ABSTRACT
        Reported is a research program to observe children at
high risk for schizophrenia and explore possibilities of prevention.
Characteristics of the high risk group (n=207) observed during 1962
are discussed, and a theory which suggests that schizophrenia is an
evasion of life is explained. Among results of a diagnostic
assessment conducted 10 years later with high and low risk samples
(20 to 30 years old) were that all of the mothers of the high-risk Ss
were seriously schizophrenic, that the birth of the schizophrenic
group was relatively difficult; and that ANS (autonomic nervous
system) recovery rate was found to predict very well to later
schizophrenia. Separate analyses were conducted for male and female
high risk individuals to examine the effects of seriousness of
illness of the mother, separation from parents during early life,
pregnancy and birth complications, and ANS recovery and
responsiveness on development of schizophrenia. Some tentative
reflections regarding sex related findings are offered. It is
concluded that the form which schizophrenia takes in men and women
may be different along with withdrawal-activity dimenison and that
these differences may be related to the hypothesized role of ANS
factors in the learning of avoidance-withdrawal. Tables and charts
with statistical data are provided. (SBH)

Preliminary Draft

Schizophrenia in High-Risk Children:

Sex Differences in Predisposing Factors[1]

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In a letter to Lancet, Gruenberg (1976) has called
attention to some unforeseen consequences of the healing
profession's increasingly sophisticated technology of treat-
ment. Progress in our capability of maintaining life and
treating disease has actually produced an increase in the
population of the chronically ill. This has, in turn, in-
creased the general level of desperateness of need for
treatment in the population. The response to this despe-
rateness has been an increased emphasis on treatment-
technology research. In this paper we will argue that in
order to reduce human suffering, some increasing propor-
tion of society's resources should be devoted to prevention-
related research.

The emphasis on prevention will be critically impor-
tant no matter what the ultimate causes of mental illness
may be. If the causes are biochemical or neurophysiologi-
cal deviance, these may prove to be irreversible; what is
even more likely, however, is that the learned reactions
to any biological inadequacy or environmental perversion
may become a fixed habit by the time the condition is well-
established and recognized. These fixed habits may be
rather resistant to treatment even if the original cause
is removed. These considerations, plus the difficulties
in interpretation of research with patients already schi-
zophrenic, (Mednick and McNeil, 1968) resulted in the em-
phasis of our research on efforts in prevention.

The overall high risk-
intervention research plan

From the beginning it was clear that preventive inter-
ventions would very likely be, at least psychologically,
invasive or intrusive. That is, they would demand time
and investment from the subject-participants. (In contrast
to preventive methods such as fluoridation of the water
supply.) A consequence of this is that one could not plan
or total population efforts in prevention such as the
smallpox or polio vaccines. The research strategy would
have to begin with the identification of individuals at
especially high risk for psychiatric conditions, and the
enlisting of their co-operation in research on prevention.
In this manner the interventions will be offered only to
those with the greatest need.

This research program was first proposed in 1960. At
that point it was planned "to test and interview a group
of normal children in the Detroit area. From these tests
and interviews we shall predict which of these children will
become schizophrenic..... We have decided to select a group
in which the prevalence rates are considerably elevated....
individuals who have one or two parents who have been schi-
zophrenic. If our predictions prove to be supported, we
are then in a position to do research which is aimed at the
prevention of schizophrenia. We might observe a normal
population with our tests, detect those individuals who

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are potential schizophrenics and then explore the possibilities of intervention." (Mednick, 1960, page 69.)

In accordance with this overall plan, in 1962 we intensively examined a group of 207 children at high-risk for schizophrenia. (They have schizophrenic mothers.) We also examined 104 control subjects. We followed this group until 1967 when 20 of them evidenced a variety of psychiatric breakdowns. In good agreement with the general theory guiding this research, an autonomic nervous system (ANS) variable, (fast recovery rate) proved to be the best discriminator of the breakdown subjects from their carefully chosen high-risk and low-risk controls. We then took this "best discriminator" to Mauritius where we examined the ANS functioning of all of the three-year old children in two communities (1,800 children). In accordance with our theoretical position (Mednick, 1958; Mednick and Schulsinger, 1973) we selected out the 6% of the 1,800 (108 children) who evidenced the fastest recovery and greatest responsiveness in the population. Half of these individuals, along with controls, were then placed in specially established and organized nursery schools. The other 54 children were considered community controls, and were only identified in our files. (For the first description of this project see Schulsinger, et al, 1975.) In a companion paper (with Peter H. Venables as first author) we shall pick up the thread of the prevention project in Mauritius and relate the promising outcomes observed.

The 20 breakdowns in 1967 ranged from schizophrenia to extreme schizoid states to antisocial behavior. The follow-up of the Copenhagen high-risk subjects continued in order to see whether ANS recovery and/or other variables would predict specifically to later breakdown with schizo- phrenia. The results of these follow-up activities will form the basis of this paper[2].

The Copenhagen 1962 high-risk project

A check on the psychiatric-genetics literature. When we began in Copenhagen in 1962 it was clear to us that we were perhaps relying too heavily on American and German re- ports that the probability of schizophrenia was relatively high among children with schizophrenic mothers. We en- couraged the efforts of Dr. Niels Reisby to conduct a com- parable Danish study; his finding of a 12.7% risk (correct- ed) of schizophrenia for children with schizophrenic mothers fell within the range of previous findings. From the Reisby article (1967) we noted that, by the age of 25 years, 52% of his sample of children of schizophrenic mothers had been admitted at least once to a mental hospi- tal. This fact determined the date of our clinical follow- up in 1972.

Method of procedure. In 1962 we intensively examined 207 children at high risk (HR) for schizophrenia. They have schizophrenic mothers. We also assessed 104 children

at low risk (LR) for schizophrenia. The identifying charac-
teristics of these samples are given in Table 1. Table 2

Insert Tables 1 and 2 about here

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presents the list of examination procedures. Some of the
measures which will be critical for our later remarks stem
from the interview made by a social worker with the indivi-
dual responsible for the rearing of the child. From this
interview we derived information on the social status and
the intactness of the family and retrospective comments on
the child's behavior as an infant and small child. From
the files of the Demographic Institute in Risskov and the
mother's hospitalization record we extracted information
relating to the form and seriousness of her illness.
Danish midwives attended the birth of our subject popula-
tion and prepared a written report on the pregnancy and de-
livery which we have coded. The psychophysiology examina-
tion yielded two important channels of information. One
on the heart rate response, and the other on electrodermal
responding. We shall center our discussion on the electro-
dermal behavior.

