autonomic nervous system characteristics possibly related to a genetic predisposition to schizophrenia*

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The aim of this paper is to review the available evidence on what, if any, aspects of autonomic nervous system (ANS) functioning might be related to a genetic predisposition for schizophrenia. The review will necessarily attempt to determine those ANS characteristics that distinguish individuals who are more vulnerable to schizophrenia on a statistical basis than the general population and those that may be predictive of schizophrenic psychopathology at a future date. The importance of developing knowledge in these areas is at least threefold. First, if a specific pattern of ANS functioning can be found reliably to distinguish persons who later become schizophrenic from those who do not, it can be used as a selective factor for studies of vulnerable children, thus helping to overcome the bias, as noted by Shakow (1973), toward selection on strictly familial grounds that exists in the current crop of high risk investigations. Second, on a more theoretical level, such knowledge can aid in our understanding of the biological substrate of schizophrenia. Since the studies of Kety and Rosenthal and their collaborators (Kety et al. 1968 and Rosenthal et al. 1971) have shown beyond a reasonable doubt that genetic factors are involved in the etiology of schizophrenia, we can ask next how this genetic factor is expressed. Current biochemical theorizing in schizophrenia is heavily focused on the catecholamines. Since catecholaminergic neurons have an important role in control of the ANS, the study of premorbid autonomic functioning might provide important clues to the operation of this system in the development of schizophrenia. Third, disturbances of ANS functioning might be more or less directly involved in the development of cognitive, attentional, or other aspects of schizophrenic symptomatology (Mednick 1958).

It is not the purpose of this paper to develop these possible implications in any detail. Rather, it is to review the somewhat sparse evidence on the ANS functioning of the offspring and other relatives of schizophrenics, including some unpublished data from our own laboratory, in an attempt to make an educated guess about the possible involvement of the ANS in the etiology of schizophrenia as a guide for further studies.

The Mednick and Schulsinger Study

The first large-scale investigation of this type is, of course, the Danish study by Mednick and Schulsinger (1968) in which the offspring of 207 chronic process schizophrenic mothers were compared, during adolescence, with 104 children who were individually matched with the high risk children on a number of important variables, and whose families (parents, grandparents) were free from serious psychopathology. In addition to an interview and IQ and word association tests, two psychophysiological recording procedures were administered, for which only electrodermal data for the first session have been reported. A series of eight mild (54-dB, 1,000-Hz) tones preceded a conditioning procedure in which the mild tone (conditioned stimulus, or CS) was followed (½-sec interval) by a 96-dB "noise" (unconditioned stimulus, or UCS). Five presentations of the CS alone were interspersed with nine CS-UCS pairs to provide a test of conditioning. This was followed by extinction and stimulus generalization trials. The

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dependent variables analyzed were base skin resistance levels (SRLs) throughout the test session and amplitudes, latencies, and recovery times of the phasic electrodermal responses (EDRs).

The first set of comparisons made by Mednick and Schulsinger was for all high risk children vs. all low risk children. These comparisons can provide information about possible predisposing factors to schizophrenia, since a higher proportion of high risk than low risk children will develop the disorder, but such a comparison cannot be definitive either as to their predictive value or the genetic or nongenetic mediation of their transmission. The results of this comparison show: (1) The high risk group had significantly lower SRLs at almost all stages of the experiment, suggesting a higher level of autonomic arousal for this group. (2) Amplitudes of elicited EDRs were significantly greater, when adjusted for differences in base SRLs, for the high risk subjects to most of the events (e.g., putting on earphones, instructions) in the experiments, to most of the presentations of the noxious UCSs, and to the generalization stimuli. Responsivity to the less intense tone was generally greater in the high risk group as well, but was statistically significant only in the case of the last CS and two estimation trials. (3) Latencies of EDRs were generally reliably faster in the high risk group, particularly to the stronger stimuli; but the low risk group responded significantly faster to several mild tones in the extinction and generalization series. (4) Time to half recovery and full recovery was measured for EDRs elicited by two events and five CS-UCS sequences. The high risk subjects had significantly faster recovery times (adjusted for response amplitude) in four cases and faster half recovery times in two cases.

Five years after the testing the investigators had identified 20 high risk children who had come to the attention of the Danish psychiatric community as having severe psychiatric problems. These subjects (sick group) were matched individually with equal numbers of high risk subjects who had not (yet) had problems (well group) and with low risk subjects (control group). These groups were matched fairly well on age, sex, social class, and level of adjustment at the time of initial testing.

