick and Schulsinger, 1968) showed that separation from the biological mother was associated with breakdown. However, this other study used gross age-of-separation categories and did not explore the role of possible substitute mother figures. In this investigation exact age of the child at the time of separation was determined by comparison

of hospital and interview information, and the presence or absence of substitute mothers was ascertained.

The present study is one of a series of studies of high-risk populations aimed at disclosing the earliest indicators of later mental illness (Mednick, 1970; Mednick and Schulsinger, 1968). These studies search for variables which can be observed in the mentally ill individual many years before he suffers breakdown. Such early indicators are necessary guidelines in the planning of research on the prevention of mental illness, which is the ultimate goal of the investigators involved.

Hypotheses

Hypothesis 1a: Familial psychiatric background. It was expected that the subjects in the breakdown group would evidence more mental illness in their family background.

Hypothesis 1b: Mother's premorbid status and behavior. It was expected that the premorbid histories of the mothers of the breakdown group would show more signs of psychological problems and adjustment difficulties.

Hypothesis 1c: The course of the mother's disease. It was hypothesized that the mothers of the subjects in the breakdown group suffered an earlier onset of illness and would be hospitalized for a longer period of their lives.

Hypothesis 2: Emotional stress during pregnancy. It was assumed that the mothers of the breakdown group suffered more emotional stress during pregnancy.

Hypothesis 3: Parental separation. It was expected that the children in the breakdown group suffered more and earlier loss of their mothers and/or mother substitutes and had less contact with their fathers during childhood.

Method

Subjects

The 40 subjects in this study are all involved in a longitudinal study of 207 children who have schizophrenic mothers and therefore have a

high risk for schizophrenia (Mednick and Schulsinger, 1968). They were initially tested in 1962. At that time, none of them were judged to be overtly ill. Since the 1962 assessment, 20 of the 207 high-risk children have become seriously mentally ill. Their clinical condition is briefly described as follows:

Male, born March 16, 1953; extremely withdrawn, no close contacts, two-months' psychiatric admission following theft, currently in institution for boys with behavior difficulties, still performing petty thieveries.

Female, born January 19, 1943; married, one child, extremely withdrawn, nervous. Evidence of delusional thinking, pulls her hair out, has large bald area.

Female, born March 29, 1946; promiscuous, highly unstable in work, no close contacts, confused and unrealistic, psychiatric admission for diagnostic reasons, recent abortion, some evidence of thought disorder.

Male, born July 1, 1946; under minor provocation had semipsychotic breakdown in Army, expresses strange distortions of his body image, thought processes vague, immature.

Male, born May 2, 1944; severe difficulties in concentrating; cannot complete tasks; marked schizoid character; marginally adjusted.

Male, born June 3, 1947; lonely in the extreme; spends all spare time at home; manages at home only by virtue of extremely compulsive routines; no heterosexual activity; marked schizoid character.

Male, born October 1, 1953; no close contact with peers, attends class for retarded children, abuses younger children, recently took a little boy out in the forest, undressed him, urinated on him and his clothes, and sent him home.

Male, born January 17, 1954; has history of convulsions, constantly takes antiseizure drug (Dilanthin), nervous, confabulating, unhappy, sees frightening "nightmares" during the day; afraid of going to sleep because of nightmares and fear that people are watching through the window, feels teacher punishes him unjustly.

Female, born March 18, 1944; nervous, quick mood changes; body image distortions, passive, resigned; psychiatric admission, paranoid tendencies revealed, vague train of thought.

Male, born March 14, 1952; arrested for involvement in theft of motorbike; extremely withdrawn, difficulties in concentration; passive,

disinterested, father objected to his being institutionalized; consequently, he is now out under psychiatric supervision.

Male, born October 19, 1947; level of intellectual performance in apprenticeship decreasing, private life extremely disorderly; abreacts through alcoholism.

Male, born January 20, 1944; severe schizoid character, no heterosexual activity; lives an immature, shy, anhedonic life, thought disturbances revealed in Thematic Apperception Test.

Female, born May 25, 1947; psychiatric admission, abortion, hospital report suspects pseudoneurotic or early schizophrenia; association tests betray thought disturbance, tense, guarded, ambivalent. Current difficulties somewhat precipitated by sudden death of boyfriend.

Male, born August 13, 1950; sensitive, negativistic, unrealistic; recently stopped working and was referred to a youth guidance clinic for evaluation. Is now under regular supervision of a psychologist.

Male, born May 28, 1947; history of car stealing, unstable, drifting, unemployed, sensitive, easily hurt, one-year institutionalization in a reformatory for the worst delinquents in Denmark.

Female, born June 1, 1945; psychotic episode, one year of hospitalization; different diagnoses from two hospitals: schizophrenia and manic psychosis.

Male, born September 3, 1946; severe schizoid character; psychotic breakdown in Army, preceded by arrest for car thievery. Now hospitalized.

Male, born January 28, 1953; perhaps border-line retarded; psychiatric admission for diagnostic reasons; spells of uncontrolled behavior.

Male, born June 23, 1948; repeatedly apprehended for stealing; severe mood swings, sensitive, restless, unrealistic; fired from job because of financial irregularities.

Female, born July 5, 1941; highly intelligent girl with mystical interest. Very much afflicted by mother's schizophrenia. Thematic Apperception Test reveals thought disorder. Receiving psychotherapy.

As indicated above, each of the breakdown subjects was matched to another high-risk subject for age, sex, social class (Svalastoga, 1959), and 1962 level of adjustment. The matched control high-risk subject was required to have improved in level of adjustment since 1962. This judgment was made by a psychiatrist on the basis of a follow-up interview conducted in 1966. The mean value for the matching variables may be found in table 1.

Table 1

Identifying characteristics of breakdown and improved group

Matching variables	Breakdown group	Improved group
Mean age	15.1	15.1
Mean socioeconomic class	1.45	1.05
Mean level of adjustment	3.0	3.0
No. females	5	5
Total N	20	20

Note. The figures in the table refer to the subjects' status at the time of the initital assessment. The social class scale was adapted from one developed for Denmark by Svalastoga (1959). The scale runs from 0 (low) to 6 (high). The level of adjustment rating is drawn from the psychiatric interview.

Data sources

The mental hospital case records of the subjects' mothers. These case records are rather copious. They all contained a careful biographic description of the mothers' premorbid life, based on interviews with the patient, her husband, and other family members. Because of the Central Psychiatric Register the case file followed the patient from hospital to hospital so that a continuous record of the illness history was available. All the hospitals at which one or more of the 40 mothers had been hospitalized were contacted. In 35 cases, all of the hospital case material was put at the disposition of the author. Of the 20 mothers in the breakdown group, 2 were excluded from the sample because at that time their records were inaccessible; in the improved group, 3 mothers were excluded for this reason.

Parent interview. In 1962 the parents or guardians of the children were interviewed concerning the early development and social functioning of the children.

Psychiatric interview. In 1962 the children were interviewed by a psychiatrist who, in the course of the interview, reported on the maternal care the child received.

The National Psychiatric Register. The Register records all psychiatric hospitalizations in Denmark during the last 40 years.

The judge who read the records and the interviews and collected the information from the Psychiatric Register was kept unaware of the

group identification of the subjects. The three hypotheses serve to organize the presentation of the results. Within each hypothesis several questions bearing on the hypothesis were asked.

Results

Hypothesis 1a: Familial psychiatric background

Question 1. How many cases of mental illness were there in the mother's family? Information on psychiatric hospitalization of the mother's relatives was obtained from the mother's hospital records, which routinely contain such information. Each mentally ill relative was weighted according to how closely related he was to the child, that is according to the

Table 2

Mental illness of fathers of the breakdown group and the improved group

Group	Fathers mentally ill	Fathers not mentally ill
Breakdown	7	11
Improved	0	18

Note. In both groups, two fathers were listed as unknown and could not be checked against the National Psychiatric Register.

percent of genes he or she probably had in common with the child. For example, grandparents were each given a weight of 25%. There was no difference between the weighted scores of the mentally ill relatives of the breakdown group and the improved group.

Question 2. Was the father of the subject ever hospitalized for a mental illness? The information for Question 2 was obtained from the National Psychiatric Register. For this calculation all 40 subjects were included since all the necessary material was available. Table 2 presents the information on hospitalization for mental illness of the father.

There is significantly more mental illness which required hospitalization among the fathers of the breakdown group ($p < 0.05$; Fisher–Yates exact test). The Fisher–Yates test was used in this case because the expected value in one cell was too low for a legitimate

use of chi-square. The diagnoses of the fathers ranged from chronic paranoid schizophrenia to chronic alcoholism. Information on hospitalization for mental illness in the fathers' family has not been included in this study. It was possible to investigate this factor for the mothers since they were all hospitalized for mental illness and the hospital records routinely contain such information. Such data were not available for all the fathers.

Hypothesis 1b: Mother's premorbid status and behavior

Question 3. Was the mother's premorbid adjustment good or poor? As the hospital records were read, all statements concerning the premorbid adjustment of the mother were recorded. Because of the uneven quantity as well as quality of information available on this question and in order to maximize reliability, the mothers' premorbid adjustment was simply classified as good or poor. The mothers of the breakdown group and the improved group divided almost identically on this measure. The differences were not significantly different.

Question 4. Did the mother premorbidly direct her emotions outward, inward (withdrawn), or fluctuate between the two? Mothers were categorized as inward who tended to be described in the case records as withdrawn, quiet, and passive. Outward mothers were described as aggressive, temperamental, easily angered, loud, and violent. Fluctuating mothers were described as switching between the two categories. The data showed the breakdown group's mothers as having a not significant tendency to direct their emotions outward or to fluctuate, whereas the improved group's mothers displayed a nonsignificant tendency to be more withdrawn ($\chi^2 = 4.92$, 2 df, $p > 0.10$).

Question 5. Was mother premorbidly promiscuous? Mothers were classified as promiscuous if their case records indicated a history of extensive switching of lovers, multiple extramarital pregnancies, and/or prostitution. About 50% of the mothers of both groups were more or less promiscuous before their psychotic break; there was no difference between the groups.

Question 6. Was the mothers' premorbid intelligence below average, normal, or above average? The case records routinely commented on the mothers' intelligence. The mothers in the breakdown group tended to be judged as having a higher premorbid intelligence. This, however, was not a

significant difference ($\chi^2 = 3.3$, 1 *df*, $p < 0.10$). Because of the small number of cases judged as having above-average intelligence, these were pooled with the mothers judged as having normal intelligence for the purpose of computing the chi-square.

Question 7. Did the mother leave school with any kind of passed examination or diploma? (The lowest official exam in the Danish school system is usually passed at the age of 15; however, some years ago it was quite common that children leave school without passing this exam). No statistical calculations were performed on these data because the numbers were too small. Four mothers in the breakdown group and none in the improved group passed an exam before leaving school.

Hypothesis 1c: Course of mother's disease

Question 8. How many years was the mother hospitalized? There was no significant difference between the groups. The mean number of years for the breakdown group was 6.67, and for the improved group, 4.17. The within-group variance, however, was very large. In relationship to the question of the course of the mothers' illness, the number of hospitalizations, the age of the mother at the onset of psychosis, and the subtype of the mother's schizophrenia was tabulated. None of these variables significantly differentiated the breakdown group and the improved group.

Hypothesis 2: Emotional stress during pregnancy

Question 1. Did the mother's mental illness begin (a) before or within a year after the birth of the subject? or (b) more than a year after the birth? As can be seen in table 3 the mothers of the breakdown group tended to become ill before or within a year after the birth of the subject, whereas the mothers of the improved group tended to become ill several years after the birth of the subject. This tendency, however, did not reach significance ($\chi^2 = 2.36$, 1 *df*, $p > 0.10$).

Question 2. Were there factors mentioned in the hospital record which would suggest that the mother's emotional life during pregnancy had been stressful or nonstressful? As an example of a stressful event, the husband of one of the mothers was jailed just after the mother became pregnant. As can be seen in table 4, the breakdown group suffered much more emotional stress during pregnancy ($\chi^2 = 5.08$, 1 *df*, $p < 0.25$).

Table 3
Age of child at outbreak of mothers' illness

Group	Less than 1 year old	More than 1 year old
Breakdown	11	7
Improved	5	12

Table 4
Number of mothers with stressful experiences during pregnancy

Group	Stressful experience	Not stressful experience
Breakdown	11	5
Improved	4	13

Hypothesis 3: Separation

Question 1. Did the children in the breakdown group lose their mothers at an earlier age than did the children in the improved group? Loss of mother was coded when after a separation the child never contacted the mother again or contacted her so sporadically that a normal mother-child relationship was never again attained. The mean age for loss of mother in the breakdown group was 4.0 years and in the improved group, 8.25 years ($t = 3.4$, 33 df, $p < 0.001$).

Question 2. Did the child have either a mother or a mother substitute from birth till age 10? As can be seen from table 5, there were significantly more breakdown subjects ($\chi^2 = 5.17$, 1 df, $p < 0.025$) who had neither mother nor mother substitute from birth to age 10. These children were raised in either children's home or by their father.

Question 3. How many years of contact did the subject have with the father between birth and age 15? To be scored as contact the children had to see their father regularly but not necessarily live with him. There was no significant difference between the groups.

Table 5

Number of subjects with neither mother nor mother subtitute between birth and age 10

Contact with mother figure	Breakdown group	Improved group
No mother or mother substitute	11	3
Mother or mother substitute	7	14

Discussion

The results cited in the previous section seem best considered if we regard them as being divided into two main categories.

(1) The first category contained data directly relevant to the subjects' mother, that is, data on her premorbid life and the course of her disease. Below we have divided the rest of the variables into genetic and environmental variables as seen in relationship with the child. The data on the mother could be regarded as contributing to the familiar disposition of the child but could also be interpreted as environmental variables.