The first 20 psychiatric breakdowns. Following the
intensive examination in 1962 an alarm network was establish-
ed in Denmark, so that most hospital and all psychiatric
admissions for anyone in this sample would be reported to

us. The number of reports of serious psychiatric or social breakdowns reached 20 in 1967. Very brief summaries of their case stories are given in Table 3. We then looked

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Insert Table 3 about here
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back to our data from 1962 to find characteristics that distinguished the schizophrenia breakdown individuals from carefully matched HR and LR controls. The most important characteristics distinguishing the Sick Group from the controls are given in Table 4.

Insert Table 4 about here .

We shall call attention to a few of these characteristics. 1) The Sick Gro:p suffered considerably more early separation from their parents than the two control groups. 2) Rather than the classic textbook picture of the preschizophrenic child, the Sick Group subjects were disciplinary problems, domineering and aggressive in their classroom behavior. 3) While a number of psychophysiological variables predicted to their Sick Group status, the one which was the best discriminator was the rate of recovery from momentary states of autonomic imbalance. 4) The Sick Group evidenced considerably more pregnancy and delivery complications. An interesting sidelight with respect ot these peri-

natal events is the fact that the high-risk group which had not suffered breakdown evidenced fewer perinatal difficulties than did the low-risk control group. This suggested to us that perhaps there is a special interaction between the genetic predisposition for schizophrenia and pregnancy and delivery complications. It was almost as if in order for a HR subject to fare well, he needed a complication-free pregnancy and delivery. In the paper reporting the findings (Mednick, 1970), mention was made of the fact that there was a marked correspondence between the pregnancy and birth complications and the deviant electrodermal behavior. Almost all of the electrodermal differences between the groups could be explained by these perinatal difficulties in the Sick Group. The perinatal difficulties in the LR group were not as strongly associated with these extreme electrodermal effects. This further suggested that the pregnancy and delivery complications trigger some characteristics that may be genetically predisposed.

A theory of schizophrenia

This theory was first stated in 1958 (Mednick, 1958). A clinical formulation of the theory was stated in 1962 (Mednick, 1962). Schizophrenia is seen as an evasion of life. It is suggested that the syndrome of schizophrenia is learned on the basis of physiological predispositions, and that this learning takes place very gradually over a period of many years. The hypothesized physiological apti-

tudes are very fast ANS recovery and ANS hyperresponsive-
ness.

The essence of this theoretical approach suggest that
schizophrenia is a learned evasion of life. To understand
the role of the ANS variables in this learned evasion we
must first clarify our view of avoidance learning. Studies
of avoidance learning have been conducted mostly with rats
and mostly in shuttle boxes. The rat is first placed in
compartment A; a bell rings and 10 seconds later the floor
of compartment A is electrified. The rat leaps up, runs
around, deficates, urinates, and eventually runs into com-
partment B and safety. After about 10 trials the average
rat will learn to avoid the shock by running into B at the
sound of the bell. Some rats learn this quickly, and some
rats learn this extremely slowly. What factors might be
important in the speed with which a rat learns this avoidance
response? Our analyses of this situation are related to
that presented by Mowrer (1960). One critical factor is
that the rat must have a response of fear to the shock and
must be capable of learning to transfer this fear response
to the bell. The greater the fear, the faster his learning
to avoid the shock. Another critical factor which perhaps
is a bit less obvious is that when the rat runs into the
safe compartment B, his avoidance response is rewarded by
fear reduction. The value of a reward is directly related
to its speed of delivery and to its magnitude. The faster
and the greater the reduction of fear, the greater the re-

ward value. In the case of the rat in the shuttle box,
the rate at which this fear is reduced depends almost com-
pletely on the rate at which his ANS recovers from a fear
state to a normal level. The faster the rate of autonomic
recovery, the faster the delivery of the reinforcement
and the greater the reinforcement. If the rat recovers
very slowly, then his avoidance response will not be re-
warded very quickly, or with any great magnitude when he
enters the safe compartment B. If, on the other hand, the
rat has abnormally fast ANS recovery, his reinforcement
will come abnormally quickly, and he will learn this type
of avoidance response quickly. Thus, we have named two
factors which are relatively independent (Lockhart and
Lieberman, 1976) and which will help to determine the rate
at which the rat will learn the avoidance response......
1. level of ANS responsiveness, 2. rate of ANS recovery.

These two factors then will function as _aptitudes_ for
learning avoidance responses, in some ways anologous to the
role of nimble fingers and absolute pitch in providing ap-
titudes for learning to play the violin.

Learning avoidant thinking. Running away is not the
only form that an avoidance respons' can take. A human
can learn to avoid threatening stimulation by simply think-
ing irrelevant thoughts. These irrelevant thoughts will,
at least partly, remove him from a fear-producing stimulus.
If he has fast ANS recovery and is highly responsive, the

avoidant thoughts will be richly rewarded and will increase
in their probability of being elicited in the presence of
anxiety. Other more complex and even more bizarre responses
may be learned to avoid threatening or unpleasant ANS sti-
mulation. Clinicians have shared the experience of ap-
proaching a chronic schizophrenic on the hospital grounds
and precipitating a display of bizarre symptoms by simply
saying "good morning". Note that if the environment does
not elicit these ANS responses, or if the ANS responses
are not threatening or unpleasant, avoidance learning will
not occur.

Beginning in childhood and through adolescence an in-
dividual with a highly responsive and fast recovering ANS
will have a tendency to learn more and more of these avoidant
responses if he is faced with unkind environments. One of
the critical life consequences for such an individual is
the fact that <u>this avoidance-learning will obviate the need</u>,
<u>and thus the possibility, for him to learn more positive,</u>
<u>"normal" manners of dealing with life's vicissitudes</u>. It
is perhaps this isolation from the experience of direct
dealings with "life" which is responsible for the social
helplessness and inappropriateness of the adolescent and
adult schizophrenic.

The theory then suggests that the combination of an
ANS that responds too often and too much and an abnormally
fast rate of autonomic recovery provide an aptitude for

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learning avoidance responses. If an individual is to be-
come schizophrenic, he must possess both the ANS respon-
siveness and recovery characteristics. If an individual
is rapidly, exaggeratedly and untiringly emotionally reac-
tive, he may become anxious or ~ve   ~ychotic, but will
not tend to learn schizophren   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 rate of recovery
will only require moderate reactiveness. Both very high
reactiveness and very fast recovery will result in a very
heavy predisposition for avoidance learning and hence for
schizophrenia.

Diagnostic Assessment, 1972

The Reisby study (1967) gave us reason to expect that
at the average age of 25 years, we should expect to be able
to diagnose approximately half of the eventual schizophre-
nics in the high-risk group. Thus, we initiated an inten-
sive assessment of the high and low-risk samples in 1972
when they reached an average age of 25.1 years. (They
ranged between 20 and 30 years of age.) The central goal
of this re-assessment was the establishment of a reliable
diagnosis and an evaluation of their current life status.