The results show that except for base SRL for which there were no group differences, the sick group was generally different from the other two groups in the same direction as in the high vs. low risk data. The well group generally fell between the sick and control groups. On the critical comparison between the sick and well high risk subjects, except for the habituation series (for which no data are given), the amplitudes of the EDRs to virtually all stimuli were higher for the sick group, about a third of the comparisons being statistically significant. There was some evidence of greater conditioning for the sick group as well, in that this group was the only one with a positive slope of amplitude across trials. However, no statistical tests of this feature were reported, nor were the greater response amplitudes and frequencies shown by the sick group to the CS demonstrated to be disproportionately greater for this stimulus than for any other. The same is true of the extinction and generalization data. Therefore, unequivocal differences for the effects of the conditioning procedure were not demonstrated.

No appreciable differences between sick and well groups were found for mean response latency, both groups having faster latencies than controls. However, there were significant differences in the trends of latency during the conditioning procedure: The well and control groups increased in latency to both CSs and UCSs across trials while the sick group did not, suggesting slower habituation in the sick group.

Mednick and Schulsinger (1968) report that the best discriminator between the three groups was in recovery. For this analysis they changed their dependent variable from recovery time, corrected for response amplitude, to recovery rate in ohms per sec to half recovery. The results show that the sick group had significantly faster half-recovery rates than the well subjects on six of the eight UCS trials analyzed. Although these results might be thought to be a secondary consequence of the larger responses given by the sick group (particularly since Edelberg [1970] found recovery rate to be correlated with response amplitude), on the one trial on which the well group had a slightly larger amplitude, the sick group still had a significantly greater recovery rate. Elsewhere Mednick and Schulsinger (1973) report that the correlation of response amplitude and recovery rate was only about .10.

In a very recent evaluation based on a 10-year diagnostic followup, Mednick (1976) reports only the recovery rates of the 34 high risk subjects found to have diagnoses in the schizophrenic spectrum. These subjects had considerably faster recovery rates than the remainder of the high risk subjects, who in turn were
faster than the low risk sample, thus confirming the earlier findings for this variable.

The data from the early breakdown group are seen as consistent with Mednick's (1958) earlier theory of the development of schizophrenia with the exception of the faster EDR recovery. However, current interpretations of recovery time of phasic EDRs, which are based on a better understanding of the peripheral mechanisms, suggest that this measure is faster as a direct function of the fullness of the sweat glands and hydration of the corneum (Fowles 1974) and as an inverse function of preceding electrodermal activity (Bundy and Fitzgerald 1975). Thus, fast recovery may reflect the stressfulness of the situation, a slow recovery from the stress, or both. This interpretation, while making the data more consistent with Mednick's theory, is inconsistent with the lack of a difference between sick, well, and control groups on SRL, a measure also purportedly reflecting stress or arousal. Since SRL is affected by extraneous factors such as sweat gland density which do not affect recovery time, however, recovery time may be a somewhat more sensitive measure of arousal and more discriminating when group sizes are relatively small. On the other hand, recovery time is thought to be influenced by the reabsorption of sweat, the mechanisms of which are poorly understood at present (Venables 1974).

The design of this study does not, of course, indicate whether the deviance in physiological characteristics of the high risk and breakdown groups are genetically determined. In fact, Mednick has found several environmental variables that strongly affect his results. Perhaps most important of these environmental factors are pregnancy and birth complications (PBCs), obtained from reports of the midwife attending the birth. Mednick and Schulsinger (1973) and Mednick (1970) report that 70 percent of the sick group had suffered one or more PBCs as contrasted with 15 percent of the well group and 33 percent of the controls. As to the relationship between the PBCs and ANS data, they state (without presenting the data): "... for the Sick group we noted a very marked correspondence between the presence of PBCs and the deviant ANS behavior" (Mednick and Schulsinger 1973, p. 260). They do present data for the entire high vs. low risk sample which show that the only electrodermal variable demonstrating an interaction between risk and PBCs was galvanic skin response (GSR) latency, a result which is claimed to hold for the sick-well-control comparison as well. Significant effects of PBCs for both high and low risk groups were found for response amplitude and recovery rate, but no interactions with risk were found. The authors claim an interaction was present in the sick-well-control data, but again do not present the data. It can be concluded that PBCs have the same effects on some ANS variables as having a schizophrenic mother does, but from the data actually presented the role of the PBC-ANS effect on the development of psychosis in the high risk group remains obscure.