(2) The second category contained data directly relevant to the subject. This latter category can be divided into: familial variables, such as "amount of mental illness in the family", and environmental variables, such as the emotional situation of the mother when she was carrying the child and the parental separation data.

Results related to mothers' illness

As far as the data on the mother are concerned, the fact that there were no significant findings in this study should not be too surprising in view of the fact that all the mothers were severely schizophrenic. Therefore, the range of the variables dealt with in this section of the data was severely restricted. Consequently our findings or lack of findings can not be generalized to other samples with wider variation in level of adjustment of the mother. However, it should be pointed out that in another study (Mednick and Schulsinger, 1968) using the same pool of subjects, a finer definition of the mothers' state of mental

health was made by a psychiatrist on the basis of her type of treatment, drug dosages, and symptomatology in the acute and nonacute phases of the disease. There it was found that the severity of mothers' illness, so defined, was related to the mental health of the child. The mothers of the breakdown group were judged to be more severely ill.

Results related to subjects' family and early environment

One of the familial variables "State of father's mental health" showed a significant difference between the groups. The breakdown group had more mentally ill fathers than the improved group. This result could be seen as a confirmation of the familial hypothesis (more mental illness in the families of the subjects of the breakdown group). However, the variable "state of father's mental health" may also be looked upon as an environmental variable. For example, a stable normal father could offer the crucial security for a child of a schizophrenic woman; whereas a mentally ill father in the home as well as a schizophrenic mother might be just too much environmental stress for a high-risk subject to bear and cause him to suffer a mental breakdown.

In order to be able to differentiate between the genetic and environmental contribution of the father's mental illness, it would be necessary to have a group of mentally ill fathers who lived with the child and a group who did not. The number of mentally ill fathers in this sample was not large enough to make this possible.

Results related to the environmental variables

Both of the environmental hypotheses stated in this study were confirmed by the results.

The hypothesis "More emotional stress during pregnancy" was supported by the data on observable emotionally stressful situations to which the mothers were exposed during their pregnancy. The result that the mothers of the breakdown group were exposed to more such situations goes well with a study by Stott (1958), who convincingly showed that emotional stress during pregnancy can be related to mental deficiency and physical health in the outcome. Related results have been found in research on pregnancies of rats (Joffe, 1969).

The mother of the breakdown subject tended to have been mentally

ill before she was pregnant with the subject or to become ill in immediate connection with the birth of the subject. This tendency adds to the support of the prenatal stress hypothesis since it seems likely that the prenatal environment supplied by a woman who is suffering from a more or less overt psychosis is not as good as the environment supplied by a woman who is not going to become mentally ill until several years later.

It must in this connection be pointed out that a genetic explanation of the data on emotional stress during pregnancy could also be suggested. In many cases this emotional stress was brought on by deviant behavior on the part of the father. It is possible that the fathers' deviant behavior had a partially genetic basis which via a polygenetic mode of transmission (Gottesman and Shields, 1972) may have increased the risk of breakdown of the children in the breakdown group.

The second environmental hypothesis (earlier maternal separation in the breakdown group) was confirmed by the results. These data on the importance of a mothering figure during childhood, and especially during the early childhood, are in accordance with studies by Goldfarb (1945, 1947) and Herrmann (1973).

In most studies of psychopathology, both the genetic and the environmental components are free to vary. When the samples under study are drawn from a Western European population the range of the environmental variables will usually be considerably smaller than the range of the genetic variables and hence interfere with, and sometimes even cover up, the effects of the environmental variable. It is in this connection interesting to note that among these schizophrenic mothers where the genetic variation is relatively limited (they were all schizophrenic and had similar loads of mental illness in their families), environmental variables are thus given greater opportunity to display their influence (age of separation, stressful life during pregnancy). On the other hand, where the sample was unselected for genetic factors (state of father's mental health), genetic factors had a greater opportunity to show their effect.

Acknowledgement

EFFECTS OF CHILD REARING BY
SCHIZOPHRENIC MOTHERS*

JERRY HIGGINS

This study follows the fifth research design suggested by Rosenthal in Section I; it examines the coaction of genetic and rearing factors in schizophrenia.

Clausen and Yarrow (1955) have observed that intrafamilial relationships are subjected to severe stress when a mentally ill individual exists in the home; this would seem particularly so when the disturbed individual is a psychotic mother. Yet studies bearing directly on the adequacy of adjustment of the children of such mothers have been few. The earliest, conducted by Sobel (1961), followed eight neonates, each with both parents schizophrenic, by means of monthly home visits by a psychiatrist. After 14 months, "Three of the 4 children raised by their original schizophrenic parents developed clear-cut signs of depression and irritability in infancy. None of the 4 infants raised by foster parents developed any such clear-cut signs of emotional disorder" (p. 516). It was concluded that the psychotic-like parental behavior of their mothers was "at least partially responsible" for the status of the three disturbed children.

Other workers, however, have not corroborated Sobel's results. Sussex, Gassman and Raffel (1963) investigated the home, school, clinic, and psychological test behavior of sixteen 6–10-year-old children whose acutely psychotic mothers were receiving outpatient treatment. These workers concluded that "the children as a group did not show

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marked evidence of being adversely affected by the presence of a psychotic mother in the home ..." (p. 854). In addition, Grunebaum and Weiss (1963) have been engaged in a pilot study intended, in part, to determine whether joint hospitalization with a psychotic mother adversely affects the young child. Their observations to date, although limited, have not revealed any undesirable consequences.

Fish and Alpert (1962, 1963) have focused upon the effects of genetic loading rather than rearing experience in their investigations. At frequent intervals they examined 13 infants born to schizophrenic mothers and raised by foster parents (9), grandmothers (3), or a foundling home (1). Presenting summary data in graph form for the first 16 weeks of life, the authors reported: "In this small, selected group, 3 infants showed excessively quiet behavior, with extremes of underactivity, hypotonia and absence of crying, which are highly unusual for young infants. A fourth showed an abnormal degree of irritability, and 3 infants showed less extreme deviations" (1963, p. 443). Three of these children were also slow to establish mature vestibular responses. Additional clinical materials covering the first 10–24 months of life were generally congruent with the quantitative data, the earlier developmental trends being observed to persist. It was thought that such findings lent support to the postulate of an hereditary factor in the transmission of deviant behavior.

Finally, Reisby (1963) traced the psychiatric fate of 242 offspring (mean age, 34 years 10 months) of chronically schizophrenic mothers. Those who themselves had developed severe or typical schizophrenia had lived with their schizophrenic mothers for a mean of 13 years 0 months; those who had been hospitalized for milder or atypical forms of schizophrenia and other less severe psychoses had lived with their mothers a mean of 7 years 5 months. While a test for statistical significance was not reported, these data suggest that the likelihood among those who develop mental illness of developing a more severe disturbance is increased with increased contact with a schizophrenic mother. Similarly, Nameche et al. (1964) found that one factor which discriminated between poor-outcome and good-outcome schizophrenics was that the former had more frequently had "no separation of any kind from [their] pathogenic families" (p. 239) prior to hospitalization.

The present study was intended to provide additional information regarding the characteristics of children reared by severely disturbed

people. Two groups of children, one group born to and reared by schizophrenic mothers, the other group born to but reared essentially apart from schizophrenic mothers, underwent an experimental regimen which included a psychiatric evaluation, a school report, a word association task, adjective check lists, and testing for psychophysiological responsiveness, recovery, and generalization. It was predicted that the children reared by schizophrenic mothers would consistently display less adaptive behavior as measured by these procedures than would the children reared apart.

Method

Subjects

All subjects were citizens and residents of Denmark.

Mothers

The resident population of four state hospitals over a 5-year period (1958–1963) was sampled for cases of mothers (motherhood prior to most recent hospitalization) who had received a diagnosis of chronic (typical) schizophrenia. Diagnoses were checked by review of each mother's medical records by one of two psychiatrists; following their concurrent training on ten cases, agreement between judgments independently made on ten subsequent cases was one hundred per cent. All mothers of children selected for the present study were "process" or severe cases as indicated by premorbid history, symptomatology, and course of illness.

Children

Following confirmation of their mothers' diagnoses, approximately 200 children were located. From this population a sample of 50 children was selected on the basis of the independent and matching variables to be defined below. This sample consisted of 26 males and 24 females. The mean age of the sample was 14 years 8 months, with a standard deviation of 3 years 3 months, and a range of 9 years 7 months to 20 years 2 months. The sample was heavily urban in character. Socioeconomic status (SES) was also obtained by rating each child according

to the occupation of the head of the household in which the child had spent the greatest portion of his life, occupation being the overriding criterion of SES in Danish society (Svalastoga, 1959). Occupational information was gathered by a social worker who interviewed an adult responsible for the child's care (typically, the male head of the child's current household). The SES rating instrument was an eight-point modification of a scale developed by Svalastoga (1959) on the basis of occupational prestige ratings. The scoring categories of the SES scale ranged from "0" (e.g. shoeshiner) to "7" (e.g. professor). Following detailed instruction in use of the scale, interjudge agreement for two judges independently rating 20 interviews from the subject population was 90 per cent, instances of disagreement being of one category in magnitude. The mean SES score achieved by the sample was 2.00 (e.g. mailman, streetcar conductor, store clerk, carpenter), with a standard deviation of 1.83 and a range of "0" to "6".

Twenty-five of the 50 children had lived virtually their entire lives with their schizophrenic mothers, except during the mothers' hospitalizations. The average child was 7 years 7 months old when the mother first entered hospital *during the child's lifetime,* and had witnessed a mean of 4 hospitalizations of 10 months total duration. In all cases the allegedly biological father was also in the home; none of the fathers had been hospitalized for psychiatric reasons. These 25 children constituted the mother-reared group.

The remaining 25 children were separated from their schizophrenic mothers at a mean age of 1 year 7 months (standard deviation 1 year 1 month, range 0–36 months). They had been reared by substitute mothers (11), children's homes* (6), their father (4), or some combination of these (4). Since separation none of these children had had extended or frequent contact with the mother; there was similarly no contact with adult blood relatives of the mother, or with any adult who had been hospitalized for psychiatric disturbance. In all but one instance it was possible to establish biological paternity; none of the located fathers had been hospitalized for psychiatric disturbance. These 25 children constituted the reared-apart group, and were matched individual to individual with children of the mother-reared group for sex, age (within one year), and SES (within two scale points).

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* Children reared primarily in children's homes received a "0" SES rating.

The adequacy of the above sampling procedures requires comment. As for the mother-reared group, it would seem that the objective of selecting a sample of children who had been reared by severely ill schizophrenic mothers was attained. Not only did the mothers' case histories attest the severity of their disturbance, but also observations made in their homes concurred. A psychologist made announced visits to a number of homes from which the mother-reared group was drawn, and almost invariably reported the mother to be overtly symptomatic. Nevertheless, it must be pointed out that the majority of the mothers of the mother-reared group did not enter hospital until some years after the birth of the children. Thus, it is conceivable that these mothers were really quite "normal" during their children's early years, thereby reducing any pathogenic effect of the later pathological behavior which required hospitalization. However, such a proposition is tempered by evidence that the premorbid histories of severely ill schizophrenics are characteristically inadequate, and impaired functioning is manifest long before actual hospitalization (Higgins, 1964). Perusal of the hospital records of the mothers strongly supported this point; in many cases it appeared that these women had been overtly schizophrenic for several years prior to hospitalization.

The selection of the reared-apart group may not be viewed with such confidence. Ideally, the reared-apart children might have been separated from their mothers at birth, and thereupon have entered family homes. Owing to the difficulties of locating such children, however, the actual group employed proved to represent a compromise between the ideal and the feasible. A closer approximation to the ideal was attempted during data analysis by use of subgroups, but the satisfactoriness of such manipulations remains questionable. Several possible ramifications of the composition of the reared-apart group are apparent, any or all of which may have pathogenic implications. First, most of the reared-apart children were exposed for a portion of their early lives to their mothers. Second, the factors which led to separation from the mother are largely unknown. For instance, it is possible that separation was precipitated by greater disorganization in the biological family, and that the child's early experience with such disorganization was deleterious. It further seems likely that the mother's symptoms had become exacerbated at the time of separation, adding to the environmental crisis. Third, separation from the mother in the first

months of life could itself have been traumatic, particularly if the relationship possessed some positive qualities which were not soon reinstated by an adequate substitute figure. There is no guarantee of the personal adequacy of the rearing agents; while none had been hospitalized for psychiatric reasons, more specific information is largely lacking. Further, the institutional environments of some of the reared-apart children may have been detrimental, although the children's homes were small and provided considerable individual attention. Fourth, while the rearing agents remained constant in most cases, a few reared-apart children experienced a change of agents which may have had adverse consequences. Therefore, it would seem that most, if not all, of the reared-apart children were subjected to some sort of untoward and possibly negative circumstance which could attenuate any positive effects derived from the mother's removal. In any event, it is clear that the reared-apart children did not receive a "normal" rearing experience. Thus the term "reared-apart" refers to the fact that early in the child's life individuals with no psychiatric history were substituted for the schizophrenic mother as the primary rearing agent. While it would have been desirable to include matched reference groups of children born to and reared by normal mothers, and born to but reared apart from normal mothers' such children were not available in sufficient numbers.

To sum up, the investigation employed two groups of 25 children matched individual to individual for sex, age, and SES. The children of one group, the mother-reared group, were born to and reared by schizophrenic mothers; the children of the other group, the reared-apart group, were born to schizophrenic females but were reared primarily by agents without histories of psychiatric illness.

General procedure

The following measures and information were obtained for each child:
(1) A psychiatric interview and evaluation.
(2) A school adjustment questionnaire responded to by the current (or most recent) classroom teacher or school principal.
(3) The Kent-Rosanoff word association test (WAT).
(4) An adjective check list (ACL) filled out independently by a psychiatrist and two psychologists.

