Chronic Schizophrenia from the Standpoint of Vulnerability

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LAYPERSON'S SUMMARY

The original view of schizophrenia as a persistent, progressive chronic disorder leading to complete deterioration of the personality has been challenged by a new outlook. This new approach regards schizophrenia as occurring only in vulnerable individuals who are subjected to stresses and strains of such magnitude that they develop a crisis. While all of us develop crises to stressful events, we can usually adjust to them and overcome them in a salutary way. However, the vulnerable individual cannot absorb the crisis and an episode of illness results. Such episodes, however, need not persist permanently, but disappear either with or without treatment in time, and then the patient returns to his pre-episode level of adjustment.

While some patients appear to have persistent chronic episodes, a careful examination indicates that the majority are victims of iatrogenic (due to type of treatment and hospitalization) and ecogenic (due to noxious environmental factors) circumstances rather than of the natural consequences of the disorder itself, and at most not more than 6 to 10% fall into the chronic category.

If we could identify the individuals who are vulnerable by discovering specific characteristics or markers that characterize the vulnerable (just as insulin deficiency identifies diabetics) and could also determine the specific contingencies which trigger episodes in these vulnerable individuals (like the presence of pollen in allergy), the way would be open for preventive intervention. This would enable us to abort episodes and thus prevent the chronic phase from developing. Current research directed at the discovery of markers and triggers has begun to show some promise, and it is to be hoped that with continued research in this direction, the scourge of mankind known as schizophrenia may yield to preventive interventions.

INTRODUCTION

The purpose of this chapter is to:

1. Indicate that the view of schizophrenia as a persistent progressive debilitating chronic disorder leading invariably to unremitting impairment or deteriora-
tion is no longer tenable. It has been challenged by a more benign outlook which regards schizophrenia as a time-limited episode of either a single or repeated occurrence.

2. Review the accumulating evidence for the episodic nature of schizophrenia.

3. Propose the hypothesis that the episodic nature of schizophrenia emerges from the graded vulnerability of individuals to triggering events (life event stressors) of either exogenous or endogenous origin.

Based on the assumption that schizophrenia is episodic, and that episodes are elicited by triggering events in vulnerable individuals, a program of research will be outlined to test this formulation and draw its implications for schizophrenia in general and for its chronic phase in particular.

As a result of the application of such a program, we may be able to identify the individuals who stand in high risk of developing an episode of schizophrenia and also identify the contingencies which trigger episodes in these vulnerable individuals. This information can provide the means for determining the most suitable preventive intervention strategies for aborting even the initial episode or recurrent episodes and in this way eliminate the development of chronic schizophrenia at its very source.

EVIDENCE FOR THE EPISODIC NATURE OF SCHIZOPHRENIA

We have postulated that schizophrenia is not a continuing condition leading to a chronic state of either deterioration or unremitting impairment and that the only persistent characteristic of the schizophrenic is his vulnerability, not his disorder. This, however, flaunts the usual view regarding schizophrenia and makes no allowances for chronic conditions. Is there any evidence favoring the episodic nature of schizophrenia?

A survey of recent studies of schizophrenia (48) indicates that the evidence for the chronic and unremitting nature of all schizophrenic illness is rather sparse and that the episodic hypothesis, at the very least, is tenable. Hospital statistics indicate that the average duration of hospitalization has dropped from several years in the custodial period before the mid 1950s to some 37 days in 1975, and this is a worldwide trend. Most of the chronic cases in our hospitals have been admitted as long as 20 years ago and probably reflect the iatrogenic influences of long-term incarceration rather than the course of the disorder itself. More recently, randomly selected experimental brief therapy groups lasting only 4 weeks have shown results as good as or better than those groups consigned to long-term therapy. In 2 to 4 weeks of therapy, symptoms subsided in the majority of cases, and the episode seemed well on its way to termination. This is additional evidence for the episodic nature of schizophrenia. Reports from England (33) indicate that the relapse rate of patients returned to hostile home environments is far greater than that of those returned to benign home environments. Thus, the relapse rate of patients, if not the rate of new episodes, may be a function not of the natural course of their illness but of the niche they
occupy in life. Perhaps the most telling comment on the disappearance or gradual reduction of the chronic unremitting schizophrenic is Manfred Bleuler’s follow-up of his 208 schizophrenic probands over their lifetime.

In the Second Rochester International Conference on Schizophrenia, Manfred Bleuler (4) summarized the long-term course for the different groups of patients that he and others studied. He reported that at least 25% were fully recovered without further relapse and without requiring drug maintenance. Only a minority required welfare agency attention, and only about 10% remained permanently hospitalized.