Method of procedure. The 1972 assessment consisted
of psychophysiological and cognitive tests, a social inter-

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view, and, most importantly, a battery of diagnostic de-
vices. The diagnostic devices included a 3 1/4 hour cli-
nical interview by an experienced diagnostician (H.S.), a
full MMPI and the psychiatric hospitalization diagnoses and
records where they existed. The diagnostic interviewer com-
pleted the Endicott and Spitzer Current and Past Psycho-
pathology Scales (CAPPS, 1972) and the Present Status Exa-
mination, 9th edition (PSE), (Wing, Cooper and Sartorius,
1974). The interview itself was structured as a clinical
procedure and not as a questionnaire.

The coded PSE and CAPPS materials were sent to New
York and London respectively; computer diagnoses were
returned. Table 5 presents information on the results of
our follow-up contacts with the subjects. Ten of the high-

Insert Table 5 about here

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risk subjects have died in the course of the follow-up,
seven by suicide, two by accidental causes, and one by
natural cause. None of the low-risk subjects have died.
This is a dramatic difference which we shall explore fur-
ther in future papers. Of the ten, six died before the
assessment began; three of the other four took part in the
assessment. Thus, of the 201 high-risk subjects available
for the assessment, 91% took some part in the interview
(10 only had a home interview by the social worker). Of

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the low-risk subjects 91 took part in the full interview,
six took part in the home interview. Thus, 93% of the
low-risk group has taken some part in the interview. Sub-
jects are still trickling in for the assessment.

Insert Table 6 about here

Table 6 presents identifying information on those who
completed the full interview. The groups seemed to be
well-matched with each other and with the total original
sample with respect to age, sex, and social class.

Reliability of the diagnosis. The diagnosis of schi-
zophrenia made by the interviewer is based on the presence
of Bleuler's primary symptoms: thought disorder, autism,
ambivalence, and emotional blunting as well as Bleuler's
secondary symptoms: delusions and hallucinations. For a
diagnosis of schizophrenia it was not necessary that all
of these symptoms were observed at the time of the inter-
view; they might also be drawn from the case history. In
two separate papers (Mednick, et al, 1975; Schulsinger,
1976) detailed descriptions of the tests of the reliability
of the diagnoses have been reported. For our purposes
here, it is sufficient to say that across the two computer-
derived diagnoses, the MMPI (analysed blindly by Professor
Irving Gottesman) and the clinical diagnosis as well as an
indenpendent diagnosis arrived at by two Danish psychiatrists [4]

listening to the audiotape of the entire interview for ten
subjects, rather excellent diagnostic agreement was achiev-
ed.

The interview was, in part, coded in the form of a
rather extensive series of questions. A very significant
portion of these questions refer to symptoms of mental ill-
ness. It is interesting that one of the Danish psychiatrists
listening to the audiotapes of these interviews had almost
perfect agreement with the interviewer's codings of the
CAPPS items. The codes for these items range from 1 to 6.
In 91% of the items his coding was no more than one unit
different.

Another indication of the reliability of the coding
and diagnoses may be found in the two important measures
of severity of illness resulting from the interview. At
the conclusion of the CAPPS interview form, the interviewer
is required to rate the severity of illness on a scale
from one to six. Ratings of five and six only occured for
those who were diagnosed schizophrenic. This rating cor-
related .70 with a rating of severity derived from the PSE.

Results of 1972 assessment

Distinguishing premorbid characteristics of those diagnos-
ed schizophrenic

The interviewer diagnosed 13 schizophrenics in the
high-risk group[6] In a previous publication we have com-
pared these 13 schizophrenics with 29 borderline schizo-
phrenics, 34 neurotics, and 23 high-risk subjects with no
mental illness. This report (Mednick, et al, 1975) sugg.st-
ed that these high-risk subjects who became schizophrenic
were characterized by the following factors:

1. All of the mothers of the high-risk subjects were
seriously schizophrenic. The mothers of the children who
became schizophrenic, developed their illness at a younger
age.

2. Most of the 13 schizophrenics had been separated
from their mother and father and many placed in children's
homes quite early in their lives. This stands in sharp
contrast to the patterns in the other diagnostic groups.

3. The birth of the schizophrenic group was relative-
ly difficult. The period of labour was longer and charac-
terized by more complications.

4. The rearing social class of the schizophrenic
group was not noticeably different from that of the other
groups.

5. The school teachers reported that the schizophre-
nics were extremely disturbing to the class, evidenced in-

appropriate behavior, were easily angered, and violent and aggressive. They posed a disciplinary problem for the teacher.

6. ANS recovery rate (measured in 1962) was found to predict very well to later schizophrenia (Mednick, in press) and especially well to individuals suffering symptoms of hallucinations and delusions and thought disorder.

Sex differences in factors
predisposing to schizophrenia

In considering these preliminary reports one factor seemed extremely striking. We were sensitized to this factor by a dissertation completed by Dr. Helen Orvaschel (at the New School for Social Research, 1976) on sex differences in high-risk children. Almost all of the findings we have listed above have been cited in the literature as being especially responsive to sex differences in schizophrenics. Gardner (1967) and Sobel (1961) have reported that the degree of mother's illness, for example, effects the level of schizophrenia in females, but not in males.

Rosenthal (1962) has commented on the higher concordance for female monozygotic schizophrenics than for males. Male discordance in monozygotic twins with schizophrenia is twice as great as for females. While there are some sampling problems in these twin studies, such information might

suggest that schizophrenia in females is more genetically
determined, and that schizophrenia in males has a heavier
environmental weight.

With respect to the pregnancy and delivery complica-
tions, in our more recent high-risk study especially study-
ing perinatal factors (Mednick, et al, 1972) we have found
differential sex effects of perinatal complications. It
is also well known that males are more vulnerable to preg-
nancy and delivery difficulties. Finally, aggressive school
behavior has been shown by Watt, et al (1970) to be asso-
ciated with later schizophrenia in men, but not women.

In view of the fact that almost all of the findings
reported in the two preliminary reports mentioned above are
highly sex dependent, we determined to conduct separate
analyses of these variables for males and females.

Hypotheses to be examined. The analysis of the factors
potentially predispositional to schizophrenia were conduct-
ed separately for male and female HR individuals. It was
hypothesized that:

1. The seriousness of illness of the mother (as in-
dicated by early onset) would be of significance for both
sexes, but would be more important for women.

2. Separation from parents during early life would

be important for both sexes.

3. <u>Pregnancy</u> and <u>birth</u> <u>complications</u> would increase
the probability of the development of schizophrenia in both
sexes. Because of the male foetus' greater vulnerability
to perinatal stress, we hypothesized greater effects for
males than females.

4. <u>ANS</u> <u>recovery</u> and <u>responsiveness</u> would be involved
in the development of schizophrenia.