The other set of environmental factors analyzed by Mednick and Schulsinger has to do with the constitution of the families of their subjects during early childhood. The effects of these on the ANS data have been looked at in two ways: (1) in terms of a separation scale "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 5 years of life" (Mednick and Schulsinger 1973, p. 258) and (2) in terms of intactness of the family between the ages of 6 and 10. They found that high separation was weakly associated with decreased GSR latencies and increased response amplitudes to the stress stimuli for the combined risk groups (p < 0.06, two-tailed) in each case and, although there were no significant interactions, the two risk groups differed more in the case of low separation than high separation. It is perhaps unfortunate that the authors chose to report the physiological data for the up-to-5-year separation breakdown, since comparison of sick, well, and control groups shows that the sick group had a significantly higher proportion of maternal absence from the home only for post-5-year age periods. In view of this finding, more dramatic physiological differences might be expected to be associated with late separation. On the more recent analysis of family intactness in relation to the ANS data, Mednick (1976) obtained the striking finding that virtually the entire difference between risk groups on all the ANS variables is due to those children with nonintact families. For these analyses the dependent variables were base resistance levels, and the latencies, amplitudes, recovery rates, and frequencies of responses over all trials, so they are not strictly comparable to the previous analyses. The other interesting feature of these data is that intactness affected the physiology only in the high risk subjects. This suggests either a genuine interaction between intactness and risk or that the reasons for the familial
breakup differ or have a different meaning in families with a schizophrenic mother than they do in those without one.

The results of this pioneering study show that the offspring of a schizophrenic mother are higher than controls on ANS arousal and lability, and faster in EDR recovery, and that the last two characteristics may be particularly deviant in high risk subjects who are soon to develop severe psychiatric problems. One of the difficulties in interpreting the findings for this early “breakdown” group is due to the mean ages of the subjects at the initial testing (15.1 years) and the relatively short length of time that elapsed between the testing and the breakdown. It is possible that the initial testing, rather than assessing true premorbid characteristics of ANS functioning, was already influenced by a developing personality disturbance. Although the sick, well, and control groups were matched on a level of adjustment scale, the school report showed more behavioral problems with the sick group. Fortunately, these ambiguities in interpretation may be clarified by later diagnostic assessments and by comparison of the results for subjects whose initial testing was done at a relatively early age (i.e., preadolescent) with those who were older.

**Other Studies of the Offspring of Schizophrenic Parents**

Other high risk studies which include psychophysiological assessment of younger subjects have not developed to the point where full reports of the results can be made, although there have been two very preliminary and sketchy reports. Anthony (cited by Garmezy 1974) reports that in a procedure involving electrodermal and plethysmographic recording from offspring (most of whom are in the 6- to 11-year-old range) of mentally ill parents contrasted with offspring of physically ill parents, the former subjects “respond more at each trial, do not habituate as well, and do not differentiate as well” (Garmezy 1974, p. 58), thus seemingly confirming Mednick’s high risk findings. On the other hand, in a study by Erlenmeyer-Kimling and associates in which 7- to 12-year-old offspring of one or two schizophrenic parents are compared with controls on a testing procedure similar to the one used by Mednick and Schulsinger, the results so far have been completely negative (Fein, Tursky, and Erlenmeyer-Kimling 1974). Mednick (1976) has recently tried to account for this discrepancy with his results in terms of the different sampling criteria in the two studies, particularly that of intactness of family. Erlenmeyer-Kimling required all of her subjects to come from intact families, whereas Mednick reports that only about a quarter of his high risk subjects met that criterion. When he breaks down his groups according to family intactness, he finds that the high vs. low risk differences in ANS functioning hold only for nonintact families. Whether this is due to the severity of illness in the mother, as Mednick believes, or to some other factor correlated with intactness, is a moot point. Although Mednick’s data show a clear effect of family intactness, the importance of this variable in explaining the negative results of Erlenmeyer-Kimling can be questioned since Anthony, who reported positive findings, also used only intact families. It is to be hoped that these conflicting findings can be clarified when more data are in.