He further pointed out that at any given point in time during the follow-up, 50% of the patients were fully recovered, though some of these relapsed later and their course fluctuated. After the fifth year of follow-up, 75% of the patients resided in the community at any given point in time and only 25% were hospitalized. This is a far cry from the persistency with which schizophrenia has been endowed. More than half worked to maintain themselves. Bleuler’s study gave a conservative estimate of the outcome of all schizophrenic patients in Switzerland since it included only a small proportion of first admissions, the majority being readmissions who comprised a larger number of more severe cases. Furthermore, many young patients and those with strong church affiliations tended to be hospitalized in private institutions.

One finding based on Bleuler’s follow-up (5) and regarded by him as most important showed that 5 or 10 years after onset, the relationship between recoveries (30%), mildly chronic (38%), moderately (17%) and severely (15%) chronic remained constant throughout the subsequent follow-up period. However, this constancy did not apply to the individual probands. The probands constantly changed back and forth between the various stages of recovery. Apparently the probands were in dynamic equilibrium, like ions in a solution: when one entered an episode, another exited from it. This dynamic equilibrium is additional evidence that the alleged persistence of the schizophrenic episode is a myth.

Since the episode does not persist, what does persist in schizophrenia? This chapter suggests that the permanent feature in schizophrenia is the vulnerability of the individual to the development of episodes.

Wing (55) found in a 5-year follow-up of first admission schizophrenics that about 75% had a good outcome (mild or no disability).

Even patients with a poor prognosis as determined by Vaillant’s 6 factors and Shepherd et al.’s 11 factors (3) showed a favorable outcome (mild or no disability) in 53% of the cases. If we take into consideration not only the hospitalized schizophrenics, but also those seeking help in outpatient clinics and community mental health centers, the proportion of permanently disabled is reduced to a small minority. The reason why schizophrenia was regarded as malignant is attributed by Manfred Bleuler to the fact that earlier generations of psychiatrists saw only the patients who returned to the clinic after discharge and never again laid eyes on those who recovered successfully without relapsing.

Even the hard core chronic schizophrenics do not need to remain hospitalized continuously if proper treatment is provided. Thus, Paul and Lentz (38) investi-
gated the effect of social-learning programs on a group of 137 hard core chronic schizophrenics who were selected on the basis of the following criteria: (a) aged 18 to 55; (b) average duration of hospitalization 17 years (nearly two-thirds of their adult life spent in a mental institution); (c) low socioeconomic status; (d) process schizophrenics without organic involvement; (e) non-sudden onset or precipitant for first episode; (f) less than 15% married without being divorced; (g) maintained on psychotropic drugs; and (h) rejected for extended care community placement because of low level of self-care and excess of bizarre behavior. The results indicated that even among these recalcitrant patients, with the lowest probability of release, a significant rate of release could be achieved. About 91% of the released patients continued to stay in the community and only 5% required rehospitalization during a 2-year follow-up period. Furthermore, by phasing the transition to the community with the help of social work follow-up, the readjustment to community living was so successful that they functioned at a level indistinguishable from that of their community peers in fully one-third of the cases. Fully 90% of the patients in the original chronic group were able to function well enough to fulfill their basic needs for food, shelter, socialization, and recreation, and 10% of these were able to live completely independently in the community.

In summary, chronic unremitting schizophrenics, certainly those of the catastrophic variety, are becoming increasingly rare, and it seems reasonable to assume that the permanent factor in schizophrenia is not the episode, but the vulnerability to the disorder.

The hypothesis appears to be consistent with two well-known characteristics of schizophrenics: (a) they do not exhibit schizophrenic behavior all the time, and even when they are in the hospital they are not always in their episode; (b) schizophrenics who exhibit good premorbid adjustment tend to recover. When the good premorbid's episodes end, they return to their good premorbid level and resume their place in society. When the poor premorbid's episodes end, they too return to their premorbid status, but it is difficult to recognize that they have actually been freed from their episode since they were unable to cope with life's exigencies premorbidly, and postmorbidly they still cannot cope. The hospitalization episode is often no promoter of better coping efforts. In such patients the episode may appear to persist, thus giving schizophrenics a bad name.

Other workers also have entertained the possibility that schizophrenia occurs in self-limiting episodes. Bockoven and Solomon (6) concluded that pre-drug-era follow-ups showed results as good as drug-era follow-ups. They discussed the common philosophy that permeated the clinical and social management of patients in the two eras:

This philosophy is based on the idea that the majority of mental illnesses, especially the most severe, are largely self-limiting in nature if the patient is not subjected to demeaning experiences or loss of rights and liberties. Therapeutic management consists first and foremost of removing these negative influences
and replacing them with a positive attitude of respect for the patient’s needs for human companionship and interest-holding activity. Somatic treatments are prescribed in this context to relieve specific kinds of suffering and thereby to expedite the spontaneous healing process. (p. 796).