In summary, we hypothesized that for female HR indi-
viduals the development of schizophrenia would be especial-
ly related to early onset of the schizophrenic mother's
illness. In males we hypothesized that the perinatal
variables would be especially predictive. In both sexes
ANS factors and early separation were hypothesized as pre-
dispositional to schizophrenia.

Method of statistical analysis:
path analysis

While a practical goal of this statistical analysis
is to develop identifying characteristics of children who
will later become schizophrenic, an underlying hope is pro-
gress toward an understanding of the etiology of schizophre-
nia. The problem is one of causation. Because we are
barred in studies of the etiology of schizophrenia from

making use of the experimental-manipulative approach, it
has been impossible for researchers in the field of schizo-
phrenia to pretend to such causal statements. As Simon
(1954), quoting Hume, has asserted, all we can ever observe
is co-variation. Certainly for research in a naturalistic
setting (such as this longitudinal project) this point
must remain unchallenged.

Methods have been developed, howeve., in the field of
genetics and later used extensively in the field of econo-
mics which allow for hypothesized causal models to be
stated in mathematical form in a way that allows their
agreement with observed co-variances to be examined. So
while we can never completely validate or prove a "causal"
statement, we can examine its expected consequences by
examining the goodness-of-fit of hypothesized co-variances
(i.e., generated under a hypothesized model) to observed
co-variances.

In this analysis we are operating with variables which
span the lifetimes of the individuals involved. We begin
with the seriousness of the schizophrenia of the mother,
examine perinatal factors, consider the intactness of their
homes, see all this in the light of their socioeconomic
status during rearing, the functioning of their autonomic
nervous system and their sex. We know that many of these
independent variables are intercorrelated. For example,
the earlier the onset of illness of the mother, the more

separation from the mother the child experiences. Other, less obvious, intercorrelations also exist in these data. Therefore, multiple analyses of individual independent variables in relationship to the dependent variable, schizophrenia, run the risk of repeatedly/a single or few common findings. Therefore, we chose a model in which all of the interrelationships are estimated simultaneously and all other intercorrelations are taken into consideration. We also foresaw the possible problems inherent in mediated effects. Thus, the seriousness of illness of the mother might not have any direct effects on her child's development of schizophrenia, but may have its effect mediated by the resulting disruption of the child's home life. We chose a statistical technique which could estimate both the direct and the mediated effects, i.e., Jöreskog's (1972) maximum likelihood estimation procedure for structural equations (LISREL). LISREL is a special case of Jöreskog's earlier analysis of co-variance structures (Jöreskog, 1970) and is an advanced form of path analysis. It is a statistical tool which has great advantages for the analysis of data from longitudinal projects.

Definition of constructs. In the Jöreskog LISREL path analysis important factors are represented as constructs. The constructs are not directly measured, but are defined by indicators. These indicators of a construct go through a process which may be seen as roughly analogous[++++] to the development of communalities in factor analysis.

These "communalities" then represent the construct. Rather than relate the individual, and relatively unreliable, indicators to one another; the constructs are interrelated. This serves to reduce some of the lack of reliability inherent in any individual indicator of a construct. For example, as indicators of the construct "separation from parents" (separation) in the first five years of life, we used three indicators from the first five years of life: 1) amount of separation from the father, 2) amount of separation from the mother, and 3) amount of time the child spent in children's homes. For the construct "age of onset of mother's schizophrenia" (mother's onset) we used two indicators: 1) age of first appearance of symptoms, 2) age at first psychiatric hospitalization. Thus, when we are interrelating separation and mother's onset we are interrelating two construct rather than individual indicators.

The indicators of the constructs. Table 7 lists the constructs and their indicators. Certain of the constructs may require explanation.

Insert Table 7 about here

Age of onset of mother's schizophrenia (mother's onset). Age of onset of schizophrenia is a rather good indicator of the seriousness of the condition. The mother's age at the beginning of symptoms was taken from her hospital case

record. Her age at first hospital admission was taken from
the Risskov Demographic Institute's Psychiatric Register.

Pregnancy and birth complications (PBCs). The scale
has been described in previous publications (Mednick, 1970;
Mirdal, et al, 1974). It is based on weights assigned by
obstetricians and pediatricians to the various pregnancy
and delivery complications noted by Danish midwives in
their reports.

ANS (recovery x responsiveness). In the above dis-
cussions of the theory we have indicated that if an indi-
viduals is relatively autonomically unresponsive, fast re-
covery will be that much less of an aptitude for avoidance
learning. Conversely, a highly sensitive ANS will not lead
to schizophrenia if not associated with fast recovery.
Thus, the theory specifies an interaction effect which can
be most simply expressed mathematically, in a single score,
as a product of recovery rate and responsiveness. "Respon-
siveness" was taken as the percent of measurable responses
in the entire 1962 electrodermal examination. Mean recovery
rates were taken from conditioning, tests for conditioning
and extinction testing. The distribution of recovery rates
in the high-risk group evidenced kurtosis. This was due
to a small group of the most schizophrenic high-risk sub-
jects who had the very fastest recovery rates. These out-
lyers (who will be the subject of special study) resulted
in highly exaggerated correlations between recovery rate

and the outcome variables (such as hallucinations and de-
lusions). Before producing the recovery-responsiveness
products we transformed the recovery rates by a square
root transformation which reduced kurtosis to an acceptable
level. The intercorrelations of recovery rates and the
three product scores were .90, .86 and .92; the intercor-
relations of the percent resposnes with the three product
scores were .73, .70, .68.

Schizophrenia in the high-risk children. The diagno-
stic interview took about three-and-one-quarter hours and
consisted of a rather extensive series of symptom descrip-
tor items. These items were subjected to factor analyses
which yielded (among others) four factors which described
the schizophrenia symptoms of the high-risk children (see
Table 8). The four factors were named 1) hallucinations

Insert Table 8 about here

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and delusions, 2) "hebephrenic" features, 3) thought dis-
order, and 4) autistic features.

Results of path analysis

We shall express the results of the path analysis in
two ways. First by means of path diagrams we shall pre-
sent the significant direct effects, then by means of bar

graphs we shall consider the sum of the direct and in-
direct effects of the hypothesized predispositional variables
on the outcome, schizophrenia.

Path diagrams. Figure 1 presents the path diagram
for men. Significant path coefficients (and their proba-

Insert Figure 1 about here

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bility levels) are indicated. Note that "PBC"s have no
direct effect on "schizophrenia; its effect is mediated by
the ANS construct. Childhood separation and the ANS con-
struct are directly related to later schizophrenia in high-
risk men, as hypothesized. Also as hypothesized, the ANS
factors are rather well predicted by PBCs. Childhood se-
paration is predicted by an early age of onset of the
mother's schizophrenia which does not evidence a direct re-
lation to schizophrenia.