(5) Psychophysiological responsiveness and recovery testing.
(6) Stimulus generalization testing.

These measures were selected with respect to a number of considerations. First, it seemed desirable to obtain a broad sample of behavior which would make possible the comparison of functioning on different "levels" of adjustment; for this reason indices of psychophysiological, psychological, and social psychological functioning were included. Second, the procedures involved had to be fairly brief, inasmuch as it was inconvenient and costly to retain the children for more than one day. Third, it was thought preferable to emulate measures which had proven fruitful in clinical or laboratory settings. Since other possible measures meet these qualifications, therefore the final choice within these limits relied upon the investigator's judgment of what would "work".

All personnel involved in the procedures were unaware of the nature of the study, including the hypotheses, and the subject groupings. Further, all personnel were involved in a broader survey (Schulsinger and Mednick, 1963), the children of the present study being interspersed among larger samples.

Psychiatric interview
While the problem of the reliability of psychiatric judgment was recognized, it was nevertheless decided to have each child undergo psychiatric examination.

A psychiatrist saw the child for a 30–40 min semi-structured interview; the same psychiatrist interviewed all children. Immediately following, the psychiatrist completed a pre-coded rating schedule concerning the child's mental status and history. From this schedule 17 items pertaining to recent level of adjustment were selected for present purposes; these items included questions of a diagnostic nature (organic, neurotic, psychotic, schizophrenic), interview behavior, social behavior, and prognosis as to the development of severely maladaptive behavior patterns.

It was predicted that where present pathology or lesser deviance was detected by psychiatric examination, or where future pathology was suspected, it would be so more frequently within the mother-reared group than within the reared-apart group.

School report

Although there existed the possibility that the schools knew of the presence of a schizophrenic mother in the homes of the mother-reared children, and consequently might be biased in their evaluations, it was decided to capitalize on the school's extensive contact with the child. An attempt to mask the purpose of evaluation and thus counter bias was made by simultaneously requesting information on a large number of other children.

A questionnaire mailed to the child's school presented 16 items concerning relationship to classmates and teacher, as well as adjustment to the demands of the classroom situation. The items were in a "true–not true" format, and were so constructed that a "true" reply indicated a manifestation of maladaptive behavior by the child.

The questionnaire was filled out by the teacher most familiar with the child or, in instances where the particular teacher had left the school, by the principal.

It was predicted that the mother-reared group would receive a greater number of "true" responses on the school report questionnaire than would the reared-apart group.

WAT

The word "mutton" was omitted from the translated version of the WAT (mutton is not part of the average Dane's diet), while the words "sun" and "star" were added, yielding a total of 101 stimulus words. Danish norms were gathered by means of paper and pencil administration to 145 school children (67 males and 78 females) between the ages of 9 and 16 years (mean 12 years 3 months, standard deviation 1 year 7 months).

The stimulus words were read to the child by a psychologist following the usual instruction to respond to each with the first word that came to mind. Responses and response latencies were recorded and the following measures derived:

(1) Number of responses matching responses given by the largest proportion of the norm sample to each stimulus.

(2) Number of deviant responses, i.e. (a) responses rated as "peculiar" by a Danish psychologist,* (b) repetitions of the stimulus word,

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* The rater was not the same psychometrician who administered the WAT. Following concurrent training on 20 cases from the sample population, independent rating

(c) failures to respond, (d) fragments of words, nonsense syllables, or other sounds and noises, and (e) multiple-word responses (excluding grammatically correct hyphenated compounds).

(3) Number of response latencies greater than 6 sec.

Unusual responses and long latencies on word association tasks have been reported as indices of pathology (Rapaport, Gill and Schafer, 1946) and associative disturbances in general are of central importance in the schizophrenic process (Bleuler, 1950). Consequently, it was predicted that the mother-reared group would achieve a lower score (frequency) on the first of the above measures, and higher scores on the latter two measures, than would the reared-apart group.

ACL

The ACL was constructed by a Danish psychologist who selected items appropriate for the subject population. The resulting list contained 241 items arranged in alphabetical order.

The child received ACL ratings from three independent judges: the interviewing psychiatrist, and two psychologists involved in the procedures and having had at least one half-hour's contact with the child. Of the 241 items, there were 28 which the three judges (independently) agreed upon as being "indicative of maladjustment in Danish society". When a child was checked for an adjective by (at least) two of the three judges, the child was considered to have "scored" on that adjective.

It was predicted that the mother-reared group would receive a higher score on ACL items judged to indicate maladjustment than would the reared-apart group.

Psychophysiological responsiveness and recovery

Mednick (1958) has theorized that individuals who eventually develop schizophrenia and other functional disorders manifest at least three conditions which distinguish them from the general population:

(1) Greater anxiety responsiveness to stress.

(2) Slower recovery from stress-induced anxiety responses.

(3) Greater generalization of anxiety responsiveness.

In accordance with this position, each child received responsiveness–

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by a second rater of 20 subsequent cases yielded an *r* of $+ 0.99$. The raters were instructed to tally responses "which would be considered by most people to be 'peculiar' or 'odd'" in content.

recovery and stimulus generalization testing procedures. Skin resistance was recorded by the Wheatstone method with zinc-zinc sulfate finger-tip electrodes and an Offner Type R Dynograph. An anxiety response was defined as change in galvanic skin conductance, the index of response being the magnitude of such change as measured by the difference in log conductance units* between prestimulus and stimulus levels. Stimuli were presented by means of a tape recorder via earphones.

The stress stimulus was a loud (96 db), raucous noise of 4.5 sec duration, and was presented 9 times at intervals varying from 35 sec to 123 sec. For each presentation of the stress the magnitude of anxiety response and the time (in seconds) taken for recovery were measured.

Insofar as greater maladaptation may be considered congruent with greater predisposition to pathology, it was predicted that the magnitude and recovery time of the mother-reared group's galvanic skin response to the stress stimulus would be greater than for the reared-apart group.

Stimulus generalization

A conditioning procedure was integrated with responsiveness–recovery testing by pairing a 1000 c/s tone of 2 sec duration with the stress stimulus and adding five interspersed presentations of the tone alone. Thus the 1000 c/s tone served as a conditioned stimulus (CS), permitting subsequent testing for stimulus generalization along the dimension of tonal frequency. The generalization stimuli were tones of 1311 c/s (GS_1) and 1967 c/s (GS_2), also of 2 sec duration.

Generalization testing began approximately 3 min after responsiveness–recovery testing, and consisted of 3 presentations each of the CS, GS_1, and GS_2 at intervals varying from 10 sec to 18 sec. In order to avoid position effects, all six possible permutation sequences of the three stimuli were employed. The index of response was again magnitude of log conductance change.

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* Log conductance $= \log 10^6 \ (1/r)$, where $r =$ ohms resistance, and $10^6 \ (1/r) =$ micromhos conductance. Conductance provides a more accurate index of general physiological activity than does resistance (Darrow, 1934), and log conductance, following the Weber-Fechner law, an approximation of concomitant psychological activity (Darrow, 1937). Logarithms are subsequently multiplied by 100 to yield more convenient numerical representation.

It was predicted that the mother-reared group would display greater stimulus generalization along the dimension of tonal frequency than would the reared-apart group.

Results*

The inferential statistics employed throughout the data analysis were the *t*-test for difference between correlated means and the computation of exact probability for correlated frequencies by the binomial expansion (McNemar, 1962). The *p* value required to reject a null hypothesis was set at 0.05 for a two-tailed test.

Primary analyses

Nondiscriminating measures.
The psychiatric interview, WAT, ACL, and stimulus generalization testing did not discriminate between the mother-reared and reared-apart groups at the five per cent level of significance. The results for these measures are summarized in table 1. With respect to the children of the reference sample, the data from the psychiatric interview indicated that the psychiatrist viewed these children as better adjusted than either the mother-reared or reared-apart groups. The same conclusion was suggested by the WAT results, although strongly only in the case of deviant responses.

School report
The schools reported only one child as having been examined by a school psychologist for behavior problems. This case was a reared-apart child, who was also diagnosed "neurotic" following the psychiatric interview.

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* While differences in coding and scoring procedures make direct comparison difficult or, in the case of the ACL and psychophysiological measures, impossible, Drs. S.A. Mednick and F. Schulsinger of the Psychological Institute, Copenhagen, have provided unpublished results for 104 children born to normal mothers. This sample consisted of 59 males and 45 females, with a mean age of 15 years 1 month, and a mean SES score of 2·30. Relevant data from this reference sample will be referred to where appropriate.

Table 1

Results for nondiscriminating measures (cell entries: integers are frequencies, decimals are means)

Group	Psychiatric interview							
	Neurotic[a]	Previous therapy	Functional somatic complaints	General tension and nervousness	Schizoid character	Relaxed during interview	Inadequate social behavior[b]	Likelihood of developing disorder
Mother-reared	3	2	0	1.80	2.12	6	0.60	3.20
Reared-apart	6	2	5	1.52	2.08	3	0.56	3.08

Group	Word association test			Adjective check list[c]	Stimulus generalization
	"Popular" responses	Deviant responses	Long latencies	"Maladjustment" adjectives	Magnitude of response[d]
Mother-reared	22.08	24.96	13.84	2.00	1.27
Reared-apart	22.24	23.68	18.04	2.30	1.23

a No child diagnosed organic, psychotic, or schizophrenic.
b Seven items.
c $N = 23$ for each group.
d Combined response to GS_1 and GS_2 (three presentations each); responses to CS by the groups virtually equal.

On the 15 remaining items exploring various facets of school behavior, the mother-reared group was checked for poor adjusment a mean of 3.52 times, while the reared-apart group achieved a mean of 2.56. The difference was not significant ($t = 1.50$, 24 df, $p > 0.10$).

The first three items of the school report are related in content and, taken together, define what might be referred to as asocial classroom behavior. The items cover failure to participate in class discussions of subject matter, failure to participate in informal class activities, and failure to initiate activity. Fourteen mother-reared and two rearedapart children received "true" responses on all three of these items, a significant difference (binomial $p = 0.0005$). Further, 10 motherreared children were reported as "very shy, withdrawn, and uncommunicative", while 1 reared-apart child was so checked, a significant difference (binomial $p = 0.02$). In addition, 8 mother-reared children and 1 reared-apart child were seen by the respondents as being "unresponsive to praise or rewards from the teacher", a significant difference (binomial $p = 0.04$). Finally, 6 reared-apart children were described as "easily upset or irritated", while this characteristic was not ascribed to any member of the mother-reared group, a significant difference (binomial $p = 0.03$).

To summarize, the school report questionnaire as a whole did not differentiate the groups. However, item analysis revealed that the respondents considered the mother-reared group to be more inhibited, passive, uninvolved, and withdrawn, as well as indifferent to the teacher's approval, and the reared-apart group to be more susceptible to emotional upset.

In terms of total score on the school report, it appeared that the teachers judged the reference sample children to be somewhat better adjusted than either the mother-reared or reared-apart groups.

Psychophysiological responsiveness and recovery
During the psychiatric interview the children were questioned as to whether they had recently received medications, and an attempt was made to assess the possible effect of any such medications upon psychophysiological behavior. In no case did a child report taking medication which the psychiatrist thought might influence testing.

One young child in each group was so apprehensive about the psychophysiological procedure that stimuli were presented at reduced

volume. It so happened that these children constituted a matched pair, and this pair has been omitted from the psychophysiology results.

As can be seen from table 2 the reared-apart group gave a greater mean response to the stress stimulus on every trial. The mean response in log conductance units over the nine trials was 2.81 for the mother-reared group, and 4.44 for the reared-apart group, a significant difference ($t = 2.72$, 23 df, $p < 0.05$). The direction of this difference was contradictory to the hypothesized direction.

Table 2

Mean response in log conductance units on each trial

Group	Trial								
	1	2	3	4	5	6	7	8	9
Mother-reared	6.49	3.31	2.39	2.63	2.32	2.16	1.94	2.24	1.85
Reared-apart	9.04	5.35	4.06	4.44	3.92	3.84	3.01	3.40	2.90

Note. $N = 24$ for each group.

Prior to comparing the groups on the variable of recovery time, it was necessary to equate them for mean response; this was accomplished by dropping those subject pairs which displayed the greatest discrepancies in magnitude of response in favor of the reared-apart group; equivalence of mean response between groups was achieved after dropping the eight most discrepant pairs, leaving 16 matched pairs for comparison. Instances of failure to recover before the next stimulus presentation were considered as maximum recovery time, and were assigned the full inter-stimulus time interval. The mean recovery time for the mother-reared group was 33.94 sec, and for the reared-apart group 31.75 sec, a nonsignificant difference ($t = 0.47$, 15 df, $p > 0.40$). Single-trial differences were negligible.

Thus, responsiveness-recovery testing revealed that the reared-apart group manifested the greater response to stress, but that the groups did not demonstrate a difference in rate of recovery from stress when the magnitude of response was held constant.

Secondary analyses

Sex

Following a review of various familial incidence and concordance rates in mental illness generally and schizophrenia in particular, Rosenthal (1962) concluded that there is greater likelihood of same-sex concordance than of opposite-sex concordance. Consequently, it was decided to compare female mother-reared and reared-apart children (12 matched pairs). The overall impression provided by the data for the female subgroups was not markedly discrepant from that obtained with the full groups. However, of the school report items which discriminated between the full groups, only the cluster suggestive of greater asocial classroom behavior on the part of the mother-reared group continued to do so. The difference in psychophysiological response to stress was also attenuated, apparently by greater responsiveness on the part of the female mother-reared children. No variables discriminated between the female subgroups which did not differentiate the full groups. (Results for male subgroupings were similar to those for females, with the exception that the difference in psychophysiological response to stress was significant.)