Extein and Bowers (13) considered the functional disorders as “states” (episodes) rather than “traits.” They indicated that:

State disorder refers to those qualitatively different mental conditions which tend to be time-limited and autonomous in that, once present, they are relatively insensitive to environmental input. They respond poorly to verbal or other psychosocial treatment but usually respond to medication or other somatic treatment. Specifically, state disorders include schizophrenic and other functional psychoses, mania, major depression, severe anxiety, acute organic brain syndrome, and seizures. Most of these state disorders probably involve a variety of environmental stressors acting on genetic or other biological vulnerability.

The more benign outlook on schizophrenia has not yet been accepted universally. This is made clear by the neo-Kraepelinian character of the newly proposed DSM-III. The reason for this may rest on the premise that codification of diagnosis, like codification of laws, must not keep up too closely with science but must stay discretely behind it, especially when the scientific results are still tentative. The more basic conception of schizophrenia provided by Kraepelin may still be the firmest thing we can offer for diagnostic codification, but not the best we can offer for research.

RELATION OF EPISODIC NATURE OF SCHIZOPHRENIA TO VULNERABILITY

In order to find an explanation for the episodic nature of schizophrenia we must first examine the causes of the schizophrenic disorder. Considerable advances have been made in the investigations of the phenomenology of schizophrenia by the development of more objective and reliable methods for describing the deviant behavior of the schizophrenic in the setting of structured and semi-structured interviews. The data obtained in this manner can be systematically organized into dimensions of psychopathology, which provide the basis for matching behavior with the diagnostic criteria required for assigning a patient to a specific category.

Description of behavior, however, is not enough to find the causes of mental disorder or to intervene successfully in the rehabilitation or even prevention of mental disorders. Ever since early man trephined skulls to eject the evil demons, attempts have been made to divine the sources of mental illness and these attempts can now be formulated as scientific models on the basis of which hypotheses are projected and experimental work done to test their tenability.

At least six models have been proposed to explain the etiology of mental disorders. They range from a molecular-biological model, primarily influenced by genetic factors, to a field-theory model which is primarily influenced by
ecological factors. Models favoring the internal environment and neurophysiology as determinants of mental disorders are more closely related to the genetic factors, whereas models favoring development and learning are more closely related to the ecological factors (58) (Fig. 1.).

The genetic model is perhaps the most advanced model in terms of tenability. It is based on the belief that predisposition to schizophrenia is inherited. This model suffered a setback when the concordance rates for monozygotic twins reported by Kallmann (26) to be between 0.69 and 0.86 were found to be considerably lower by other investigators who used more representative samples of monozygotic twins. However, the model regained strength from the adoption studies begun by Heston (21) in Minnesota and by Kety, Rosenthal, Wender, and Schulsinger in Denmark (28). It is acceptable now to state that genetics may be a necessary but not a sufficient cause for schizophrenia, although not all researchers (including some geneticists) subscribe to the necessity of a genetic etiology for schizophrenia (29). At the opposite pole is the ecological model. It has not yet gained as much general scientific acceptance. One advantage the genetic model has over the ecological model is its use of consanguinity as a measure of degree of genetic similarity. There is, as yet, no comparable measure for assessing degree of similarity of ecological factors, though one will be suggested in this chapter. Nevertheless, some components of the ecological model have been generally accepted as being associated with schizophrenia: i.e., socioeconomic status, physical and social characteristics of the milieu, social network supports, minority status, etc. Claims that these components are necessary or sufficient to elicit a schizophrenic episode have not been pressed as hard as the claims for the genetic model.

The developmental model dealing with the ontogenesis of behavior has focused attention on perinatal factors, nutritional factors, and lag of maturational development as indicators associated with the development of schizophrenia. Recently, research by Kinney and Jacobsen (29) revealed that the season in which an individual is born and cerebral injury after birth increase the likelihood of schizophrenia in probands of low genetic risk (i.e., those with no known schizophrenia in their immediate family). They conclude that schizophrenia in at least some of the low-risk probands is environmentally induced or a phenocopy, thus giving the developmental model and the other nongenetic models considerable etiological support. But there is no conclusive evidence yet that the developmental factors are either necessary or sufficient as etiological agents in the occurrence of schizophrenic episodes.

The eminent Adolf Meyer was a progenitor of the learning theory model for the etiology of schizophrenia. He stressed that the accumulation of faulty habits in reacting to life’s exigencies could become a cause for the initiation of dementia praecox. Accordingly, the development of ineffectual social and interpersonal relationships, whether learned actively in maladaptive situations or passively through modeling on inappropriate models, can render individuals
more vulnerable to later life-stressors. In this way early learned helplessness may lead to depression in adulthood under sufficient stress. The family unit, which transmits attitudes, habits, values, and communication patterns, is an important etiological agent according to this model. Yet there is still no cogent evidence for causality here.