The LISREL computer program calculates a multiple r
of .62 for the prediction of schizophrenia by these pre-
dispositional variables for the high-risk men.

Figure 2 presents the path diagram for the women. In
this path diagram the only construct which is significantly
directly related to the development of schizophrenia is
the age of onset of the mother's schizophrenia. The pat-

Insert Figure 2 about here

tern for the women is quite different from that seen in
Figure 1 for men. The ANS construct (a reliable predictor
for men) is not significantly related to schizophrenia in
women, nor is childhood separation. Comparison of the path
diagrams strongly suggests that some aspects of the etiolo-
gy of schizophrenia are quite different in high-risk men
and women. The multiple r for the prediction of schizo-
phrenia for women is .49.

Direct and indirect effects. Before leaving the path
diagrams, note that in these reported relationships social
economic status (SES) is included and consequently held
constant. SES has no direct, significant relationship with
the construct schizophrenia. It does, however, influence
schizophrenia via the mother's age of onset (in men and,
women) and amount of childhood separation (in the case of
the men). The indirect effect of SES on schizophrenia via
separation may be calculat' by simply multiplying the two
relevant path coefficients (.26 x .40), yielding an indi-
rect effect of .104. Note that we have earlier observed
a similar interaction of social class and separation ex-
perience in relation to breakdown (Stern, et al, 1974).

By adding the direct and indirect effects onto schi-
zophrenia, the total effect of each construct in this path

diagram can be calculated. Figure 3 presents a bar graph

Insert Figure 3 about here

---

depicting the total direct and indirect effects of each of
the constructs on the construct schizophrenia.

Discussion of path analysis results

From the lives of our high-risk subject we have
chosen a small group of childhood variables to explore
their relationship to the subject's current diagnosis of
schizophrenia. These early factors seem to relate to the
development of schizophrenia quite differently for men and
women.

In interpretting these results we must keep in mind
the fact that for women, schizophrenia tends to have a
later onset (greater incidence for women of the age of 35,
Yolles and Kramer, 1969). This assessment took place when
the subjects ranged from 20-30 years of age; the results
for the later-onset women may be different.

Aside from this age factor we cannot suggest other
serious reservations regarding these findings. Perhaps,
in some cases, the 1972 interviewer learned about the se-
paration factor (and even something about the mother's age

of onset) while talking to the subjects. It seems rather

unlikely. however, that this would affect her coding of

the schizophrenia symptoms listed in Table 7. It seems

even more unlikely that her ratings would be influenced

differently for men and women. At the time of the inter-

view (and in fact to date) the interviewer was totally

blind regarding the perinatal and psychophysiological data.

It should perhaps also be pointed out that at the time

these early variables were recorded, there was no informa-

tion available regarding who, among the high-risk subjects,

would become schizophrenic.

It does not seem overly imprudent to begin to accept

the possibility that these four factors have some relation-

ship to the development of schizophrenia in these high-risk

individuals. The interpretation of the meaning of these

results, some of which were rather unexpected, may be less

straightforward.

Early detection

Our initial aim is the identification of factors which

might be useful in the early detection of individuals in

the general population who are at high risk for schizophre-

nia. With respect to this aim, these four early factors

are worthy of some consideration and testing. However, it

should be pointed out that we have only demonstrated that

they predict reliably within a group of children born to

schizophrenic women. The level of separation from the
parents experienced by these children is unusually high.
In a general population, this factor may not account for
as high a proportion of the variance as it does for these
high-risk families. The variable, age of onset of the
mother's schizophrenia, is also not generally and directly
applicable to population studies. Perhaps when we under-
stand better what role mother's early onset plays in their
daughter's schizophrenia, some hypotheses regarding pre-
dictive measures may be suggested.

The ANS construct (the product of recovery and respon-
siveness) is an individual measure which is more promising
for utilization in early detection in general populations.
It has been a central variable in the theoretical frame-
work of our research for the past 20 years. It predicted
quite well the 1967 psychiatric breakdowns; almost all
published studies with schizophrenics (with one exception,
Maricq and Edelberg, 1975) have supported the hypothesis
of faster ANS recovery for schizophrenics (see Mednick,
in press; Mednick, et al, 1975). Interestingly enough,
almost all of these studies have been carried out on **male**
schizophrenics. Our path analysis suggests that these re-
ported results would not replicate with female schizophre-
nics. One of us, in informal attempts, (P.H.V.) has re-
peatedly failed to find ANS differences between female
controls and female schizophrenics. The ANS measures
would seem to be a useful addition to an assessment of risk

in a male general population.

These ANS results also support our reliance on fast
ANS recovery and responsiveness for selection of the high-
risk three-year olds in Mauritius. These sex-specific ANS
results will now send us back to our Mauritius data to at-
tempt to find analogous relationships.

Interpretation of findings

It is the fate of longitudinal researchers to continual-
ly be presenting interim results. Now we must await the
next wave of schizophrenic breakdowns as we have indicated
above. In addition to these inexorable developments and
changes in our subjects over the years, we also face the
problem of analysing literally lifetimes of data. In our
case we are slowly and more or less systematically (but
certainly slowly) analysing the individual and life-event
factors related to the outcome, schizophrenia. This is an
analysis which is very much in progress. Thus, this report
port must be understood as interim also for this reason.
We now will attempt to transmit to you our reflections on
the meaning of these results. These reflections will sug-
gest our strategy for future data analyses. We present
these reflections very tentatively for each of the early
factors which were shown to relate to the construct, schi-
zophrenia.

Mother's age of onset.: Figure 3 depicts the direct and indirect effects of mother's age of onset on the construct of schizophrenia for both men and women. Note that while there is a strong tendency for "onset" to relate to schizophrenia in the males, the relationship is almost completely mediated by "separation". Sons of "early-onset" women have an especially heightened risk of themselves becoming schizophrenic. This relationship seems to be almost completely explained by the separation from parents which follows the mother's early onset of illness.

In the women, the "onset" variable also has an important relationship to later schizophrenia. However, in the case of the women the indirect effects are negligible. This simply means that either the effect is actually only direct, or that the critical mediators were not included in this path analysis. We examined correlation matrices including some early childhood variables and "onset" for the male and female high-risk children. Early onset of the mother's illness is associated mildly and significantly with the girls evidencing low verbal IQ, disturbed and peculiar word associations and continual associations, and adult thought disorder. Curiously enough, in males none of these relationships are observed. For the males,

mother's early onset is better related to adult charac-
teristics associated with a diagnosis of "psychopathy".

Some tentative reflections

1. Perhaps the seriously ill mother is genetically
transferring some language deviation to their daughters
and not to their sons. This sex-linked transmission is,
of course, a possibility which we must contrast with an
identification-learning hypothesis. We must relate the
seriousness of the daughter's illness to the amount of
contact she had with her mother. The course of illness
for the HR parents and their children is currently being
compared in a doctoral dissertation by Ms. Shelley
Kramer-Dover.