If one were to remove differences in child-rearing practices as a source of variance from the analysis of high risk psychophysiology in order to assess the more purely biological aspects of the problem, one method would be to study the children as early in life as possible. This strategy has been used by Schachter et al. (1975) who assessed heart rate responsivity to clicks of four different intensities over a 3½-hour sleeping period in newborns on both the second and third postnatal days. Three groups of infants, whose mothers were all of low socioeconomic class, were compared: (1) those with schizophrenic mothers whose diagnosis was highly certain (N = 22), (2) those with nonschizophrenic parents and parents' first degree relatives (N = 64), and (3) a low certainty group where there was some evidence of schizophrenia in either a parent or a parental first degree relative (N = 25). A replication was carried out with 16, 18, and 23 subjects in the three groups. The data on 17 variables derived from the data were examined by analyses of variance that included the main effects of diagnostic groups and interactions with race, sex, amount of medication for delivery, and complications of pregnancy. Using a 0.01 level of significance Schachter et al. found three significant results in the first experiment, of which they identify only one: an interaction between maternal medication and diagnosis on change in tonic heart rate over the testing session on the second postnatal day. This finding was due primarily to a marked trend for heart rate acceleration
over the session for offspring of schizophrenic mothers with high medication. The only result reported for the second experiment was a "tendency for replication" of this finding.

Thus, with the exception of this one finding, which is difficult to interpret in terms of prevailing theories about the psychophysiology of schizophrenia or its development, the results of Schachter et al. seem to be largely negative. The possibility exists that the environmental factor of medication or its interaction with clinical condition may have influenced the results, although the authors argue against this possibility. It should be pointed out also that the conservative style of reporting the results would tend to lead to type 2 errors—accepting null hypotheses that are really false. Since genetically determined effects would be expected to occur in only half or less of the infants, depending on the mode of transmission, it would seem that only relatively strong effects could be discovered using these conservative criteria for significance.

Studies Using an Adoptive Strategy

The most definitive test of genetically determined psychophysiological characteristics in the offspring of schizophrenic parents is the Denmark study by Van Dyke, Rosenthal, and Rasmussen (1974) in which the electrodermal functioning of adults, one of whose biological parents was schizophrenic but who had been adopted by nonschizophrenic foster parents at an early age (index group), was compared with that of a matched group of adoptees for whom both sets of parents were free of schizophrenia (control group). The procedure consisted of a rest period, presentation of 19 54-dB tones (orienting) and a long interval (5-sec) conditioning procedure using the 54-dB tone as a CS and a 96-dB white noise (4.5-sec in duration) as a UCS. The study was carried out in the same laboratory used by Mednick and Schulsinger and, although there were procedural differences, the recording and stimulating apparatus was the same. Van Dyke, Rosenthal, and Rasmussen found no differences in skin conductance level (SCL) or spontaneous response frequency in any part of their procedure, nor were there differences in mean latency or recovery time to any of the classes of stimuli used. They did find significantly larger EDR amplitudes to the 54-dB tone in the orienting series by the index group and a similar trend in the conditioning procedure. In addition, index subjects gave significantly more EDRs to the UCS in the conditioning procedure and tended to give a larger number of "second interval" conditioned responses. With respect to trends in responsivity across trials, the index group tended to decline in the amplitude of the CS at a slower rate than the controls. Similarly, on the frequency of EDRs to the UCS, the index group habituated significantly more slowly.