The internal environment model has perhaps been the most prolific in providing hypotheses for the etiology of schizophrenia. It stimulated the search for biochemical abnormalities in schizophrenia. To date, research conducted in this area has probably done more for biochemistry than for psychopathology. However, considerable progress has been made in psychopathology as well. A search began in the 1940s for peripheral metabolic correlates of schizophrenia, observable in the blood and the urine (27). It failed primarily because the metabolic changes which were found turned out to be nonspecific. More recently the search has shifted to an investigation of central synaptic mechanisms. Our improved understanding of synapses was summarized recently by Kety (27) as follows: “The recognition that these are chemical switches provides crucial loci at which metabolic processes, hormones, and drugs may affect these junctions and influence the psychologic processes they mediate” (p. 85). The psychological processes which are mediated through the biochemical reactions occurring at synapses include perception, cognition, attention, motivation, mood, and other emotional and mental states. Kety concluded that: “Although . . . the mechanisms of action of the drugs effective in the treatment of mental disorders are becoming well defined, the metabolic and biochemical factors involved in schizophrenia and the affective disorders have not been elucidated.” Here again, we have no definite evidence.
The neurophysiological model has been instrumental in stimulating investigators to use a considerable array of techniques for examining deviations in those functions of the schizophrenic’s brain which affect information processing and to probe how the central nervous system and the autonomic nervous system might deviate from normal expectations. Deviations could occur at any level of information processing, beginning with: (a) reception of the energy and information in the stimulus; (b) encoding and processing of the information in higher centers; (c) interaction of the arriving information with stored memories of previous experiences and wired-in patterns of networks, and (d) emission of the final response. Among the techniques which have been found useful in differentiating schizophrenic from other mental patients and normals according to Spring and Zubin (49) are various reaction time measures including Shakow’s crossover index and our own cross-modality effect and Steffy’s redundancy effect; event-related potentials, especially Sutton’s P300; pupillography à la Hakerem and Steinhauer and Rubin; and smooth pursuit eye movements à la Philip Holzman. Thus far the results are still only promising. A more recent review of the neurophysiological and psychophysiological techniques has been provided by Spohn and Patterson (47).

ETIOTYPES

The advanced state of the genetic model based on consanguinity as a measure of genetic similarity and on well-developed biologically anchored genetic theories had cast a pall on etiological claims of the other five models. But the preeminent position which genetics held in the etiology of schizophrenia until recently has been eroded by the new evidence that suggests that phenocopies for schizophrenia may exist so that the disorder may develop in individuals who do not possess the genotype for schizophrenia (29).

Thus we can now postulate other etiological types or “etiotypes” to represent the other scientific models in a manner analogous to the way the genotype

<table>
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<td>Vulnerability</td>
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*Suggested by E. I. Burdock from the Greek root for growth.

*Young by K. Salzinger from the Greek root for learning.

*Because Rado and Meeli have preempted the term schizotype, a new term had to be provided for one prone to schizophrenia without exhibiting schizotypy.
represents the genetic model. This is shown in Table 1. Each of the etiotypes in Table 1 characterizes individuals vulnerable to schizophrenia on the basis of the model from which it is derived. Some of the potential markers which might identify these etiotypes are also shown in Table 1.

**CURRENT IMPASSE**

Having described the advances made possible in the past by considering the implications of each model, and having postulated etiotypes for each of them, we will now turn to their current status.

The genetic model represents the most advanced etiological approach to schizophrenia. According to this model the etiological agent is the genotype which is transmitted from one generation to the next. If we accept a monogenic model, this genotype contains the genetic “anlage” for schizophrenia in the form of a deviant allele in a particular location on a specific chromosome. If we accept a polygenic model, the genotype is the result of deviant alleles in various locations. It is clear that the person possessing the genotype for schizophrenia does not always develop the phenotype.

It has been demonstrated that some individuals have a higher risk for developing an episode of schizophrenia by virtue of their consanguinity with probands, but no further advances on the basis of the genetic model have been made in locating any allele or alleles presumably responsible for the disorder. Nor has it been possible to explain why some genotypes develop into phenotypes while others do not. Nor has it been possible so far to link the DNA structure of the genes with the biochemical action of the internal environment. Despite the notable advances made with the use of each of the models, we have not yet found any necessary or sufficient causes for schizophrenia. To overcome this impasse is our immediate problem.

**VULNERABILITY MODEL**

In trying to fathom why we have reached the current impasse, I realized that the six etiological models have been working until very recently in relative isolation from each other. Thus, although each model has the common goal of finding the etiology of schizophrenia, each fails to provide the means for either confirming or negating hypotheses emanating from competing models. But is there a common thread that may bind them together?