2. The earlier development of language behavior in
girls than in boys, and the fact that girls tend more to
identify with their mothers may combine to differentially
influence the associative and verbal responses of daughters
of severely schizophrenic women. Maccoby and Jacklin (1974)
suggest that this childhood advantage of girls in the ac-
quisition of language behavior probably exists only before
the age of three. In future analyses this suggestion may
help us to pinpoint possible critical periods of develop-
ment for further intensive analysis. Careful analysis of
our case files should enable us to estimate the amount and
closeness of the contact between the mothers and their

children at various age levels as well as the relation be-
tween the child's age at the time of mother's breakdown
and the child's adult diagnostic status.

3.   It is also possible that the more seriously schi-
zophrenic mothers pass on some specific characteristic to
both their daughters and their sons.   But perhaps this.
characteristic predisposes to schizophrenia only in the
daughter because of differences in the manner in which
society deals with the two sexes.   We shall return to this
thought when we discuss the ANS construct.

4.   In male, high-risk children, "onset" is not di-
rectly related to schizophrenia.   As mentioned, inspection
of the case material for the boys indicates that for them,
"mother's early-onset" is significantly associated with
adult symptoms of psychopathy.   We know that the schizo-
phrenic mothers (in this sample) tend to mate with crimi-
nal men (Kirkegaard-Sørensen and Mednick, 1976; see also
Lewis, 1976).   We intend to examine the possibility that
for the most early-onset schizophrenic women this tendency
is even stronger.   If this is true, it might explain the
heightened psychopathy of the sons who have early-onset
mothers (Schulsinger, 1972; Hutchings and Mednick, 1974).
It might also suggest hypotheses regarding the mother-
daughter findings.

Separation in childhood (0-5 years).   Early separation

from parents is highly and significantly related to later /

schizophrenia for male, but not for female, high-risk

children. The path coefficient for the females is in the

same direction as for the males, but not statistically sig--

nificant. Differences between the girls and boys in <u>amount</u>

of separation are minimal and not statistically significant.

1. The amount of separation experienced by the boys
(but not the girls) is related negatively to their social

class status. It is possible this social class factor may

mean that the treatment of boys separated from their parents

is of a different (poorer) quality than than the treatment

of girls. We shall attempt some modest examination of

this possibility by interviewing individuals who worked in

these children's homes in the 40's and 50's. We must also

check to see whether reasons for selection of children to

be placed in children's homes are different for the two

sexes. We do have some suggestive evidence, for a subsample

of the HR group, that children's home placement is partly

dependent on pre-placement infant characteristics (Herrmann,

1973).

2. Perhaps the reason early separation is a more im-

portant variable for boys than girls is that boys experience

more "separation anxiety". While the research evidence on

this issue is far from unequivocal, Maccoby and Jacklin

(1974) suggest that where sex differences exist "boys cry

more when the mother or father leaves the room; and at the

early age of 9-10 months they are more likely to crawl
quickly after the mother if she moves into an adjacent
room" (page 196). Perhaps the boys in this study (because
of their sex-linked immaturity) did suffer a stronger se-
paration reaction than did the girls. This may have, in
some way, been involved in the chain of events leading to
their eventual schizophrenia. Unfortunately, our longi-
tudinal project does not contain reliable data concerning
the children's reactions to their separation from their
parents. The high ANS reactiveness of the boys who even-
tually became schizophrenic could suggest that separation
from their parents may have produced a relatively strong
emotional reaction.

PBC factors. The high-risk boys suffered slightly
more serious and a greater number of perinatal complica-
tions than the girls (not statistically significant).
This direction of results is in keeping with our expecta-
tions. For boys there is a large significant relationship
between PBCs and later schizophrenia (Figure 3). The re-
lationship for the girls is actually negative (not statis-
tically significant). For the boys, most of the PBC-schizo-
phrenia relationship is mediated by ANS-schizophrenic re-
lationship which is not found in the girls.

There is evidence that females' electrodermal respon-
siveness is related to their menstrual cycle (Bell, et al,
1975). One could suggest the hypothesis that the lack of

a relationship between ANS factors and schizophrenia for
the females is due to a menstrual cycle-related lack of
reliability of the ANS measures in the females. (We fail-
ed to note menstrual data in 1962.) Note, however, that
the PBC-ANS relationship is at least as strong in the fe-
males as it is in the males. It is unlikely that this
would be true, unless the females' ANS responsiveness
was as reliable as the males'. ANS reactiveness and re-
covery are reliably related to PBCs in the girls, but
this increased reactiveness is not associated with an in-
creased risk of schizophrenia.

‐ANS factors. We have observed unexpected sex dif-
ference in the effect of the ANS factor on schizophrenia.
These differences are puzzling; we offer some observations
related to sex-differences in ANS-relevant emotional be-
havior.

What are the nature of sex-differences-related emotional
reactiveness?

Maccoby and Jacklin (1974) suggest that if there are
sex differences in amount of emotionality, they are very
small. The self-reported lower fearfulness of boys is al-
most certainly explained by their unwillingness to admit
their fears and anxieties. Boys are much more defensive
than girls. For a boy to admit emotionality, is to admit
a weakness and to risk being called a "sissy". Girls "are

simply more willing than boys to admit that they feel an-
xious" (Maccoby and Jacklin, 1974, page 186). It is not
unfeminine to admit being afraid. Boys conceal and avoid
such emotions more than girls do. Under some conditions
and in some social circumstances, emotionality in women
may be seen as a positive, feminine attribute. In males
it is often regarded with considerable suspicion; it is
not masculine.

Little girls are freer to express fear and to cry
when disappointed without being judged a sex-role deviant.
"Parents show considerable more concern over a boy being
a "sissy" than over a girl being a tomboy" (Maccoby and
Jacklin, 1974, page 362). Perhaps girls have less need
than boys to avoid expressing fear or anxiety. In that
case perhaps little girls need not learn deviant ways of
thinking and behaving to avoid emotional expression.