Age

Since characteristic behavior patterns may become more pronounced with age, it was decided to compare mother-reared and reared-apart children of 15 years of age and over (13 matched pairs). However, only the item from the school report which described the mother-reared group as more withdrawn continued to discriminate, while no further differences appeared. (Results for the younger children were similar, with only the school report cluster suggestive of asocial classroom behavior continuing to discriminate.)

Family home

In order to render the rearing milieu of the groups more comparable, subject pairs which included a reared-apart member who had spent some or all of its life in an institutional setting were dropped. This left 16 "family home" pairs for comparison. The results under this condition were similar to those obtained with the full groups. The school report continued to provide evidence that the mother-reared children were

considered to be more asocial in the class situation, and also more withdrawn in general, but the remaining items failed to discriminate. The reared-apart children showed a greater stress response, repeating the psychophysiological responsiveness results of the full groups. No further differentiation of the groups appeared.

Reared-apart separation

In the early stages of data analysis it appeared that those reared-apart children who had lived with their mothers for more than 24 months were contributing unusually large maladjustment indices. Thus it was thought that 24 months might represent some sort of critical separation date, and the 7 subject pairs containing the reared-apart members in question were dropped, permitting analyses which employed the 18 reared-apart members who had been separated from their mothers at 24 months or earlier. This modification did not, however, result in any basic change of the picture presented by the data from the full groups. Again, the mother-reared children achieved higher scores on the school report items assessing asocial class behavior and general withdrawal, and the reared-apart children displayed greater psychophysiological responsiveness to stress, with no further differences appearing.

Mothers' subtype

Twenty-four of the mothers of the mother-reared children, and 16 of the mothers of the reared-apart children, carried a subtype diagnosis of paranoid schizophrenia. (The remaining mothers were diagnosed as either hebephrenic or catatonic schizophrenics, although *all* mothers were severely ill as indicated by their diagnosis as chronic and by their case histories.) Consequently it was considered desirable to compare the 15 matched pairs of children who had been born to paranoid schizophrenic mothers. While the basic impression afforded by the full-groups data was unaltered, it may be noted that the school report items concerning responsiveness to praise and susceptibility to emotional upset, and the psychophysiological responsiveness index, no longer yielded statistical significance. While a differential paranoid-nonparanoid schizophrenic inheritance pattern could account for these instances of attenuated differences, the reduction in sample size seems the more parsimonious explanation.

Discussion

The results did not support the hypothesis that children reared by schizophrenic mothers would consistently display less adaptive behavior as measured by the various procedures than would children reared apart. The psychiatric interview, WAT, ACL, and stimulus generalization testing did not differentiate the two groups. The school report found the mother-reared children to be more generally asocial in their classroom behavior, more withdrawn in their interpersonal contacts, and less responsive to social rewards administered by the adult figure in the situation, i.e. the teacher. On the other hand, the schools reported the reared-apart children to be more easily upset or irritated by minor incidents. In agreement with the latter finding, the reared-apart children (at least the males) displayed greater psychophysiological responsiveness to stress than did the mother-reared children.

Before discussing those measures which discriminated between the mother-reared and reared-apart groups, those measures which failed to discriminate may be considered. Two sources of possible measurement inadequacy suggest themselves: unreliability and insensitivity. As for the former source, the psychiatric interview and ACL were particularly suspect. No reliability check was available on the psychiatrist's judgments, and the extent of inter-judge agreement on the ACL was not high. It is certainly possible that some of the negative findings of the study could be attributed to measurement unreliability. As for the latter source, it is conceivable that the measures concerned were insufficiently "sensitive", i.e. that their properties were too gross to detect relatively small differences in adjustment. While such a rationale is, of course, highly speculative, one concrete example may be offered from the psychiatric interview. Discussion with the examining psychiatrist revealed that he felt the diagnostic portion of the interview schedule should have been more differentiated so as to permit the recording of subdued but strong personality trends which were not adequately represented by the more traditional diagnostic labels used. Thus, a diagnosis of neuroticism could be registered; however, the behavior of an individual who, although displaying less overt anxiety than the "neurotic", was judged to be less adequately equipped in general could not be coded unless quite serious impair-

ment was manifest. The greater psychophysiological responsiveness and social excitability found among the reared-apart children is consonant with the (nonsignificantly) greater number of reared-apart children diagnosed neurotic and judged to have difficulty relaxing during the psychiatric interview. It is possible that the psychiatrist may also have observed other sorts of maladaptive behavior patterns in the mother-reared group, as did the school report respondents, but was unable to record his impressions properly because of limitations imposed by the relative crudity of the interview schedule.

A related problem regarding the observational measures concerns the time interval over which observation was made. It is of interest that the observational measure which yielded statistically significant differences, i.e. the school report, reflected judgments made on the basis of observation over an extended time period, whereas the non-discriminating psychiatric interview and ACL data were based on relatively short observation periods. One inference which might be drawn is that the latter measures failed to discriminate because they depended upon short-term observation, and by implication, that only long-term observation may be expected to produce meaningful judgments of behavior.

Another possible explanation for the failure of several of the measures to separate the groups is the inaccuracy of the original hypothesis and its underlying assumptions, i.e. the consequences of being reared by a schizophrenic mother may not be great, at least not uniformly across all areas of functioning. A more stringent test of this proposition might employ more rigorous criteria for the selection of subjects and rearing environments, as well as include more standard clinical evaluative techniques.

Lastly, it simply may be the case that the effects of being reared by a schizophrenic mother do not become sufficiently magnified to permit reliable assessment by current techniques until an age considerably in excess of that of the present sample.

The differences which did emerge between the two groups in this study are suggestive of differences in orientation to the environment. It seems tenable to argue that orientations to the environment may be divided into two main categories which might be labeled "approach orientations" and "avoidance orientations". Either class of orientation may result in successful or unsuccessful coping with the environment,

depending upon the nature of the problem at hand. For instance, it is probably more adaptive to avoid a dangerous situation than to approach it, while opportune moments usually call for the opposite response. Hutt (Mednick and Higgins, 1960) has proposed a similar categorization of psychological defense mechanisms into "adient defenses" and "abient defenses" (pp. 79–80). An example of an abient defense might be denial, whereas compulsivity could be classed as an adient defense. These notions bear a similarity to the Jungian extraversion–introversion concept, without necessarily taking on the latter's connotations of the external and objective versus the internal and subjective. Likewise, a simple active–passive classification does not adequately incorporate the active component often markedly present in avoidance behavior.

An approach–avoidance classification of orientations to the environment would seem congruent with the social and psychophysiological behavior of the mother-reared and reared-apart groups as described by the school report and psychophysiological responsiveness measures. The basically approach-oriented individual approaches the environment, entering into situations and responding vigorously to stressful encounters: the greater social and psychophysiological reactivity of the reared-apart group are possible manifestations of such an orientation. In contrast, the predominantly avoidance–oriented person avoids contact with environmental challenges and stresses or, this failing, simply withdraws, an orientation perhaps reflected in the relatively low level of social–psychophysiological responsiveness found in the mother-reared group. Thus, the orientation of the reared-apart group appears primarily to be one of approach, and that of the mother-reared group one of avoidance. Of particular note is the fact that on each of the school report indices which discriminated between the mother-reared and reared-apart groups, the "normal-born" reference sample fell intermediately. Such ordering would support an interpretation of the mother-reared and reared-apart groups' behavior as representing divergent tendencies from a reference group of apparently superior adjustment. Should these tendencies become intensified with increasing age, severe maladaptation may arise, which at present does not seem to be the case.

It would seem worthwhile to briefly attempt some rationale as to how such divergent orientations between the two groups of children

might have arisen. One such explanation lies in the possibility that rearing by a schizophrenic mother does not so much determine level of adjustment as determine a general orientation to the world. Thus, the children of the mother-reared group may have learned to avoid, discount, or ignore their schizophrenic mothers, and this habit may have eventually generalized to diverse social relationships and cues. (This would seem to be especially true if the behavior of the mothers was punitive; in this regard it is noteworthy that all but one of the mothers of the mother-reared group were paranoid schizophrenics, thus suggesting critical maternal attitudes.) Such avoidance habits are especially invidious, since they automatically reduce anxiety and thus are self-reinforcing and highly resistant to extinction (Solomon and Brush, 1956). Inconsistency of behavior on the part of the schizo-phrenic mothers might also have led to a mistrust of social rewards or signs of approval. Identification by the children with the mothers' asocial behavior could have occurred as well. These children may continue in such an avoidance orientation for life, some finding benign niches in society, others drifting over the line of environmental toler-ance. The reared-apart children, in contrast, may have learned to respond forcefully and energetically, albeit not always constructively, to their environments. It could be argued that this more labile affective responsiveness may have come about as a reaction to the earlier-discussed vicissitudes and uncertainties in relationships experienced by the children of the reared-apart group (Bowlby, 1951), or as a result of approval and support by their rearing agents for more assertive behavior. Such an approach orientation may later serve them ad-equately as long as problems are of the sort which yield to aggressive solution. This is not to say that one group is better equipped to handle reality than the other, but rather that the groups maintain different response sets, either of which may be more or less effective depending upon situational demands.

SOCIAL CLASS, INSTITUTIONALIZATION AND SCHIZOPHRENIA

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In this article, some extra-familial environmental variables are considered. It is demonstrated that the possible influence from institutionalization is dependent on the socio-economic background.

There is general agreement within the field that both hereditary and environmental factors are necessary for the development of schizophrenia. Investigations are being conducted into the dynamics of schizophrenic breakdown in three areas:

(1) the nature or mode of operation of the genetic factor,

(2) the critical aspects of the psychological and sociological stresses, and

(3) the intervening mechanisms through which genetic and environmental effects interact and become translated into disordered behavior.

This paper focuses upon the second set of factors, specifically the dimensions of social class and institutionalization as related to schizophrenic breakdown.

The continuing uncertainties within the literature can be related largely to the fact that research on the etiology of schizophrenia has generally relied on retrospective data or current assessments of "sick" patients in an attempt to ascertain the underlying factors associated with the disease process. While studies utilizing the retrospective model have resulted in the development of hypotheses and guidelines for further investigation, they are severely limited in their ability to distinguish between behavioral manifestations that precede, and possibly contribute to the onset of the psychosis, from those that follow it.

This fact is particularly evident in the body of literature which examines the role of social class in the development of schizophrenia. Melvin Kohn, 1968, in reviewing the literature on social class and schizophrenia for the past thirty years, concluded that there is little doubt, regardless of the measure of social class, that a disproportionate number of urban schizophrenics are in the lowest social class. The difficulty which previous investigators faced, and which the present investigators also face, is in interpreting the significance of such a finding.

The difficulty centers around the interpretation of the direction of causation. The first position, developed following the pioneering work of Faris and Dunham (1939) is generally known as the "social causation" hypothesis. It suggests that the stresses and dynamics of the life style of the lowest social class are etiologically associated with disorder. Two types of evidence have been presented to support this position. The Faris and Dunham study supported this interpretation with evidence of higher rates of prevalence of schizophrenia in the lowest social class ecological areas. Clark (1948, 1949) and Hollingshead and Redlich (1958) have shown the highest rates of schizophrenia for the lowest status occupational group.

The second position is referred to as "social selection" or "social drift," and proposes that schizophrenics tend to be overrepresented in the lowest strata as a consequence of their illness and its precursors. The "social selection" hypothesis suggests that schizophrenics fail to attain expected occupational success in terms of their father's occupation, while the "social drift" hypothesis implies that schizophrenics exhibit downward career mobility as they tend to "drift" to the lowest status occupational group as a result of impaired functioning during their lives. Turner and Wagenfeld (1967) found that rates of first treatment for schizophrenia are overrepresentative of the lowest social class based on both father's occupation and patient's own occupation. Thus, there is evidence for both the "social causation" and the "social selection" or "social drift" positions. Turner and Wagenfeld suggested that the overrepresentation within the lowest social class resulted more from the failure of the subject to attain expected occupational levels than downward mobility within the patient's own occupational career.

A further problem exists today in assessing the literature on social class and schizophrenia; that problem is related to recent findings

concerning the genetic component. Kety et al. (1968) have provided evidence that there is a genetic component which cannot be ignored in schizophrenia research. To determine if certain environmental factors related to lowest social class membership are important etiologically, it could be useful to study samples in which the genetic variance is restricted. Only after one examines social class independent of the genetic factor can one conclusively investigate those specific aspects of lowest social class life style which either promote or are conducive to the development of schizophrenia.

In a typical sociological study of schizophrenia both the genetic and environmental components are free to vary. While the total range of environmental differences, both social and cultural, in the world varies tremendously, the environmental variance between classes in a western society is generally less. The genetic component, however, varies considerably. Thus, when socio-economic-status is examined, the genetic component provides a considerable amount of variance and should not be ignored. When studying genetic influence in rats, the environment can be controlled so as to restrict differences allowing the effect of genetic factors to be exhibited. Conversely, when studying environmental differences it is equally important to restrict genetic variance. This study, therefore, will attempt to examine the influence of social class within a population in which the genetic variance is relatively restricted. We hypothesized highest levels of breakdown in the lowest social class.

The present study employs a high-risk sample providing a situation in which the genetic variable is more restricted than it would be in the general population. The restriction of the genetic component is also important because of concern regarding genetic differences between social classes (Gottesman, 1968). It is possible that the lowest socio-economic-status group has more schizophrenic genes than can be found in the general population. This might explain the higher incidence of breakdown within the lowest status group quite apart from lower class life styles. The investigators recognize, however, that while the genetic component is relatively restricted in our sample, genetic variance is still present. Neither the genetic characteristics of the fathers nor the genetic background of the grandparents were controlled, and while all the subjects' mothers were schizophrenic, they did not all have the same genetic makeup. The high-risk method,

however, does allow one to examine the relationship between social class and schizophrenia while placing some restriction on the genetic component. The restriction of the genetic component makes it more likely for social differences to be exhibited. This, in turn, makes it possible to observe the important social factors, and, specifically, to examine the impact of these factors.