A logical analysis of all these models would indicate that it is the interaction of these models rather than their individual main effect which produces the schizophrenic episode. If we squeezed all of these models into a goblet, what would their common elixir contain? I suggest that it would contain the common denominator of vulnerability. This vulnerability is composed of contributions from the various etiological models. The vulnerable individual—the schizotrope—may bear the genotype for schizophrenia, any one of the other five etio-
types discussed earlier, or any combination of these etiotypes. Thus, though no single etiotype is in itself a necessary and sufficient etiological agent, the interaction between these etiotypes can produce a schizotrope who may suffer an episode if triggered by a sufficiently stressful life event.

Once an episode has occurred and the symptoms of the disorder are visible, what maintains the symptoms? Do such episodes have a natural history which runs its course, or are there certain life events or contingencies which tend to maintain the episode and whose elimination or prevention would tend to shorten the episode? A behavioral analysis of episodes seems necessary to answer this question.

It is important to determine the various kinds of events which trigger a crisis. Specifically, a triggering event is defined as an event which elicits a crisis in a vulnerable individual, this crisis leading to an episode depending on the degree of vulnerability. Triggering life events should not be confused with etiological life events which give rise to the various etiotypes (ecological, developmental, learning). The latter are long-term influences formative of vulnerability. An example given by van Praag (53) of such a long-term influence is the long continued exposure to serious emotional neglect during childhood which results in the "deprivation dwarfism" syndrome. In this condition somatic growth and mental development are retarded despite normal and even excessive food intake, but this retardation is quickly overcome after hospitalization without hormonal substitution. In comparison, the "triggering" life events are recent life event stressors of short duration which induce sufficient stress to produce a crisis. They can be either somatic or psychosocial in nature. Thus, the somatic effect of childbirth may be a sufficiently stressful life event to serve as a trigger, or the psychosocial loss of a beloved relative may trigger a crisis.

A useful distinction has been made by van Praag (53) between "stable" and interactional life events. By stable life events he refers to immutable or irreversible events like the loss of a spouse. Interactional events involving interpersonal interactions such as sharp exchange of words, hatred, jealousy, or rejection may be quite potent in triggering a crisis but are not as easily traceable. Thus, the critical attitude of family members towards a returned patient may hasten either a relapse or a new episode. Brown and Rutter (7a) have developed techniques for monitoring such life events.

In searching for criteria to distinguish between life events that serve as triggers and those that do not, the following classification has been suggested: those that (a) produce losses; (b) are undesirable; (c) are novel; (d) are unexpected; (e) are unanticipated; (f) are uncontrollable; and (g) require considerable readjustment of daily routine. It would be well to find a common denominator for these criteria. It has occurred to the writer that the impact of the life event on the social network support system that surrounds the individual may serve as the common denominator which triggers the crisis and episode. One could argue that the other criteria bring about their stressor effects only insofar as they overwhelm the defenses provided by the social network supporting system.
This is why, for example, the presence of a confidant protects against depression (7) and the reason why certain losses can be withstood as long as the social network remains intact. It is interesting to note that of the 43 items in the life event schedule provided by the Social Readjustment Rating Scale of Holmes and Rahe (22), fully 37 or 86% involved reduction in the social interconnections of the individual (death of spouse, divorce, etc.).

As long as the stress is below the threshold of vulnerability, the individual responds to the stressor with a minor crisis in an elastic homeostatic way and remains well within the limits of normality, his coping ability remaining intact. When the stress exceeds the threshold, his coping ability collapses and he is likely to develop a major crisis, followed by a psychopathological episode. Furthermore, we postulate that the episode is time limited. When the stress sinks below the vulnerability threshold, the episode ends and the patient returns to his pre-episode level of coping.

A considerable amount of evidence has been collected on the role that triggering life event stressors play in the elicitation of both physical and mental disorders (7,12,40). The strain of readjustment to the consequences of the life event, if

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**FIG. 2.** Relation between vulnerability and challenging events. (The equation for this hypothetical curve is \( VS = K \), where \( V \) is the degree of vulnerability, \( S \) is the degree of stress induced by the challenging event, and \( K \) is a constant.)
severe enough, appears to trigger first a crisis, which in the case of a vulnerable person—schizotrope—then leads to an episode of illness as shown in Fig. 2, relating life event stressors to vulnerability.

**VULNERABILITY MARKERS**

In order to test the tenability of the vulnerability model and of the hypotheses emerging from it, markers are needed that will identify the vulnerable individual. A marker is an identifying indicator of a specific condition such as a disorder. In genetics it indicates a gene of known location and effect, which makes possible the determination of the distribution of other less conspicuously effective genes. In psychometrics it denotes a test of known factorial structure which can be used to identify the presence of the factor with which it is highly correlated. Here we shall use the term marker to designate a specific performance or characteristic which characterizes individuals who have demonstrated vulnerability specifically to schizophrenia. To assure the validity of a marker we must establish its presence in individuals who have already exhibited vulnerability by succumbing to at least one episode of schizophrenia and establish its absence in matched controls. Once the marker is established as an index of vulnerability, it can be used to discover vulnerable individuals who have never had an episode.