Little boys tend to learn that they must avoid emo-
tional expression. The little boy who has an extremely re-
active ANS may often be pushed by parents, guardians,
teachers, and peers to suppress this emotionality. Thus,
any response (such as irrelevant thought or bizarre be-
havior) which will avoid an encounter with a potentially
emotion-provoking stimulus (such as an approaching person)
will be reinforced and quickly learned. Fast ANS recovery
will assure a relatively powerful reinforcement for such
an avoidance response and will increase its probability
3ა

of being elicited. The repetition of this learning se-
quence over the years could produce an effective screen of
avoidance behavior which will function to isolate the schi-
zophrenic and support his withdrawal. What about the fe-
male schizophrenics? This discussion implies that (not
being influenced by the ANS factors) the women should de-
velop a less withdrawn form of schizophrenia. The clinical
picture for the male schizophrenics is dominated by with-
drawal, isolation, thought disorder, and hallucinations.
The women evidence serious thought disorder, but are fre-
quently quite promiscuous and socially "active". The fact
that schizophrenic women become married three times as
often as schizophrenic men (Forrest and Hay, 1972) probab-
ly has many explanations, but in any case does testify to
less avoidant, withdrawn behavior than is the case for male
schizophrenics. Forrest and Hay (1972) express some su-
spicion regarding early onset diagnoses of schizophrenia
in women. They report that it has been their experience
(over a specific two year period) that "almost every female
patient first admitted under the age of 20 years with a
presumptive diagnosis of schizophrenia later has this diag-
nosis revised to personality disorder or manic-depressi -
illness" (page 55). This statement is probably too extreme
for most clinicians to accept.

These reflections suggest two related notions which
may repay some consideration by investigators. First, per-
haps the condition we call schizophrenia takes a different

form in men an women; second, perhaps the etiology is, in part, different for men and women.

Most investigators (including ourselves) have until now neglected to consider the possibility of sex differences in the schizophrenics. Frequently, an area of research which has almost exclusively studied male schizophrenics is reviewed (with no mention of the sex variable) and the conclusions generalized to all schizophrenics. These analyses suggest that we may explain more variance if we consider the sexes separately.

Conclusions

The presence of schizophrenia in HR women is related negatively to the age of onset of their mothers' illness. The factors of early parental separation, ANS recovery and responsiveness and perinatal complications did not relate significantly to the development of schizophrenia in these HR women.

In men the pattern is quite different. The age of onset of the mother's illness is related to schizophrenia in her son only because it produces parental separation. Parental separation relates directly to the development of schizophrenia in the HR boys. Perinatal complications in male HR children relate to their later development of schizophrenia. This apparently results in large part be-

cause the perinatal complications seem to produce ANS-
fast recovery-responsiveness effects in the HR children.
In the HR boys the ANS deviance is reliably related to the
later development of schizophrenia.

The discussion suggests that the form which schizo-
phrenia takes in men and women may be different along the
withdrawal-activity dimension (Depue, 1976; Plovnick, 1976).
These differences may be related to the hypothesized role
of ANS factors in the learning of avoidance-withdrawal.

Footnotes

[2]For those familiar with the 1962 Copenhagen high-risk project and its theoretical basis, it might be less boring for them if they proceed directly to page 11 or 14.

[5]This analogy is presented for heuristic purposes only. The actual process is not mathematically related to factor analysis.

[6]Of the interviewer's 13 schizophrenics, six were female and seven were male.

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Table 1

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*	15.1	15.1
Mean social class**	2.3	2.2
Mean years education	7.3	7.0
Per cent of group in children's homes (5 years or more)+	14 %	16 %
Mean number of years in children's homes (5 years or more)+	8.5	9.4
Per cent of group with rural residence++	22 %	26 %

*Defined as age to the nearest whole year.

**The scale runs from 0 (low) to 6 (high) and was adapted from Svalastoga (1959).

+We only considered experience in children's homes of 5 years or greater duration. Many of the Experimental children had been to children's homes for brief periods while their mothers were 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.

++A rural residence was defined as living in a town with a population of 2500 persons or fewer.

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TABLE 3

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 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 27 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 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 convulsion, constantly takes anti-seizure 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; hisotry of car stealing, unstable, drifting, unemployed, sensitive, easily hurt, one year institutionalization in a reformatory for the worst delinquents in Denmark.

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 cahracter; psychotic breakdown in Army, preceded by arrest for car thievery. Now hospitalized.

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.

Table 4

Distinguishing characteristics of the Sick Group

1. Lost mother to psychiatric hospitalization relatively early in life.

2. Teacher reports disturbing, aggressive behavior in school.

3. Evidence of associative drift.

4. Psychophysiological anomalies.

      A. Markedly fast latency of response.
      B. Response latency evidence no signs of habituation.
      C. Resistance to experimental extinction of conditioned GSR
      D. Remarkably fast rate of recovery following response peak.

5. 70% of the Sick Group had suffered serious pregnancy and/or birth complications.

Table 5

1972 FOLLOW UP RESULTS WITH 1962 SAMPLES

	High Risk (N = 207)	Low Risk (N = 104)
Full assessment complete	173	91
Home interview only (social worker)	10	6
Not yet contacted[+] (Parent objected or the subject could not be located)	6	2
Living abroad[+]	6	0
Deceased	10	0
Subject refused	6	5

Table 6

IDENTIFYING CHARACTERISTICS OF HIGH AND LOW RISK SUBJECTS
PARTICIPATING IN FULL INTERVIEW
(1972)

	High Risk		Low Risk	
Number - full interview	173	207	91	
Mean age at 1962 assessment	14.9	15.1	15.1	
Mean social class	2.1	2.3	2.4	
Number males	97	121 (24)	53	59 - 6
Number females	76	86 (10)	38	45 - 7

FIGURE 1
PATH DIAGRAM FOR MEN

MULTIPLE R = .62

.50 -- PATH COEFFICIENT

(.01)-- SIGNIFICANCE LEVEL

BIRTH 5 10 15 20 25

AVERAGE AGE OF SAMPLE IN YEARS

FIGURE 2

PATH DIAGRAM FOR WOMEN

MULTIPLE R = .49

-.37 (.002)