While these results are considerably less dramatic and in many ways different from the Mednick and Schulsinger findings in that no differences between index and control groups were found in SCL in the latency and recovery times of EDRs or in the amplitudes of the EDRs to the loud noise, the findings are nevertheless similar in a conceptual sense, since Van Dyke, Rosenthal, and Rasmussen observed greater electrodermal responsivity, slower habituation, and a trend for more conditioning in subjects with a schizophrenic biological heritage than in controls. If one accepts the results of these studies at face value, a possible conclusion is that autonomic hyperresponsivity to sensory stimulation and slow habituation are accompaniments of being at high risk for schizophrenia that are determined by genetic factors (or by interactions of genetics with early environmental variables such as PBCs) and that the high tonic arousal found in high risk subjects is determined by a pathological childhood environment. Aside from the inherent and obvious difference between these studies in the rearing to which the subjects were exposed, however, there are several other differences that may have helped produce the more striking findings in the Mednick and Schulsinger study. Among these are its inclusion of only process schizophrenic mothers together with a more stringent screening of the controls and the larger Ns (which would increase the significance of small differences) or possibly the younger age of the subjects. In addition, Mednick (1976) has raised the intriguing possibility that the genetic contribution of the father in the three-fourths of Van Dyke, Rosenthal, and Rasmussen's cases in which the pathological biological parent was the mother might be partly responsible for their results. On examination of the diagnostic protocols from that study Mednick reports that the biological fathers of the index adoptees had spent more than twice as much time in jail on the average as those of the control adoptees, suggesting more psychopathy in the index fathers. Further, Mednick (1976) found from his earlier study that subjects having a schizophrenia
spectrum diagnosis and "criminality in the family" had longer recovery times than spectrum subjects without familial criminality, and from his later study that children of criminal fathers gave fewer orienting responses and had longer latencies and recovery times than children with noncriminal fathers, the data being for both high and low risk cases. In view of the abundant evidence that psychopaths evince lower electrodermal arousal and responsivity—including slow recovery time—than nonpsychopaths, the evidence that these electrodermal features show a significant genetic component in their transmission, and the fact that Mednick and Schulsinger's earlier high and low risk subjects were not different with respect to paternal criminality, the hypothesis that the differences between the findings of Van Dyke, Rosenthal, and Rasmussen and those of Mednick and Schulsinger are due to differences in familial criminality must be taken seriously. However, it is not known if the difference in the number of criminal fathers in Van Dyke, Rosenthal, and Rasmussen's index and control groups compared to the total sample size is large enough to make a large difference in the results. Until a more direct test of this psychopathy hypothesis is available, it should perhaps be considered an interesting and possibly significant speculation.

Another approach to the study of genetic factors involved in the psychophysiology of schizophrenia is a study comparing the biological/rearing parents of schizophrenics ($N = 7$ pairs) with nonbiological/rearing parents ($N = 10$ pairs) whose adopted children became schizophrenic (Wender et al. 1971). In an unpublished aspect of this study, skin conductance was recorded during presentation of a series of mild tones, a word association test, and a stress procedure consisting of two sets of mental arithmetic problems and a cold pressor test. During the tones the biological parents exhibited nonsignificant trends in higher SCL and spontaneous EDR frequency and gave more frequent but smaller amplitude orienting responses to the tones. The only significant difference between the groups was a smaller increase in SCL to the first mental arithmetic procedure by the biological parents (figure 1, bottom). Although these data must be interpreted very cautiously because of the small $N$s, the trends of high resting arousal and diminished response to stress seen in the biological parents are similar to findings in hospitalized schizophrenic patients (Zahn 1975), but in general are inconsistent with the findings of the other studies on biological first degree relatives of schizophrenics discussed earlier.

**Discordant Monozygotic Twins**

A potentially quite useful strategy for studying genetically determined mechanisms in schizophrenia is the use of nonschizophrenic monozygotic (MZ) co-twins of schizophrenics. Differences on a given variable between the co-twins and a comparable nonschizophrenic sample whose families are free of psychosis would suggest possible genetic involvement of that variable in schizophrenia if, in addition, the variable was shown to be under genetic control. The discordant twins described by Pollin and Stabenau (1968) were tested in a four-session testing procedure in which skin conductance and heart rate were recorded during rest and the mental arithmetic and cold pressor stress series of tones that were followed by motor responses, a simple reaction time procedure, a word-association test, and the mental arithmetic and cold pressor stress procedures described earlier. Unfortunately for the purposes of this paper, suitably matched control subjects were not available. The twins lived with their families in the National Institutes of Health Clinical Center for a 2-week period during which they were exposed to an intensive series of a variety of testing procedures. Only four sets of normal twins were exposed to the same regimen and they were somewhat younger than the discordant pairs. While other normal subjects were tested on most of the psychophysiological procedures, they were otherwise new to a research environment. Because of the sensitivity of autonomic variables to such situational factors as habituation and fatigue, it was felt that the co-twins could not be legitimately compared to these subjects.

Nevertheless, comparison of the difference between the twin pairs with the difference between unrelated schizophrenics and controls can suggest the extent to which a variable is affected by schizophrenic symptomatology independent of a genetic difference. If the co-twins resemble the index twins on a variable in which there is a significant difference between unrelated schizophrenics and controls, then that variable might be genetically related to schizophrenia.