It should be pointed out here that we have extended the term marker beyond its usual more limited boundaries as used in genetics where, strictly speaking, a marker denotes a condition but is itself not associated in any direct way with the condition (e.g., color blindness and manic-depressive psychosis). Because of the open-ended definition of schizophrenia, it is unrealistic to expect that every schizophrenic patient will exhibit a marker, and we must, therefore, investigate every differential characteristic between schizophrenia and other conditions to determine whether the characteristic can serve as a potential marker of vulnerability.

At present, most research is conducted with patients during an episode, hence, it is difficult to determine without further follow-up whether a given marker is a vulnerability marker or an episode marker. If the marker persists after the end of the episode there is a greater chance that it will be a vulnerability marker, while those markers which disappear with the episode are episode markers. A further check for a vulnerability marker is possible by examining unaffected siblings of patients. If these siblings show the marker with a frequency higher than would be expected in a normal population, it would be evidence in favor of a vulnerability marker.

The vulnerability markers can be classified in accordance with the etiological model from which they spring. In addition the descriptive approach also provides certain marker-like characteristics which are claimed to be unique to schizophrenia. Among these are Schneider's (45) first-rank symptoms, Jasper's (25) concept of ununderstandability, and a variety of other phenomenologically based claims which could eventually be exploited as markers if they could be established.
on a more objective basis. The Chapmans (11), for example, have shown that
the clinical concept of anhedonia and of body-image distortion can be quantita-
tively scaled through an inventory. Some day, perhaps, we can establish the
physiological underpinnings of “thought insertion” or “thought stealing” in
the manner that we established the underpinnings of dreams through the dis-
covery of rapid eye movement (REM) which accompanies dreaming.

Investigations of vulnerability markers are still in their infancy. A review
of the current status of these markers as of 1977 was published in 1979 (59).
The following discussion will be confined to two opposite models—the ecological
and the neurophysiological.

Ecotype Markers

We have already discussed life event stressors as immediate, short-term ecological
triggers of episodes in the vulnerable. Now we shall deal with long-term ecological factors in the formation of vulnerability and try to find markers for
identifying those who are vulnerable on ecological grounds. Among the potential
factors formative of vulnerability are low socioeconomic status, degree of commu-
nity disorganization, crowding, minority status in the community, high mobility,
migration, ethnicity, and cultural influences. All of these factors and many others have been implicated as etiological agents in the development of schizophrenia. The controversies regarding the relative importance of these fac-
tors and whether they are causes or effects are too well known to be discussed
here. It would be highly desirable to find a common denominator for integrating
the impact of these forces so that this common denominator could provide
the markers we are seeking.

As was previously suggested by us and by Hammer et al. (20), the social
network of the individual and the degree of support, constraint, or freedom
imposed on it by the ecological niche may be such a common denominator.
The relationships that make up the social network “may be thought of as the
basic building blocks of social structure; and their formation, maintenance, and
severance are universal and fundamental social processes” (20). They may pro-
vide insight into the relationship of various social factors with psychiatric disor-
ders. Thus, a ghetto niche may impose restraints on the size and mutual intimacy
of the network by having poor physical facilities which discourage network
development. Bereavement and other losses due to such factors as moving away
from a neighborhood also tend to disrupt networks.

Just as the vascular network serves to nourish and maintain the homeostasis
of the internal environment, the social networks serve similar functions for
the external environment. The vascular network provides some biological bases
for identifying and classifying an individual by indicators such as blood types
and other genetic markers. In a similar fashion, the social network could provide
by its branching structure, density, quality, and quantity of interconnectedness,
indicators to classify and identify individuals in the social sphere. It is possible
that the social network analysis could do for the ecological model what consanguinity did for the genetic model.

The importance of the social networks is not limited to the social sphere. Berkman and Syme (2) report that social network ties are an important determinant of survival even when the other important determinants of mortality are kept constant: (a) self-estimate of physical health; (b) year of death; (c) socioeconomic status; (d) smoking; (e) consumption of alcohol; (f) obesity; (g) physical activity; (h) utilization of preventive health services and health practices.

Since the impact of any ecological factor depends on the stress it induces, we may postulate that unless the stress is more powerful than the countervailing effects of the social network in which the individual is imbedded, a schizophrenic episode may not develop.

Is there any evidence that social networks are important in the etiology of episodes of schizophrenia?

Though the literature on the relationship between network characteristics and schizophrenic disorder is not entirely consistent, some trends are emerging. Individuals with schizophrenic disorders seem to have smaller networks than those nonpsychiatrically ill (37a,46a,52a). Schizophrenics who have small, low-density, nonmultiplex networks run a higher risk of rehospitalization (46a).