.50 -- PATH COEFFICIENT

(.01)-- SIGNIFICANCE LEVEL
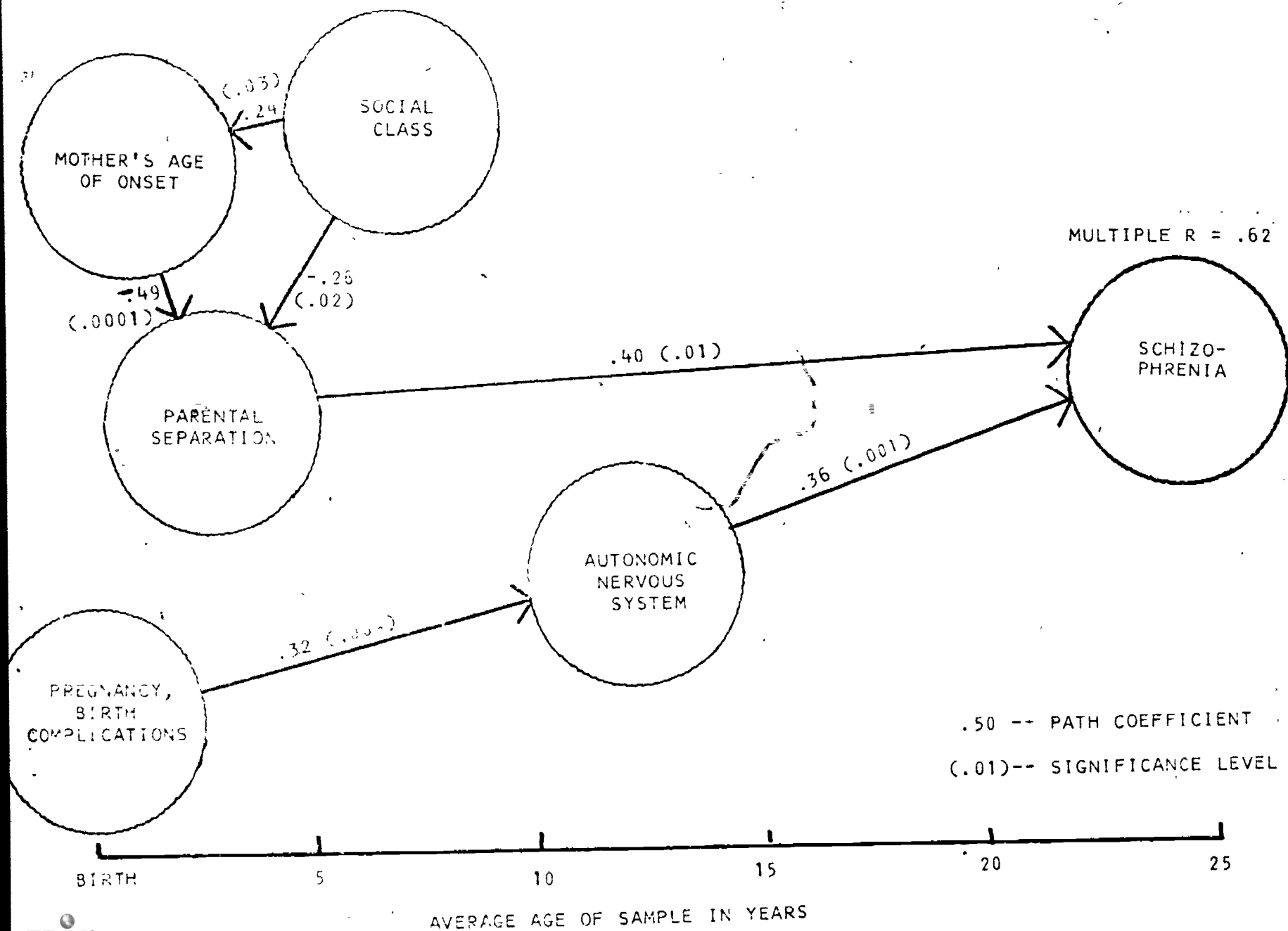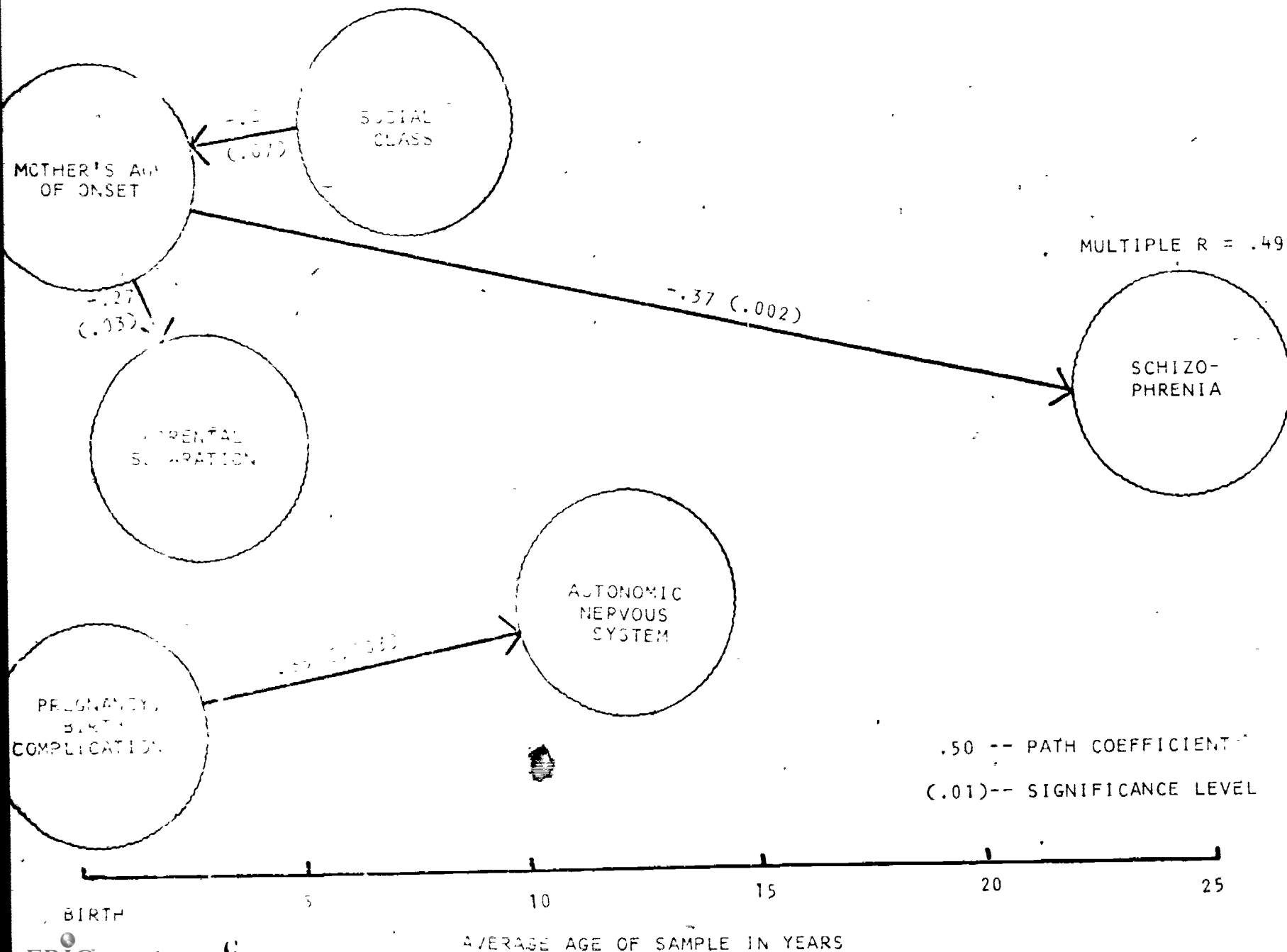
FIGURE 3

DIRECT AND INDIRECT EFFECTS OF CHILDHOOD

CONSTRUCTS ON SCHIZOPHRENIA CONSTRUCT