Data collected under resting conditions show that while the SCL of the co-twins is somewhat lower than that of the index twins, these groups do not differ as
much as unrelated schizophrenics and controls (Zahn 1975). The same is true of another arousal index, the frequency of spontaneous EDRs, but on heart rate the difference is just reversed: The twin pairs are more different than the unrelated groups, the schizophrenics having higher heart rates in each case. Regardless of whether differences in EDR amplitude were controlled for, half recovery times of phasic EDRs did not differentiate the index twins and their co-twins. Although recovery time has not been analyzed for the unrelated groups, there is evidence that schizophrenics have faster recovery times than controls (Ax and Bamford 1970 and Zahn, Carpenter, and McGlashan 1975). Thus, the electrodermal measures suggest that the higher arousal usually found in schizophrenic patients may have a genetic basis, but the heart rate data are inconsistent with this conclusion. The co-twins have lower levels than the unrelated controls on all these measures and the schizophrenic twins are lower than the single-born schizophrenics only on the electrodermal variables. Whether this is due to the intensive testing regimen that the twins were exposed to or to some unknown sampling factor cannot be determined.

A more consistent picture is provided by the data on phasic and tonic responsivity to the stimuli and tasks. Both the unrelated controls and the co-twins showed marked increases in phasic electrodermal responsivity to the more “meaningful” or demanding stimuli (reaction time stimuli), while the responses of the schizophrenic groups were much smaller. The two control groups were quite similar on response frequency, but when amplitude was considered the co-twins were considerably higher than the unrelated controls. This recalls the similar increased amplitudes found by Mednick and Schulsinger to intense stimuli and those found by Van Dyke, Rosenthal, and Rasmussen to weak stimuli in subjects sharing genes with a schizophrenic person. However, hyperresponsivity was not manifested in the tonic EDRs to the task situations. Figure 1 (top half) shows that while the co-twins were more reactive than their schizophrenic siblings to the mental arithmetic procedures, they were somewhat (but nonsignificantly) less reactive than controls, the controls in this case being eight normal MZ twins, who, it will be recalled, were younger than the discordant pairs. If one accepts the conclusion that the co-twins were not different from controls in this situation, then it is probable that the diminished responsivity of the biological parents compared to that of the adoptive parents of schizophrenics shown in the lower half of figure 1 is not directly due to a genetic factor related to schizophrenia, but is more likely related to the greater psychopathology manifested by the biological parents (Wender et al. 1971). The comparison of the twin and adoptive parent studies is a good illustration of how different conclusions about genetic effects can be drawn from different methods of investigation.

The one conclusion that can be drawn with any certainty from this study is that overt schizophrenic symptomatology is related to attenuation of autonomic responsivity to demanding and/or stressful stimuli and situations. The data fail to rule out high electrodermal base levels and fast EDR recovery times as possible genetically determined accompaniments of a schizophrenic genotype, but the generally low base levels found in both index and co-twins do not add support to that hypothesis either. Previous findings of greater EDR amplitudes in nonschizophrenic subjects with a schizophrenic genotype received some support.

Another relevant aspect of this study is the relationship of differences in PBCs on differences in autonomic functioning in the discordant twin pairs. The differences between index twins and their co-twins on a number of ANS variables for those pairs in which the index twin had an excess of two or more PBCs compared to his co-twin were compared with pairs in which the PBC difference was zero or in the opposite direction. The only significant finding from this analysis was that overall SCL was higher in the group with more PBCs ($p < .05$). The results thus do not confirm the findings of Mednick and Schulsinger (1973).

Genetic Determination of Autonomic Variables

A final consideration that is critical for the assessment of the role of genetics in autonomic functioning in schizophrenia is the role of genetics in determining individual differences in the general population. Mednick (1974) reports an unpublished study by Bell comparing MZ and DZ twins in which recovery time of phasic EDRs showed highly significant genetic effects but in which base levels, frequency, amplitude, latency, rise time, and recovery rate did not. Other studies using the twin method (Hume 1973 and Lader and Wing 1966)
Figure 1. Maximum SCL during various periods in the stress procedure