Hammer et al. (20) have summarized the evidence for the relation between social network characteristics and the development of schizophrenic episodes from the point of view of the ecological model. The following ecological factors have been found to be associated with higher risks of schizophrenia: migration, social marginality, lack of acculturation, underprivileged ethnic origin, and social isolation. These factors tend either to prevent the development of normal social networks or to disrupt them. They are also highly associated with lower socioeconomic status. This may be the reason why lower socioeconomic status brings with it a higher risk of schizophrenia.

Thus, it is quite clear that a benign social network may be the bulwark against the development of vulnerability to episodes, and an inadequate or malignant social network may be etiological in the development of vulnerability.

How to classify social networks into benign and malignant and how to quantify their protective or malignant influence is a task facing the psychopathologist, and fortunately there is a growing literature on this question (1,20).

Neurophysiotype Markers

The neurophysiological model deals with the way the brain processes information, a field in which considerable work is going on both in normals and in patients.

Regardless of which etiotypes contribute to the schizotrope status, the end result is aberrant behavior, which may be the result of an aberrant nervous system. The neurophysiological model is eminently suited to detect such aberrations in a systematic, objective fashion. Therefore, we have focused our efforts
in this direction. We must, however, not attribute all aberrant behavior to endogenous biochemical or genetic influences on the nervous system. We are cautioned by the possibility presented by the learning model that deviant patterns of behavior may have occurred through learning without involving genetic or endogenous biochemical influences. That such a possibility exists has been indicated by the evidence that chronically hospitalized schizophrenics sometimes exhibit behaviors that are iatrogenic (17), having been learned as appropriate during their hospitalization, and are not related to the illness directly (38).

Neurophysiological markers involving psychomotor control which have been found to characterize mental patients as well as their first degree-relatives have recently been summarized by Zubin (59). Among them are: (a) Cancro’s measures of eye movements during visual mental tasks; (b) Holzman’s recording of smooth pursuit eye movements; (c) Kornetsky and Orzack’s vigilance task of continuous performance. Among other neurophysiological markers that have been proposed, the EEG, evoked potential, and autonomic markers have been most prominent (57,60).

It appears most likely that the evoked potentials, which have smaller amplitudes in schizophrenics than in depressives and normals, are episode rather than vulnerability markers. The amplitude of all the components tends to be universally related to the severity of clinical symptoms, returning to their normal size during periods of remission. Whether they become entirely normalized is not clear yet.

However, there is some evidence that the pattern of augmentation or reduction as a function of stimulus intensity, as reported by Buchsbaum (10), may indeed be a vulnerability marker. This author defines augmentation as the tendency for the amplitudes of the early components of the cortical evoked potential to increase with the intensity of the stimulus. Reduction refers to the opposite tendency.

Haier, Buchsbaum, and Murphy (18) sampled a college population to obtain blood samples for MAO determination and applied the Minnesota Multiphasic Personality Inventory (MMPI) and the Schedule for Affective Disorders and Schizophrenia (SADS) as well as the Research Diagnostic Criteria (RDC) for determining the presence of psychopathology. They found that individuals with the pattern of either low MAO and an augmented average evoked potential or high MAO and a reduced average evoked potential showed sufficient psychopathology to qualify as affective disorder patients on the RDC.

In connection with a series of ongoing studies of vulnerability launched while the author was Chief of the Biometrics Research Unit of the New York State Psychiatric Institute (NYSPI), several techniques have shown some evidence of serving as potential markers. (These studies are continuing under the direction of Dr. Samuel Sutton, Department of Psychophysiology at NYSPI, Dr. Bonnie Spring, Department of Psychology and Social Relations at Harvard University, Dr. Harvey Babcock, Bar Ilan University, Israel, and the author at the VA Medical Center, Highland Drive, Pittsburgh, and the Department of Psychiatry,
University of Pittsburgh School of Medicine.) Some of the results of these studies follow:

Sensory Thresholds

Schizophrenia is supposed to exist in an intact sensorium, and no evidence was available until recently that the sensory thresholds of schizophrenics differed from those of normals. Recent studies, aided by the new signal detection and forced-choice techniques, have shown the original supposition to be in doubt (8,37).

The vision laboratory of the Department of Psychophysiology at the New York State Psychiatric Institute, Dr. Mitchel Ketzman, director, has collected detection threshold data in two separate studies involving 101 subjects—55 patients (schizophrenics and depressives), 15 siblings of schizophrenic patients, and 31 nonpatient control subjects. Results from these studies indicate that approximately 50% of the patients have higher visual thresholds (are less sensitive) than any of the nonpatient subjects. Furthermore, five clinical factors obtained from semi-structured interviews—auditory hallucinations, hypomania, reported belligerence, bizarre behavior, and grandiose delusions—are significantly and positively correlated with higher visual thresholds.