Methods

In Denmark in 1962–63, Mednick and Schulsinger intensively examined 207 "normally functioning" children with a high risk for becoming schizophrenic (these children all have chronic and severely schizophrenic mothers) and 104 control subjects. [...]

An advantage of a high-risk study is that it restricts the hereditary factor and allows the researcher to examine the environmental differences between those who succumb to the disorder and those who do not. This makes for a particularly interesting test of the social class hypothesis.

The index of social class utilized in this study was based on scales developed for Denmark by Kaare Svalastoga (1959), and adapted by Edward Mednick in 1962 for the present study. The index rates social class from 1 (low) to 7 (high). The subjects' social class was based on the occupation of their fathers, except for a number of subjects who had spent their lives in children's homes. These subjects were classified as being in the lowest social class, which more accurately reflected their life experiences. The subjects were not yet old enough, when these data were collected, to allow for a test of the "social selection" or "social drift" hypothesis, although this is planned for the future. It does allow for a test of the "social causation" hypothesis. It is, therefore, suggested that, within this genetically restricted population, a higher incidence of breakdown within the lowest social class would give support to the "social causation" hypothesis.

Results

As of 1967, the first wave of twenty breakdowns within the high-risk group had been identified. Eleven had been admitted to psychiatric

hospitals with many diagnoses including schizophrenia or have been subjected to forms of psychological treatment. The remaining nine included some who are most likely schizophrenic. The clinical status of all twenty subjects was ascertained by follow-up procedures. At present none of the control subjects have exhibited any detectable breakdown, and thus they were excluded from the present analysis.

Table 1 presents the data for social class and breakdown. The lowest social class had a breakdown rate of 16% as compared to 0, 5, 7, or 10% for the remaining six social classes. Given the large number of social classes compared to the relatively small number of subjects who have exhibited breakdown, it became necessary to combine groups in order to facilitate analysis. Since previous results of our hypothesis predicts a higher rate of incidence of breakdown in the lowest social class, the second through seventh social classes were combined. The combined group of social classes (other classes – two through seven) had an average breakdown rate of 7%. The results supported the hypothesis that there was a higher rate of breakdown within the lowest social class ($\chi^2 = 5.11$, $p < 0.05$).

Table 1
Social class of fathers and breakdown of their children

Social class	Breakdown	No-breakdown	Total
1. Unskilled worker	11 (16%)	55 (84%)	66 (100%)
2. Group leader but unskilled worker	2 (7%)	26 (93%)	28 (100%)
3. Skilled worker	1 (5%)	22 (95%)	23 (100%)
4. Clerical sales	0	14 (100%)	14 (100%)
5. Skilled handworker with own business	4 (10%)	37 (90%)	41 (100%)
6. Leaders or owners of smaller business	1 (5%)	22 (95%)	23 (100%)
7. Academic occupations	1 (5%)	7 (95%)	8 (100%)
			203*

* Four of the 207 subjects in the high-risk group could not be coded on social class. Comparison of social class 1 and combined social class 2 through 7, $\chi^2 = 5.11$, $p < 0.05$.

This finding can be considered as giving support to the "social causation" hypothesis for the kinds of disturbance evidenced by these children. Thus, it might be suggested that the stresses and dynamics of the life style of the lowest social class are etiologically associated with disorder. Given that the subjects are not classified by their own social class, but rather by their father's social class, one is not dealing with "social selection" or "social drift." It is important to note that the higher incidence of breakdown within the lowest social class does not appear to be the result of a linear relationship between social class and breakdown*, but is rather related to lowest social class membership per se. Thus, it is not the case that as class membership decreases incidence increases. Rates of breakdown are fairly uniform and constant except for the lowest social class, where there is a distinct increase in the rate of breakdown.

In view of the fact that many of the children were classed with the lowest social class because they had been reared in an orphanage or children's home (institutionalization), it was deemed necessary to examine the inter-relationship between social class, institutionalization, and breakdown. Does institutionalization relate to breakdown? If institutionalization is controlled, will the relationship between the lowest socio-economic-status group and breakdown still exist?

Given the indications in the literature on the relationship between institutionalization and breakdown (Ainsworth, 1962; Beres and Obers 1950; Goldfarb, 1943), it was not surprising to find that those subjects who were institutionalized for some period of time during their lives were more apt to exhibit breakdown. Table 2 presents the findings that 18% of those subjects who have experienced some institutionalization and five percent of those subjects who have never been institutionalized exhibited breakdown ($\chi^2 = 6.585$, $p < 0.05$). Over three times as many institutionalized subjects have exhibited detected breakdown. Thus, institutionalization appears to be an important factor along with social class in the etiology of psychiatric breakdown. The question still remains as to the interaction effects of institutionalization and social class.

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* There could still be a linear relationship between stress and breakdown with a threshold effect related to social class membership.

Table 2
Institutionalization and breakdown of children

| | Institutionalization | |
	some	none
Breakdown	15 (18%)	5 (5%)
No breakdown	82 (82%)	101 (95%)
Total	97 (100%)	106 (100%)

$\chi^2 = 6.585, p < 0.05$.

Table 3 presents the findings of the examination of the interaction between institutionalization and social class. It is important to keep in mind that the reference to institutionalization does not imply mental illness. Institutions in this study refer to orphanages and children's homes. When social class, institutionalization, and breakdown were compared, a significant interaction effect was found. Compared with subjects in the other six social classes, those subjects who were in the lowest social class and were institutionalized were most apt to break down. But the lowest social class subjects who were not institutionalized were least likely to break down of all subjects in the sample.

Table 3
Social class of fathers, institutionalization and breakdown of their children

| | Lowest social class | | Other social class (2–7) | |
	Inst.	No-Inst.	Inst.	No-Inst.
Breakdown	11 (22%)	0 (0%)	4 (8%)	5 (6%)
No breakdown	38 (78%)	17 (100%)	44 (92%)	84 (94%)
Totals	49 (100%)	17 (100%)	48 (100%)	89 (100%)

$\chi^2 = 4.567$ $p < 0.05$. $\chi^2 = 0.372$, n.s.

Twenty-two of the lowest social class subjects who were institutionalized have exhibited breakdown, while none of the lowest social class non-institutionalized subjects have exhibited breakdown ($\chi^2 = 4.567$, $p < 0.05$). This relationship is in sharp contrast to the relationship between institutionalization and breakdown in the combined other

social classes. In regard to breakdown, there was no difference between the institutionalized subjects within the combined social classes two through seven. Eight % of the institutionalized and six % of the non-institutionalized subjects have exhibited detectable breakdown ($\chi^2 = 0.372$, n.s.). Thus, it is not social class per se, nor institutionalization per se, that makes a significant difference in regard to breakdown, but rather the interaction of institutionalization and social class. It is the institutionalized subjects within the lowest social class who exhibit the greatest incidence of breakdown.

Discussion

The findings suggest an interaction effect between social class and institutionalization, such that those subjects who are both in the lowest social class and institutionalized are most apt to exhibit breakdown. While the finding that there are higher incidence rates of schizophrenia in the lowest social class is undoubtedly accurate, our findings suggest a number of possible alternative explanations for this result. Previous research has not restricted the genetic component. Those studies that have preceded the present investigation have relied on retrospective examination and current assessment of "sick" patients. Furthermore, the interaction of institutionalization and social class appears to be a critical factor. One explanation of this interaction might be that lower class families, for financial or other reasons, might be more apt to institutionalize their children earlier and for longer periods of time. It is also more likely that the lowest social class families have fewer resources when it comes to choosing an institution. Another important possible explanation is that the lowest social class children who suffered breakdown may have been problem children to begin with, and were placed in institutions because family members preferred not to take them in when the mother was hospitalized. Maybe the child's institutionalization is correlated with the father being ill, and being unable to take care of the child when the mother is hospitalized. This would suggest that those children who are institutionalized might have fathers who are genetically impaired.

Heston et al. (1966), in examining a sample of adults, found no relationship between early institutionalization and later psychiatric

breakdown. There are a number of possible explanations for this apparent contradiction in results. First, their study examined only the effects of early institutionalization. Second, our subjects tended to be institutionalized for longer periods of time. Third, their sample examined a much older subject population. Thus, it is possible that we are dealing with the affects of institutionalization on early psychiatric breakdown and, as we follow these subjects, we will find a diminishing impact of institutionalization on later psychiatric breakdown.

Finally, the finding that the lowest social class subjects are more likely to be institutionalized may be unique for children with schizophrenic mothers. However, if this finding also holds true for lowest social class children in the general population, then the examination of institutionalization in the lowest social class becomes particularly interesting. For this fact could partially account for the consistent finding of a higher rate of incidence of breakdown in the lowest social class. The problem faced in this study is that institutionalization and social class were partially confounded in the rating of social class. It is, therefore, difficult from this study to examine the total effect of both factors.

In presenting these findings the investigators take full cognizance of their tentative and suggestive nature. It is intended that these findings will lead to future research, and additional data are presently being collected which should more fully clarify the relationship between institutionalization, social class, and breakdown. Finally, the longitudinal design utilized in this study allows for continual reexamination of these interpretations when future waves of breakdown are analyzed.

CHARACTERISTICS OF PEOPLE WHO REFUSED TO PARTICIPATE IN A SOCIAL AND PSYCHOPATHOLOGICAL STUDY

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The majority of studies conducted at the Institut have been carried out with volunteer subjects. Inevitably a number of potential subjects refused to participate. The extent to which non-participation on behalf of some individuals introduces a bias with respect to the final results was the question asked in the study which follows.

Volunteer bias has been the subject of considerable research (Cochrane and Duffy, 1974; Rosenthal and Rosnow, 1969). In this final contribution an attempt is made to describe not only the sociological and demographic variables but also the psychopathological characteristics of a group of individuals who consistently maintained their refusal to take part in the adoptees study (chapter 1 of Part III) over a period of several years.

The subject who refuses to participate in an investigation represents to a great extent an unknown quantity. Essentially, this leads to the question of whether the results ultimately obtained would have been different if these refusal subjects had agreed to participate.

Several studies have been carried out to assess the bias caused by incomplete samples (Rosenthal, 1965; Tune, 1969; Wallin, 1949). Extensive reviews have been made by Rosenthal and Rosnow (1969) and Scott (1961). The area of research covers a wide range of situations from small volunteer samples in experimental studies to large survey samples and poll studies. In the smaller experimental studies the bias has been in favor of the college student (Schulz, 1969) who is exposed in the main to a variety of manipulated situations which variously range from the demanding to the boring and from the uncomfortable

to the innocuous. In general, the larger samples are interviewed briefly or are requested to return a short questionnaire. The smaller experimental studies which have considered the import of refusal have included personality variables, whereas the survey investigations have largely considered refusal in terms of sociological and demographic variables.

The following brief review draws upon Rosenthal and Rosnow (1969) to which the reader is referred for a fuller exposition of the problems of volunteer bias. The variable of age can be regarded as being somewhat complex since it is confounded with rank and social status; non-volunteers, late-responders and non-responders have been found to be older than participants, this being especially the case with female subjects (Britton and Britton, 1951). Various studies have found no significant effect for age (Edwards, 1968; Scott, 1961).

Rosenthal and Rosnow (1969) suggest that the evidence to date indicates that males are more likely to refuse to participate. However, data provided by Schulz (1969) and Bell (1973) would appear to support the conclusion that females are considerably under represented in the experimental type of study. The possibility exists that this represents a bias on the experimenter's behalf and not on that of the potential subject.

Social status appears to be a factor in refusal whereby the participants are more likely to be from a higher social class (Mayer and Pratt, 1966; Tune, 1969). Gotfredsen (1972) discusses the possibility that participation may be represented as a U-shaped curve in that both low and high status individuals are under-represented in studies. Marital status has been shown in some studies (Gotfredsen, 1972) to introduce bias such that participants are more likely to be married and have children.

Hood and Back (1971) found that male participants were more "self-disclosing" than refusals. Rosenthal and Rosnow (1969) are in general agreement with Bell (1962) who suggested that the individual who participates is less authoritarian, more adjusted psychiatrically and scores higher in intelligence tests; the need for more extensive research, however, is emphasized by both sets of authors.

Psychopathology is to a certain extent subsumed under many personality variables. Specifically, it has been defined broadly as bad adjustment and has been measured with various tests of self-esteem,

self-actualization, MMPI-scores of neuroticism, and emotional stability. One study by Lasagna and von Felsinger (1954) employed the Rorschach test and clinical interviews in order to formulate a diagnosis. The results suggested that there was a higher incidence of psychopathology among volunteers for a drug study than amongst their comparison group. An analysis of non-attenders and attenders during a mass campaign for tuberculosis screening in Denmark (1950-1952) did not indicate any significant differences attributable to sex, age or rural versus urban residence (Horwitz and Wilbek, 1971). However, a follow-up over sixteen years demonstrated that there was a significant over-mortality amongst the non-attenders.

It is evident that research into sampling bias with regard to participation and non-participation has produced extremely divergent results. Additionally, the subject who refuses to participate in psychopathological studies has been largely disregarded in favor of extrapolation from the outcome of non-clinical studies. In this study an attempt is made to determine the sociological and demographic status of a group of refusal subjects in a large-scale study dealing with schizophrenia. Further, the psychiatric status of these refusals, who maintained their negative attitude to cooperation over a period of several years, was assessed in relation to a spectrum of schizophrenia by means of a field interview carried out by a psychiatrist who visited the home of the refusal subject. The purpose of this follow-up was to determine the extent to which bias may have been present in the participant sample. Additionally, it was considered that such an investigation may potentially be of benefit to those investigators planning studies in psychopathology in non-patient population groups.