Note.—Upper half shows data from the twin study and the lower half data from adoptive vs. biological parents of schizophrenics. MA₁ and MA₂ are two mental arithmetic procedures and CP is a cold pressor procedure. PRE is a 3-minute rest period; I and A refer to instructions plus a 30-second anticipatory period during which the subject waited for the start of the procedure; STR refers to the stress procedure itself.
have not studied EDR recovery, but significant genetic effects for SCL, spontaneous EDRs, latency, habituation, and the tonic response to stress have been reported. In an unpublished study from our laboratory, done in collaboration with Monte Buchsbaum, in which we tested 34 pairs of MZ and 34 pairs of DZ twins, about equally divided as to sex, we obtained somewhat different results. The tests included presentation of a series of 20 tones (orienting), a reaction time test, and mental arithmetic. Some results from a preliminary analysis of the data are presented in table 1. It can be seen that variables reflecting resting arousal, response frequency and recovery, and the tonic EDR to stress show evidence of genetic effects. Several indices of the habituation of the orienting responses produced no evidence of being under genetic control. It is interesting that half recovery rate rather than time shows strong genetic effects, since it will be recalled that recovery rate was the measure reported by Mednick (1976) to differentiate the high risk subjects who had a schizophrenia spectrum diagnosis on their latest assessment.

Of other electrodermal measures that have been found to differentiate persons sharing at least half their genes with a schizophrenic, base SCL and tonic response to stress appear to have the strongest support in the literature for a genetic basis, with some evidence that the frequency, latency, and rate of habituation of electrodermal orienting responses may also be genetically determined in part. No significant genetic effects for phasic EDR amplitude have been found to the author’s knowledge.

Summary and Conclusions

This review has had the primary aim of determining whether some deviance in the functioning of the autonomic nervous system might have a significant role in the genetic etiology of schizophrenia and to this end has reviewed studies of ANS functioning, based primarily on electrodermal data, in persons who, in the great majority of cases, were not schizophrenic themselves but were related to schizophrenic patients. The pioneering work of Mednick and Schulsinger on the adolescent offspring of schizophrenic mothers obtained clear-cut findings of higher skin conductance base levels and responsivity to stimuli (high amplitude, fast latency and recovery) and some evidence of slow habituation in high risk children compared to matched controls. These findings appear to have been, in general, replicated by Anthony (see Garmezy 1974) but not by Fein, Tursky, and Erlenmeyer-Kimling 1974, according to incomplete preliminary reports. An investigation by Schachter et al. (1975) of the heart rate response in newborn children of schizophrenic mothers was basically negative. In a study designed more specifically to assess genetic influences in that adult adopted-away offspring of schizophrenic parents were compared with control adoptees (using a testing paradigm similar to Mednick and Schulsinger’s [1968] study), Van Dyke, Rosenthal, and Rasmussen (1974) found greater electrodermal responsivity and slower habituation in their index cases. Although their results were conceptually somewhat similar to Mednick and Schulsinger’s, they did not match in detail. In a pilot study comparing adoptive with biological parents of schizophrenics, Zahn (unpublished data) found only a diminished response to stress in the biological parents to differentiate the groups significantly. A study on MZ twins who were discordant for schizophrenia (Zahn 1975) showed that the index twins had a damped autonomic response to demanding and stressful stimuli; the finding of only small differences in skin conductance base levels, responsivity to meaningless stimuli, or speed of recovery suggested that for these variables genetic influences may be relatively more important than the effects of symptomatic schizophrenia.

In assessing the earlier autonomic findings of their high risk subjects who manifested severe behavior pathology during the first 5 years after the testing, Mednick and Schulsinger (1973) found that compared to matched high risk controls the sick subjects had given SCRs with larger amplitudes and faster recovery and that the data were explicable by a high frequency of PBCs in the sick group. In a recent followup based on diagnostic evaluation of all subjects, fast recovery rate during adolescence was highly discriminative for subjects who later had a schizophrenia spectrum diagnosis.

It is clear that no characteristic of ANS functioning has been shown unequivocally to be involved in a predisposition for schizophrenia. Although most studies have obtained some positive results, these have not been the same from one study to another. Each of the studies reviewed has had its own peculiar sampling biases and methodological idiosyncracies which may have affected the results in ways that are not fully understood. Some of these which have been pointed out are PBCs, family...
Table 1. Intraclass correlations and within-pair variance ratios on several electrodermal measures for MZ and DZ twins

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intraclass r</th>
<th>F (VDZ/VMZ)</th>
<th>P</th>
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<tr>
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<td>MZ</td>
<td>DZ</td>
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<td>A. Tones</td>
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<td>Resting SCL</td>
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<td>-0.19</td>
<td>1.07</td>
</tr>
<tr>
<td>Half recovery time</td>
<td>-0.11</td>
<td>-0.20</td>
<td>1.80</td>
</tr>
<tr>
<td>Half recovery rate</td>
<td>0.79</td>
<td>0.38</td>
<td>4.39</td>
</tr>
<tr>
<td>B. Reaction time stimuli</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SC level</td>
<td>0.53</td>
<td>0.43</td>
<td>1.31</td>
</tr>
<tr>
<td>No. of SCRs</td>
<td>0.57</td>
<td>0.05</td>
<td>1.44</td>
</tr>
<tr>
<td>Amplitude</td>
<td>-0.01</td>
<td>0.12</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Latency</td>
<td>0.18</td>
<td>0.50</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Rise time</td>
<td>0.18</td>
<td>0.24</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Half recovery time</td>
<td>0.30</td>
<td>0.18</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Half recovery rate</td>
<td>0.58</td>
<td>0.48</td>
<td>2.60</td>
</tr>
<tr>
<td>C. Mental arithmetic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SC response to instructions</td>
<td>0.42</td>
<td>0.11</td>
<td>2.35</td>
</tr>
<tr>
<td>SC response to mental arithmetic</td>
<td>0.51</td>
<td>-0.01</td>
<td>3.15</td>
</tr>
</tbody>
</table>

intactness, separation from the mother, characteristics of the other parent, and age.

Nevertheless, a few promising findings have emerged from these early studies. Fast recovery rate of phasic EDRs, the most striking predictor of later pathology to emerge from the Mednick and Schulsinger (1973) study, seems to be influenced by genetic factors and did not differ in twins discordant for schizophrenia. However, the negative results for recovery time obtained in the adoptive study by Van Dyke, Rosenthal, and Rasmussen (1974), the ambiguity in the interpretation of this variable by psychophysicists, and the uncertainty of whether rate or time is the better measure makes the significance of this finding obscure at the moment. Heightened phasic electrodermal responsivity of one kind or another has shown up in several studies as a possible accompaniment of a schizophrenic genotype, but the specific measures by which it is manifested are different and there is little or no evidence that two of its components—amplitude and latency—are influenced appreciably by genetic factors. Similar conclusions can be drawn about slow habituation. Low tonic reactivity to task-produced stress seems to be influenced by genetic factors and was characteristic of biological parents of schizophrenics, but it may be strongly affected by schizophrenic symptomatology and has not as yet received much attention in the literature.

Autonomic functioning is not a static property of the individual like color blindness or (perhaps) brain dominance. It has a developmental course, and is influenced by learning and psychological state. Therefore high risk studies of infants or young children (where differences in developmental level may be an important factor); studies of adolescents (some of whom may be in the early stages of process schizophrenia); studies of adults who are through the high risk period for schizophrenia (and who may have learned to cope with a genetic predisposition for schizophrenia
with varying degrees of success); studies involving an adoption; and studies of discordant twins (where the family dynamics may produce unique attitudes toward the test procedure) may not all produce results that lead to the same conclusions. Such heterogeneity of method seems essential if bias is to be avoided. However, replication of results within a given type of study will be necessary in order to determine just how these different methodological approaches affect the findings.

References


Wender, P.H.; Rosenthal, D.; Zahn, T.P.; and Kety,


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**litigation and mental health services**

A new monograph, *Litigation and Mental Health Services*, which discusses recent legal developments in relation to mental health practices and services, has been published by the National Institute of Mental Health, a component of HEW's Alcohol, Drug Abuse, and Mental Health Administration.

Bertram S. Brown, M.D., Director of NIMH, points out in the foreword that involvement of courts of law in mental health issues accomplishes two purposes: The voice of the mental health consumer is given previously unrealized strength through the judicial process, and this added democratization of policymaking “revitalizes the concern that is shared over the availability of equitable, effective services rendered through the mental health system.”

The monograph by Louis E. Kopelow, M. D., Alvira B. Brands, D. Sc., John L. Burton, and Frank M. Ochberg of the NIMH Division of Mental Health Services Programs contains a historical perspective of NIMH's concern for patients' rights, an interpretation of recent litigation, a listing of cases cited, and suggested readings. It is noted that litigation on behalf of the mentally disordered and the retarded is increasing at all levels of the judicial system across the Nation. Involved are the rights of citizens to adequate care and to the least restrictive kind of care, to privacy, to due process, and to protection from forces threatening their dignity as human beings and as citizens. The monograph emphasizes that this concern must continue, but must be tempered by the patient's and by society's recognition of the need to provide adequate and appropriate treatment.