Primary sample

The scope of the main project has been outlined earlier in the chapter by Rosenthal et al. (p. 149).

A total of 361 adults were identified as potential subjects for this "adoptee" study. This initial sample was reduced to 334 since 27 subjects were found to have died, emigrated or were not traceable. The final sample who were contacted comprised 279 adoptees and 55 non-adoptees (NA). The adoptee group was further subdivided

into an index adoptee group (IA), an index control group (IC) and a cross-fostering group (CF).

Over a four year period full cooperation in the study was obtained from 258 subjects: the remaining 76 subjects were finally designated as "refusals". Details of the participant subjects and refusals in terms of adoptive group are given in table 1. Across the four genetic groupings the refusal rate is 22.8%. There is no significant difference in rate of refusal between the groups.

Refusal sample

The criteria by which a potential subject was finally designated a refusal or nonparticipant are best illustrated by a brief description of the procedure used to recruit the subject sample. The initial contact with each subject was by a standard letter indicating that the respondent had been selected by a careful process to take part in a study dealing with "the relationship between health and general life conditions" being carried out at the Kommunehospital, Copenhagen. It was emphasized that it was most important that all those who had been selected did in fact take part. The letter indicated that the study comprised an interview "about personal conditons" with a physician at the hospital and that all expenses and any loss of income would be reimbursed together with an honorarium for participation. This initial letter concluded with a statement a social worker would visit the individual personally in order to make further arrangements. It should be emphasized that no indication of the "adoptive" design was given in this letter.

The second phase in the recruitment procedure was carried out via letter by the social worker. She indicated to those subjects who were known to possess a telephone that she would ring to appoint a time for a visit. Where there was no telephone, a time for a visit was suggested with a request that the subject should ring or write if it proved to be inconvenient; a stamped addressed envelope was included.

All subjects were contacted until they had given a definite negative reply. Vague refusals by letter such as "lack of time" or "not interested" were followed-up by unannounced home-visits until the social worker finally met the subject. When a categorical written refusal was sent

the social worker abandoned the subject. This was also the case when an attempt to make contact was abruptly interrupted by broken telephone contact, or in the case of a house-visit when the door was slammed shut.

The social worker's policy in contacting a subject was to avoid as far as possible a definite negative decision against participation and she attempted to maintain the possibility of making additional approaches at a later date. This was particularly the case in telephone contact where a decision was avoided so that she might be allowed to make a home-visit when a thorough explanation of the study could be given. Consequently, contact was maintained over several years with a number of subjects of whom some were tested and others were classed as refusals.

Some subjects were abandoned without hesitation because they proved to be controls to index cases who had themselves refused and had been abandoned. Further, towards the final stages of the main investigation when it was not possible to maintain contact with a subject over a long period, a less categorical negative response was accepted: this was especially the case with subjects in the non-adoptee (NA) group since they were contacted initially at a later point in time during the course of the study.

The contact method can be illustrated by the following example, subsequently designated as a refusal:

Example 1 (re 11): The subject responded by letter, at the first approach in January 1968, that she was "a healthy and happy harmonized person" and therefore did not "see herself in a condition to participate". The principal investigator subsequently sent a personal letter with a request to meet the social worker. This was well received; the subject agreed to participate and allowed herself to be interviewed by the social worker. A practical problem arose in connection with babysitting arrangements, and the social worker came again a couple of days later to appoint a final date. At the next approach to the subject, she had obtained employment and could not participate for this reason. In the autumn of 1969 the subject was not working when she was approached by the social worker (who was again allowed access). An appointment was made. The subject rang and postponed the arrangement. A new appointment was made. The subject turned up in autumn 1969 but after 15 minutes conversation with the psychologist left the hospital because she had "received incorrect information as to what it was all about". On the psychiatrist's visit two years later, the door was immediately slammed in his face.

In conclusion, the refusal sample consists of all those potential

subjects to whom an approach to participate was made but who did not subsequently take part in the testing; to this extent, the group is somewhat heterogenous since it includes all degrees of refusal ranging from the categorical written refusal to individuals who, after being interviewed by the social worker, promised participation but failed to keep the appointment. Similarly, the group also includes a number of persons who, as in the previously cited example, attended the hospital but who subsequently terminated the interview before its completion.

Method

With an overall refusal rate of 22.8% there was the possibility that the tested group might no longer be representative. For this reason, and because of the expense incurred in the project, it was judged essential to take extraordinary measures to obtain as much data as possible which might indicate possible psychopathology amongst the refusals: a field psychiatric interview was chosen as being the most appropriate form of investigation. Attempts to carry out such an interview were made in most instances after a two year period following the first indication of refusal by a subject.

During the collection of material and data both the social worker (BJ) and the psychiatrist (HP) were unaware of the genetic group to which the subject belonged. This was also the case during the first stage of data analysis.

When the subject was abandoned there was already some information from the social worker which will be described below. These data were used for this investigation and were supplemented by approaching institutions and registers from which further information was obtained for all subjects.

Register information

Uniform data for both participants and refusals was collected initially through the National Registration Bureau (*Folkeregisteret*). The following data points were obtained: sex, age (including age of spouse), number of children, marital status, address, residential status (i.e. whether living alone or with parents or spouse), social class and social

mobility. All data derived from the *Folkeregister* were corrected to the time when the subject was contacted by the first letter.

A check was made in the files of the National Police Register (*Rigsregistraturen*) for participants and refusals. *Rigsregistraturen* lists each person who has been accused of some form of criminality, traffic offense or juvenile delinquency. The type of crime is recorded together with the sanction: in some instances, there is also an extended record of biographical information. The data derived for this project does not include those registrations unconnected with criminal behavior (for example, the withdrawal of a driving license).

A search was carried out in the records of the Mothers' Aid Agency (*Mødrehjælpen*) for all female subjects: this data has not been corrected for time of initial contact.

There is no central register in Denmark of a person's contact with the public assistance or child welfare authorities. Information of this kind is maintained by each local authority and is not transferred when an individual moves from one municipality to another. Accordingly, inquiries were made on a limited basis for only the refusal group.

The final register source which was employed was the National Register of Psychiatric Admissions: this was checked for all refusals following the visit to the person's home by the psychiatrist. Any relevant medical notes were requested from the appropriate hospitals.

Letters from subjects

A number of subjects wrote in reply to the first letter from the Institut. It was felt that many of these letters gave an indication of psychopathology by their style and content. Additionally, some indication of the subject's reason for refusal could be determined. The letters were seen by the psychiatrist before making the home-visit. One or more letters formed the only direct contact with a number of subjects.

The psychiatrist's home-visit

When it became apparent for a given subject that further and protracted attempts at persuasion to participate would be without effect, the only remaining opportunity for a psychiatric interview

would be for the psychiatrist to appear unannounced at the subject's home. For each subject the intention was to obtain:

1. a description of the conditions under which the subject lived,
2. the subject's reasons for refusing to participate, and
3. a general indication of the subject's psychiatric status, with particular weight being placed upon possible concomitants to the schizophrenia spectrum

In those instances where a subject was cooperative, the interview was carried out according to a scheme which had been used previously by researchers at the Institut (see the chapter by Goodwin et al.). For those subjects with negative attitudes, the intention was to extend the proceedings for as long as possible on the doorstep of the home: this procedure was rapidly abandoned since it was felt that such an approach may be construed as totally unwarranted intrusion. The home-visit was carried out at those times when subjects could be expected to be available. Several varying times were tried following unsuccessful visits. Further, it was the policy to accept a very short interview rather than make an appointment for another occasion.

In all instances, the psychiatrist (HP) was not aware of the subject's genetic group: he knew only that some of the subjects had schizophrenic biological relatives. The interviews were carried out over the course of a year and it was decided that a subject could be abandoned after five unsuccessful attempts at contact had been made.

Referrals to the subject's own physician

Contact was made with each subject's doctor whenever this was possible: each individual in Denmark who is registered with the Social Insurance organization is assigned to a general practitioner. A request was made to borrow all relevant material. In addition, the physician was asked whether it was his impression that the subject was mentally ill.

Questionnaire to persistent refusals

In an attempt to obtain at least some information on the reasons for refusal from subjects who were not seen by the psychiatrists, a simple questionnaire was mailed. The text was:

Put at least one cross

I will not participate in the study at the Psykologisk Institut because:

(1) I do not like to talk about myself and my problems with an unfamiliar physician.

(2) I do not wish my name to be entered onto a file. One can never know to what use the information will be put.

(3) I have been unable to find out the reasons for the study.

(4) My spouse is against my taking part.

(5) Any other reason: please specify.

Results

It is evident that an individual may have varied reasons for refusing to take part in a psychological investigation. The primary intent in this study was to determine whether the refusals could be considered as being weak in a psychiatric sense or whether they feel themselves to be in a socially less acceptable situation, as a consequence perhaps of previous unfortunate experience with "institutions". Conversely, it may be that the refusing subject is better equipped both in a social and personality sense so that he has the ability to withstand pressures in favor of participation.

It is possible on the basis of the available data sources to present a description of the participant and refusal groups with regard to a series of demographic and social variables. Further, an attempt can also be made to portray the refusal group with respect to the manner of refusal and likely motivation for doing so. Data derived from the interview enable a diagnostic picture to be drawn for the refusals in relation to the schizophrenic spectrum.

Demographic and social variables

In all cases where a chi-square value is reported the test was applied to frequency data. The distribution of participants and refusals over the four genetic groups is given in table 1: the refusals are evidently evenly distributed between the groupings. There is no indication that either a family history of schizophrenia (IA and NA groups) or a

schizophrenic environment (CF and NA group) resulted in more refusals than amongst a control group (IC).

Table 1

Distribution of participants and refusals over the four subject groups

Total	IA	IC	CF	NA
Participants 258 (77.2%)	79 (77.5%)	99 (77.3%)	38 (77.6%)	42 (76.4%)
Refusals 76 (22.8%)	23 (22.5%)	29 (22.7%)	11 (22.4%)	13 (23.6%)
334 (100%)	102 (100%)	128 (100%)	49 (100%)	55 (100%)

In table 2 the sample is subdivided into sex. There is no significant sex difference in refusal rate ($\chi^2 = 1.23$). When the sample was further distributed into the genetic groupings there was a slight tendency towards more refusals among IC females than IC males.

Table 2

Distribution by sex

Group	Males	Females	χ^2	p
Participants	117 (80.1%)	141 (75.0%)	1.23	n.s.
Refusals	29 (19.9%)	47 (25.0%)		
Total	146 (100%)	188 (100%)		

Table 3

Age of subjects

Total sample	Mean age years
Particip. males ($N = 117$)	30.7
Refus. males ($N = 29$)	31.3
Particip. females ($N = 141$)	33.0
Refus. females ($N = 47$)	32.6

The mean ages of the participants and the refusals are outlined in table 3: there is no significant difference attributable to age although the females (both participant and refusal) were slightly older (32.8 years) than the males whose mean age was 31.0 years.

Data relating to marital, parental and residential status are presented in table 4. There are a larger number of refusals who were unmarried, this being equally applicable to both males ($\chi^2 = 11.57$, $p < 0.001$) and females ($\chi^2 = 8.66$, $p < 0.01$). Fewer refusals than participants were or had been parents (males $\chi^2 = 5.79$, $p < 0.025$; females $\chi^2 = 5.08$, $p < 0.05$). Proportionately, the married participant women had twice as many children as the unmarried refusals. Residential status is also indicated in table 4: significantly fewer male refusals lived with a spouse and children; unmarried male refusals showed a tendency to live with their parents. No effect was attributable to urban or rural residence.

The possession of a telephone (or access to one) has been found previously (Rosenthal and Rosnow, 1969) to be less frequent amongst refusals. In the upper section of table 5 the data refer to telephone access irrespective of residential status; there are no significant differ-

Table 4
Marital, parental and residential status

Item	Males							Females						
	Partici-pant %		Re-fusal %		χ^2	p		Partici-pant %		Re-fusal %		χ^2	p	
	Yes	No	Yes	No				Yes	No	Yes	No			
Subject is or has been married	74	26	41	59	12.35	< 0.001		85	15	66	34	8.66	< 0.01	
Subject had children	69	31	45	55	5.79	< 0.02		75	25	57	43	5.08	< 0.05	
Subject lives alone	16	84	24	76	0.98	n.s.		6	94	15	85	2.08	n.s.	
If single, subject lives with parents	43	57	71	29	3.24	< 0.10		38	62	63	37	2.17	n.s.	
Subject lives with spouse and children	62	38	31	69	9.05	< 0.01		53	47	43	57	1.7	n.s.	
Subject lives in the city	30	70	41	59	1.42	n.s.		31	69	38	62	0.75	n.s.	

Table 5
Access to telephone

	Males						Females					
	Participant		Refusal				Participant		Refusal			
Item	%		%		χ^2	p	%		%		χ^2	p
	Yes	No	Yes	No			Yes	No	Yes	No		
Telephone access	56.4	43.6	58.6	41.4	0.05	n.s.	61.0	39.0	51.1	48.9	1.43	n.s.

	Males not with parents						Females not with parents					
	Participant		Refusal				Participant		Refusal			
Item	%		%		χ^2	p	%		%		χ^2	p
	Yes	No	Yes	No			Yes	No	Yes	No		
Telephone access	57.3	42.7	47.1	52.9	0.62	n.s.	60.9	39.1	37.8	62.2	6.25	< 0.025

Table 6
Social class status

	Males						Females					
	Partici-pant		Re-fusal				Partici-pant		Re-fusal			
Item	%		%		χ^2	p	%		%		χ^2	p
	Yes	No	Yes	No			Yes	No	Yes	No		
Subject is in a low class	36	64	59	41	4.98	< 0.05	27	73	26	74	0.04	n.s.
Subject is in a middle social class	49	51	34	66	1.87	n.s.	66	34	70	30	0.28	n.s.
Subject is in a high social class	15	85	7	93	1.42	n.s.	7	93	2	98	1.57	n.s.

ences between participants and refusals. In the lower section of table 5 the data are derived from only those subjects who did not live with their parents: here, there were significantly fewer female refusals with access or possession of a telephone ($\chi^2 = 6.25$, $p < 0.025$).

Placement of subjects by social class was made after Svalastoga (1959). Initially, a division into eight classes was made, and married women were classified according to their husband's social rating unless their own was higher. For the purposes of analysis (table 6) the eight classes were collapsed into three "mean" divisions, low-class, middle-class and high social class. There were significantly more male refusals in the lower social classes ($\chi^2 = 4.98$, $p < 0.05$).

Previous contact with other organizations

It was hypothesized that there would be more persons in the refusal group who had previously applied for some form of aid from an official agency and that relatively more would have been rejected. An investigation of those who had been in contact with the Mother's Aid Agency did not provide any positive indication that this was the case. In particular, there were no more refusals who had been denied *abortus provocatus* than participants.

There was no significant difference between participants and refusals as regards registration in the Criminal Records Office (table 7). Equally, there was no significant difference in imprisonment rates,

Table 7

Criminal status

	Males				Females			
	Partici-pant %	Re-fusal %	χ^2	p	Partici-pant %	Re-fusal %	χ^2	p
Item	Yes No	Yes No			Yes No	Yes No		
Subject is listed in criminal register	46 54	52 48	0.29	n.s.	9 91	13 87	3.33	n.s.
Subject has been imprisoned	14 86	24 76	1.92	n.s.	1 99	4 96	0.67	n.s.

although the percentage of refusal males who had undergone a prison sentence was slightly greater.

As was stated previously, the information from other official agencies, such as the Public Assistance Office and the Child Welfare Authorities, are not maintained in any systematic manner and, thus, were not suitable for analysis. In those cases where such records were available for a refusal subject the content has been used in the overall evaluation of the individual.

A descriptive analysis of the refusal group

The description of the refusal group is given in three main sections. First, an account is presented of the subject's refusal to the social worker. Secondly, there is the account of the psychiatrist's house-visit and its outcome. Thirdly, an outline is made of the relationship between the subject's reactions toward the social worker and subsequently toward the psychiatrist on his house-visit.

The social worker's contact

The social worker made extensive, although not systematic notes, on her contact with the subject. It is possible to describe a subject's refusal

Table 8

Force of rejection in relation to form of social-worker contact

Response to social-worker	Social-worker contact			
	Not seen (letter)	Telephone	House visit No access	House visit Access
Categorical rejection (N = 48)	16	18	5	9
Half hearted rejection (N = 6)	0	6	0	0
Promise (later refused) (N = 20)	1	4	0	15
No response (N = 2)	2	0	0	0
Total (N = 76)	19	28	5	24

in terms of the force of refusal and also in relation to the means of contact used.

The force of refusal was classified as being: (1) categorical, including rejection by letter or a representative, (2) half-hearted rejection, (3) a promise to take part or a favorable attitude but subsequently refusing, or (4) no response and no contact. Table 8 indicates the force of refusal together with a classification in terms of the type of social worker contact. The majority of refusals were categorical and most of those were by letter or telephone contact. The next most frequent refusal was that of a promise to take part followed at a later point in time by an absolute refusal. There were no significant effects attributable to genetic group.

The psychiatrist's home-visit

Since some subjects had indicated an attitude of strong non-cooperation at the time of the social worker's approach, it was with a certain amount of apprehension that the psychiatrist made an unannounced visit. However, it became apparent that there was not always a direct correspondence between a subject's verbal or written rejection and their attitude to the psychiatrist's visit. Some were equally definite in their refusal to the psychiatrist, but several were extremely obliging. The following two examples can serve as illustration:

Example 2 (Re 46) : 35 year-old married women. Husband rings to social worker and announces that the subject asked him to say that she will not participate. He forbids the social worker to visit the subject. The social worker's attempt to convince over the telephone is in vain. A few days later the social worker receives a letter, consisting of a piece of white, undated paper with the following text written in block letters and underlined three times "visit strongly denied". With an unannounced visit some 2 years later the psychiatrist was received with extreme friendliness, was invited in and given an interview lasting several hours. An impression was formed that the subject was a little unsure of herself, but otherwise she was psychiatrically unremarkable. She seemed not to want to participate because she could not obtain sufficient information as to what was to take place.

Example 3 (Re 35): 48 year-old divorced woman. By way of answer to the social worker's approach the following type-written letter was received; "On several grounds, which I do not wish to explain, I will not participate in the investigation at Kommunehospitalet in Copenhagen referred to in the letter of the said date and thus I do not wish to receive a visit from you on the said date – *Finally I express strongly*

that I do not wish further approaches in this case, either written, verbal or by telephone. With
kind regards. NN"

The psychiatrist was received in an extremely friendly manner. The subject
apologized for her refusal and explained that she thought we had obtained her
address through a psychiatrist whom she had previously consulted. The subject was
an insecure, chronically depressive, intelligent person who was aware of the bio-
logical loading of schizophrenia.

In those cases where the psychiatrist was not invited into the house
the face-to-face contact varied between a few minutes to twenty
minutes. In general, it was found that if the subject was seen for less
than five minutes, the amount of information gained was not sufficient
for a judgment to be made as to whether the subject was psychiatrically
inadequate or not. Nine subjects were included in this category out
of a total of nineteen who were only seen on the doorstep: in five
instances the contact was less than five minutes because the door was
slammed as soon as the subject understood the purpose of the visit.
In one case it transpired that the psychiatrist was in danger of being
physically attacked:

Example 4 (Re 72): The subject was a 44 year-old married woman, living on a farm.
Previously, the social worker had only had telephone contact with the subject who
presented disjointed and incoherent thought processes. The subject refused to allow
the social worker to visit her. The psychiatrist arrived at the farm in the afternoon.
He was allowed in by the subject who began to speak incoherently. After about ten
minutes the interview was interrupted by the husband's arrival. As soon as the
subject explained who the psychiatrist was, the husband became very angry and
ordered the psychiatrist to leave at once. The psychiatrist tried unsuccessfully to
explain but, since the husband was much taller and in strong affect, he was forced
to flee. The husband then turned loose a dog and pursued the psychiatrist with threats
out to the main road.

Following this experience, the psychiatrist chose not to visit those
subjects by whom the social worker had been threatened! In two other
instances the psychiatrist determined that the spouse had expressed
strong objections to the participation of the subject. In one case (Re 9),
the psychiatrist was allowed to interview the subject, but the latter
could hardly converse since her husband continually interrupted and
asked why a particular question was being put. In the second case, the
psychiatrist did not have an opportunity to meet the subject but
carried out a half-hour long negotiation with her husband who main-

tained that there was a case of "persecution" by the Psykologisk Institut. This was the only instance of its kind in the entire investigation.

It should be emphasized that the evaluation of those subjects whom the psychiatrist saw only for a brief time is to be regarded as a general impression. Even where a full interview was obtained with a subject who had a relatively positive attitude, the interview situation often proved to be so awkward that the data collection was of a highly variable quality, and should be viewed with this proviso in mind. The interview frequently took place within the hearing of the spouse or casual visitors. Some weight must be given to the low motivation evident in many subjects to give correct information. Restrictions on available time prevented the indirect validation of many answers.

The chaotic conditions under which some interviews took place can be judged from the following example:

Example 5 (Re 17): Subject was approached on a Saturday afternoon. It appeared that he was a member of the so-called "Wild Angels" who were holding a party at the home of the subject. The psychiatrist felt somewhat insecure, but was received in a friendly manner and offered a beer; a naked girl in a corner of the room offered herself also. The subject had a positive attitude towards being interviewed and an appointment was made for the psychiatrist to return on Monday evening. At that time the party was not yet over; however, the subject was now prepared to carry out the interview within the hearing of several halfdrunk guests. During the entire interview the girl who had previously offered herself sat on the subject's lap. The unusual surroundings (iron chains, swastikas and pornographic posters, which will not be described further) necessarily contributed to the psychiatrist's evaluation of the subject just as much as the answers to the questions.

The psychiatrist's choice of approach was to attempt to persuade the subject to be interviewed, saying that it would take approximately thirty minutes; it soon became apparent that a refusal was most often motivated by a lack of time. In general, it proved possible to extend a majority of the interviews to about one hour: it was more difficult to make the interview last much longer. Accordingly, it must be stated that much of the information obtained was somewhat superficial; it was necessary to give some weight to a general impression of the subject with particular emphasis being placed on disturbances in emotional contact, language use and thought processes.

The diagnostic presentation has, therefore, been restricted to three

broad categories: outside the schizophrenia spectrum, suspected schizo-phrenia spectrum and schizophrenia. Subjects who presented one or more of the above symptoms but from whom the psychiatrist was unable to get a consistent impression were included in the suspect category. Diagnosed cases of borderline schizophrenia were classed as schizophrenic.

Table 9 indicates that an interview was achieved with approximately half the total refusal group, the remainder being divided almost equally between the "briefly seen" and the "not seen" groups.

Table 9

Outcome of psychiatrist's house-visit

Outcome of house-visit		Females	Males
Interviewed	($N = 37$)	23	14
Seen	($N = 19$)	12	7
Not seen	($N = 20$)	12	8
Total	($N = 76$)	47	29

When the psychiatrist met the subject an attempt was made to evaluate the motive for refusal. Although a direct question was asked in every case, the data given in table 10 are based on the psychiatrist's evaluation of the subject's reply (insofar as an answer was given to the question). Conditions which were judged as being realistic obstacles to participation (for example, travel, imprisonment, objections by the spouse) are considered to be in the practical grounds category. Some individuals expressed that they did not want to talk about themselves and their problems, or did not wish to be reminded of childhood; others suspected that they would be asked questions dealing with sexual matters, and some revealed that they were afraid of hospitals and doctors. These subjects are included in the "uneasy" category. The "suspicious" category includes subjects who defended their refusal with statements that they had no wish to take part in an "American project" or that they did not want their name on a register or file. Subjects whose overt behavior suggested to the psychiatrist a suspicion of the project's intent are also included in this group. Table 10 gives a breakdown of the reasons for refusal by outcome of the home-visit. Amongst the interviewed subjects the reasons for refusal are distrib-

uted fairly evenly across the three categories, whereas the "seen" group has a bias in favor of refusal due to suspicion.

Table 10

Interviewees' reasons for refusal

	Reason for refusal			
Outcome of house-visit	Practical grounds	Uneasy	Suspicious	Without information
Interviewed ($N = 37$)	15	11	9	2
Seen ($N = 19$)	2	1	8	8
Total ($N = 56$)	17	12	17	10

Diagnostic impressions

A diagnostic impression was made for a total of 45 refusals; of these, 37 were derived from an interview, and the remainder were based on a short contact with the subject in the open door. In table 11 the relatively high figure for the "suspect schizophrenia" category is a result of the psychiatrist's bias in that minor evidence of psychopathology resulted in a diagnosis weighted towards inclusion in the spectrum. Diagnoses subdivided across the four genetic groups are outlined in table 12. Grounds for refusal are distributed across the diagnostic groups in table 13: within the spectrum and suspect schizophrenia have been collapsed to form one category. Subjects classed as being within the spectrum indicated a tendency to be more suspicious whereas

Table 11

Outcome of psychiatrist's house-visit by diagnosis

	Diagnosis			
Outcome of house-visit	Outside spectrum	Suspicion of schizophrenia	Schizophrenic	No diagnosis
Interviewed ($N = 37$)	24	8	5	0
Seen ($N = 19$)	3	3	2	11
Not seen ($N = 20$)	0	0	0	20
Total ($N = 76$)	27	11	7	31

Table 12

Diagnosis by genetic group

Diagnosis	Genetic Group			
	IC	IA	CF	NA
Outside spectrum (N = 27)	7	9	7	4
Suspicion of schizophrenia (N = 11)	4	5	1	1
Schizophrenic (N = 7)	2	2	0	3
No diagnosis (N = 31)	16	7	3	5
Total (N = 76)	29	23	11	13

those outside the spectrum tended to give practical reasons for failing to participate.

Diagnostic reliability

The field investigator's diagnostic impressions were made with a large amount of uncertainty. This might be contrasted with the diagnoses (table 14) on the participants which were based on reports of interviews which varied between three to six hours. Any comparison

Table 13

Reasons for refusal and diagnosis

Reason for refusal	Diagnosis		
	Outside spectrum	Within spectrum	No diagnosis
Practical grounds (N = 17)	12	4	1
Uneasy (N = 12)	9	2	1
Suspicious (N = 17)	4	10	3
Without information (N = 30)	2	2	26
Total (N = 76)	27	18	31

between the two investigations must be made with reservation. It may be noted that the two psychiatrists involved had the same bias but the interview situations were very different.

Table 14

Participants' relation to the schizophrenia spectrum by genetic group

	Genetic Group			
Participants	IC	IA	CF	NA
Outside spectrum (N = 193 = 75%)	82 = 84%	54 = 68%	28 = 74%	29 = 69%
Within spectrum (N = 63 = 25%)	15 = 16%	25 = 32%	10 = 26%	13 = 31%
Total (N = 256 = 100%)	97 = 100%	79 = 100%	38 = 100%	42 = 100%

Table 15

Interviewed refusal's relation to the schizophrenia spectrum by genetic group

	Genetic group			
Interviewed refusals	IC	IA	CF	NA
Outside spectrum (N = 24 = 65%)	6 = 55%	10 = 67%	6 = 100%	2 = 40%
Within spectrum (N = 13 = 35%)	5 = 45%	5 = 33%	0 = 0%	3 = 60%
Total	11 = 100%	15 = 100%	6 = 100%	5 = 100%

Table 16

Refusal's relation to the schizophrenia spectrum by genetic group after perusal of case material

	Genetic Group			
Interviewed refusals	IC	IA	CF	NA
Outside spectrum (N = 27 = 73%)	9 = 82%	10 = 67%	6 = 100%	2 = 40%
Within spectrum (N = 10 = 27%)	2 = 18%	5 = 33%	0 = 0%	3 = 60%
Total (N = 37 = 100%)	11 = 100%	15 = 100%	6 = 100%	5 = 100%

A second investigator (FS) carried out a diagnostic classification using the reports obtained by the field psychiatrist for the 37 interviewed refusals. The field investigator's diagnoses for these subjects are given in table 15; the second classification resulted in only minor modification to these results, seven subjects being placed outside and four within for the IC group. No other changes were made. A comparison between tables 14 and 15 shows that the 25% of the participants versus 35% of the refusals were placed within the schizophrenia spectrum. After a perusal of the available case material only two IC refusals were placed within the schizophrenia spectrum (table 16): the overall percentages for the within and without classification for both participants and refusals were thus approximated at 27% and 25% respectively.

Subjects who were not seen by the psychiatrist

The psychiatrist made a total of approximately two hundred home-visits and contacted fifty-six subjects. Table 17 shows that a little more than a third of the refusals were contacted on the first visit. However twenty subjects were not seen at any time by the psychiatrist, despite repeated visits to their registered address.

It is possible to present a brief summary for each of these refusals which has been derived from information obtained through various agencies, the subjects' letters and the social worker's impression. Following each description is an indication of whether the subject was not seen after five visits (5) or because of other reasons (0). The genetic group is given in parentheses after the refusal number.

Table 17

Number of house-visits

Number of visits	Successful contact
1 visit	28
2 visits	12
3 visits	9
4 visits	2
5 visits	2
> 5 visits	3

Re 2 (IA): Punished for theft. Has tried to avoid call-up. Wife dead 6 months before social worker's visit. Subject was alone with a daughter. Said he was afraid to give information which would be written down and put on magnetic tape. Frequent removals. (0).

Re 4 (IC): Refused socialworker politely but firmly in the door-way. "Neither time nor interest". (5)

Re 6 (IC): Separated from minor criminal spouse. Received financial help from national assistance and Mothers' Aid. Positive towards social worker on two un-announced house visits. Excused by claiming lack of time. Answered questionnaire: "Future approaches will not be answered". (5).

Re 8 (IC): Letter "... no interest and further approach not desired." Answered questionnaire with a cross in all 3 columns and a text with schizophrenia-like syntax. (5).

Re 10 (IA): Subject's mother had confidentially informed the social worker over the telephone that the subject had "an awkward mind", was afraid to live in her own apartment, and that she spent a lot of time with her parents although she was married. The subject could stand all evening, and "poke in a cupboard". Received drugs from own doctor, but did not take them. Subject sent a formally positive answering letter, but was never found at her address either by the social worker or the psychiatrist. Moves frequently. (0).

Re 26 (IA): Possible minor criminality and misuse of alcohol. Mother informed us by telephone that as an 11 year-old the subject was admitted to a psychiatric department because of behavior difficulties and that she still held a grudge about this. Trained teacher, but working as a travel leader. Never at home. (5).

Re 27 (IC): Accused of prostitution. Spouse minor criminal. Requested help from Mothers' Aid for *abortus provocatus* twice. Separated shortly after social worker's visit. (5).

Re 30 (IC): Subject had left spouse shortly before social worker's approach. Categorical refusal by telephone. (5).

Re 33 (IA): Categorical refusal by telephone towards social worker. Cannot be found at the address listed in the *Folkeregister*. (0).

Re 36 (IC): Minor criminal (receiving stolen property, violence, traffic offenses, illegal firearms). Was very tense and threatening towards social worker. "So, you dared to come". In the hall the social worker saw a collection of helmets and military epaulettes. (0).

Re 38 (IA): Unmarried. Five children with two different fathers, who are both asocial and have criminal records. One possibly schizophrenic. Manages badly socially, received national assistance through several periods and help from Mothers' Aid, but never applied for abortion. (0).

Re 40 (IC): Letter: "... Not had time to deal with your correspondance before now. Had taken it as quite a good joke ... don't find it quite as funny now ...". (5).

Re 49 (IC): Polite and positive towards social worker. Sent postponement, but offered to come another time. In questionnaire subject claimed to be prevented by work from participating. (0).

Re 53 (IC): Subject showed a positive attitude towards the social worker over the telephone, but before a visit was arranged, the subject's own doctor rang and forbid us to contact the subject, "She is a girl with problems, she must be spared". (0).

Re 56 (IA): Reluctantly consented to participate, but sent excuses twice. (5).

Re 61 (IC): Punished several times in connection with court cases (espionage and treason, theft). Married and divorced three times. Abortion and sterilization through Mothers' Aid. This subject had been admitted several times to Kommunehospitalet with severe paranoid schizophrenia. (0).

Re 67 (NA): Rejected categorically by telephone. Lives in the provinces. (0).

Re 70 (NA): Punished several times (theft, desertion, drunken driving, breaking and entering; longest punishment–eight months). Several periods of financial help from national assistance; owes a five-figure sum in paternity payments and tax. Never answered letters, neither did he answer our approaches and was never at home; apparently does not live at his post address. (5).

Re 75 (NA): Short rejecting letter. Lives in the provinces. (0).

Re 76 (NA): Five traffic fines. Post address unoccupied. Moves often. (5).

Approximately half of these refusals were not seen simply because they were not contacted at home after at least five visits. Three were abandoned after one unsuccessful visit since they lived some distance away from Copenhagen. Four subjects were not to be found at their registered address.

It would appear that most of the refusals who were not seen by the psychiatrist were at the time of the investigation in adverse social situations. The extent to which this reflects a more chronic state can only be conjecture at this time, but several had been repeatedly involved in criminal behavior and many were found at the time of the socialworker's contact to be in difficult marital situations.

Relationship between refusal to the social worker and the outcome of the psychiatrist's visit

Table 18 indicates that about half the categorically rejecting subjects gave an interview to the psychiatrist although he had arrived without any prior arrangement.

Table 18

Relationship between subject refusal and outcome of house-visit by the psychiatrist

		Psychiatrist's visit		
		Interviewed	Seen	Not seen
Refusal to Social worker	Categorical ($N = 48$)	20	16	12
	Halfhearted ($N = 6$)	5	1	0
	Agreed, but never came ($N = 20$)	11	2	7
	No reaction ($N = 2$)	1	0	1
	Total ($N = 76$)	37	19	20

Additionally, it seems that whatever the initial contact by the social-worker the percentage of subjects who were interviewed by the psychiatrist lies at approximately 50%. Slightly fewer subjects (36%) who refused by letter gave an interview (table 19).

In all cases where the social worker had failed to obtain permission to enter the home the outcome was the same on the psychiatrist's visit. There was little indication that the sex of the socialworker and that of the psychiatrist had contributed any significant effect.

Table 19

Type of social worker contact in relation to outcome of house-visit by the psychiatrist

			Psychiatrist's visit		
			Interviewed	Seen	Not seen
Social worker's contact	Not seen or spoken	($N = 19$)	7	4	8
	Telephone contact	($N = 28$)	15	9	4
	Seen but no access	($N = 5$)	0	3	2
	Seen and allowed access	($N = 24$)	15	3	6
	Total	($N = 76$)	37	19	20

Admissions to psychiatric institutions

The Central Psychiatric Register indicated that seven of the entire refusal group had been previously admitted to a psychiatric department, hospital or sanitorium. Relevant information concerning these persons is given in table 20. All five subjects whom the psychiatrist met gave an interview. Two of these said that dissatisfaction with their earlier hospitalization was the reason for refusing to participate. One of the unseen wrote directly, however, indicating that it was memories of her previous hospital stay which led her to refuse. None of the previous admission cases was from the NA group.

Information from subject's doctor

Essentially, little additional information was forthcoming from the referral to general practitioners. There was information which partially contributed to the formulation of a diagnostic impression for only eleven replies out of a total of 47.

Only ten of the twenty unseen subjects had a personal physician. Nine doctors replied of which three provided relevant information; the remaining six subjects seemed to be scarcely known by their own doctor.

Questionnaire

The response rate to the postal questionnaire sent to the twenty unseen subjects was 30% and the six replies provided only minimal information. One subject indicated that he was suspicious and without confidence (Re 8; see above). Four replies were unmarked; the final reply was marked under point 5 that the subject did not recollect being approached and that he was unable to spare the time. Four of the six who answered the questionnaire belonged to the IC group.

Discussion

The primary intent in carrying out this investigation was to determine whether there was a predominance of mentally ill persons amongst those who refused to take part in the adoptees study (Rosenthal et al.,

Table 20

Psychiatric admissions amongst the refusal group

Refusal number	Hospital diagnosis	Group	Degree of refusal	Refusal reason	Psychiatrist's house-visit	Diagnosis
Re 8	Neurotic depressive	IC	Categorical	anxious frightened suspicious	Not seen	Suspected schizophrenic
Re 17	Psychopath	IC	No reaction	practical	Interview	Suspected schizophrenic
Re 20	Character disorder	IA	Promise	suspicious	Interview	Suspected schizophrenic
Re 25	Neurotic depressive	IA	Categorical	anxious	Interview	Outside schizophrenic spectrum
Re 32	Alcoholic	IA	Half-hearted	suspicious	Interview	Suspected schizophrenic
Re 61	Paranoid schizophrenic	IC	Categorical	no information	Not seen	Schizophrenic
Re 63	Psychopath	CF	Categorical	practical	Interview	Outside schizophrenic spectrum

1971). If this was indeed the case, there was the possibility that psychopathological deviancy would be under-represented amongst the participants: conversely, if the subject who refused to participate has a particularly strong and well-integrated personality which facilitates resistance to participation in something in which he has little or no interest, it may have been that psychopathology would be over-represented in the participant group. Additionally, the study was aimed at further determining the role of socioeconomic and demographic variables implicated by earlier studies (Scott, 1961) of participation and refusal groups.

There was no significant effect attributable to either age or sex which differentiated the refusal group from the participants. However, it was found that the refusals were less likely to be married, had fewer children, lived more frequently with parents and, in the case of male subjects, were of a lower social class. These findings if they are considered as indicative of a less well-developed social competance, which in turn reflects a poorly integrated personality structure, support the hypothesis that the refusal subject differs markedly from the person who takes part in psychological experiments. Nevertheless, there was no indication that the refusal group had more previous "unfortunate" experiences with official organizations which may have led them to resist approaches from a scientific institution. Registered criminality was not significantly higher in the refusal group, nor was there evidence that female refusals had more contact with the Mothers' Aid Agency. The percentage (approximately 10%) of refusal subjects who had been admitted to psychiatric institutions was similar to that found in the participant group.

The evidence from the psychiatrist's interview procedure showed that a similar percentage (27%) of refusals to participants (25%) were placed diagnostically within the schizophrenia spectrum. In the case of the two largest subgroups (IA and IC) there was no difference between refusals and participants with respect to inclusion within the spectrum. To this extent, it may be concluded that schizophrenic psychopathology was correctly represented in the original adoptee sample. Mention has been made earlier of the differences between the formal interview situation and that encountered by the visiting psychiatrist; however, both psychiatrists (participant and refusal) were unaware of each individual's genetic group, and since they knew that

the study was of schizophrenia it is likely that both were equally receptive to possible psychopathological indicants of the disorder. The diagnostic information available to the participant psychiatrist was considerably more systematic since it was obtained under more uniform investigative conditions.

Out of some 200 house-visits made by the psychiatrist approximately half resulted in a refusal subject being interviewed. More than 80% of the subjects were contacted after three visits to the home. Efforts to contact the remaining 20% cost a total of 120 home visits. Twenty of these final twenty-seven refusals were not contacted despite the fact that the psychiatrists made at least five visits to their address. It is evident that the refusals represent a "hard core" group since most of them were subjected to massive and repeated attempts at persuasion to participate, which included the offer of compensation for financial loss and an honorarium to offset other difficulties caused by taking part in the study.

Ethical problems occassioned by the contact and follow-up procedure were evident at both the planning and data-collection stage. It can be argued that a personal repeated and clear rejection to participate ought to be respected without question since a subject might have strong reasons, both realistic and in some instances psychopathological, for not allowing a psychiatric interview. For certain poorly integrated individuals the psychiatric interview cannot be considered as a matter-of-fact experience. In an attempt to minimize this effect the psychiatrist was extremely reticent in his attempts at persuasion in the open doorway: to a degree, there is some surety that an interview was not forced upon subjects who through shyness or insecurity were not capable of maintaining their resistance when in a face-to-face situation with a physician.

The extent to which the procedure, which involved repeated attempts at contact over several years, could be construed by an individual as a particular form of persecution can be illustrated by the fact that there was only one instance where this was maintained by a subject's spouse. Additionally, there was no case of a complaint being made to the hospital or civil authorities. Since subjects were contacted repeatedly there was a possibility that it may have become clear to some that they had not been chosen for the reasons originally stated: subjects in the IA group were (and naturally should continue to be) ignorant of their genetic loading.

Despite the difficulties inherent in the investigation, it is considered defensible in that those subjects who were thought to take their initial refusal seriously would have few qualms in slamming the door shut on the visiting psychiatrist – this proved to be the case. In addition, the psychiatrist when he was face-to-face with the subject was able not only to clear up possible misunderstandings but he was also able to apologize when this was justified.

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