These visual threshold findings are unique and can not be extended to other modalities as shown by the findings of the audition laboratory of NYSPH, Dr. Gerard Bruder, director. Bruder, Sutton, Babkoff et al. (8) used a forced-choice staircase procedure to measure thresholds for detecting a click. High click thresholds in patients were associated with a diagnosis not of schizophrenia but of affective psychosis. The click thresholds were significantly and positively correlated with the factor based on degree of speech retardation ratings. Ratings on other clinical factors usually associated with affective disorders (depression or hypomania) and those usually associated with schizophrenia (delusions, hallucinations, flat affect, incomprehensibility) were not significantly correlated with click thresholds. These findings have been recently replicated in two additional studies (8,9).

Yozawitz, Bruder, Sutton et al. (56) have also tested patients and controls on measures of central auditory processing and lateralization. They used a forced-choice threshold procedure to measure summation of dichotic two-click stimuli. The ear asymmetries for affective psychotic patients were similar to those for right temporal lesioned controls and differed from those of schizophrenic patients and normal controls. The implication of their findings for cerebral asymmetry in psychopathology falls in line with recent research linking affective disorders and right hemisphere involvement.

Pupillary Response

Reduction in the amplitude of the pupillary contraction to light and the related dilation to the onset of darkness has been reported consistently for schizo-
phrenic patients as contrasted with normals (19). The data indicating that such response decrements are maintained even after the end of an episode suggest that the pupillary response may serve as a vulnerability marker. The influence of phenothiazines on pupil contraction has been discounted in most studies, although scattered reports suggest that long-term phenothiazene administration may produce additional reduction temporarily, which rebounds after withdrawal of drugs (23,35,41,42).

Schizophrenic patients also show a marked deviation in psychosensory dilation to nonvisual stimuli (pupil contracts only to light—to other stimuli it dilates). Under “uncertain” conditions when they guess whether the coming stimulus will be one or two clicks, schizophrenics fail to show dilation while normals have a marked dilation.

Pupillary reactions of acute schizophrenics and their healthy siblings were studied by Steinhauser, Hakerem, and Spring (50). Most normal subjects and siblings showed a large dilation to auditory stimuli under uncertain conditions when guessing, as compared to the smaller response produced when subjects were certain of the nature of the stimulus. All patients, as well as several siblings and control subjects, failed to show a dilation when guessing, and the evoked potentials in these subjects were also reduced. Further study of individuals with aberrant pupillary and evoked potential characteristics is in progress. Whether this is an episode marker or a vulnerability marker remains to be demonstrated.

**EPISODE MARKERS**

Thus far we have dealt with markers that presumably earmark vulnerability. The markers which indicate the onset, duration, and offset of an episode have not been studied as actively as the vulnerability markers. The difficulties in pursuing such studies have been described elsewhere (61). Since most of our investigations deal with patients during their episodes, we must be able to distinguish episode markers before we can find vulnerability markers.

Episode markers can be classified in accordance with the etiological models from which they emanated.

**Ecological Markers**

It has been shown, using the Holmes and Rahe scale, that an accelerated rate of occurrence of life events forebodes the development of episodes. Thus, if we were to monitor the rate we could use this as an index of a forthcoming episode and by the same token use it to indicate the end of an episode when the rate normalizes (39).

The beginning of an episode often follows close on the heels of a period of coping failure. Similarly, once the episode of disorder has subsided, one may expect the patient once again to be able to resume coping at his characteristic premorbid level and style. The concurrence of periods of coping dysfunction
and restoration with episodes of psychiatric disorder and recovery opens the way for investigation of another type of episode marker. If we were to have knowledge of the patient’s premorbid level of coping ability, we could use evidence of a sharp plummeting of coping effectiveness and a return to the usual capacity for efficiency as rough boundaries to index the course of a psychopathological episode. Following Goldfried and D’Zurilla’s (15) behavior-analytic model for assessing competence, Goldsmith and McFall (16) have experimented with simulated interpersonal contexts to evaluate the effectiveness of patients’ social coping strategies. The entire spectrum of role performance should actually be sampled to see whether the capacity to cope has returned to its premorbid level. Weissman (54) has recently reviewed 15 scales available for assessing performance in occupational, marital, extended family, and community roles. These might serve to probe for fluctuations in coping capacity that occur during hospitalization, particularly if it were possible to tap the significant role contexts in simulated situations (15).

Learning and Developmental Markers

The speech and thought processes of the patient, which may be highly dependent on learning and reinforcement, are often found to deviate from the usual during an episode. Monitoring the speech and thinking characteristics at the onset, duration, and offset of an episode can provide markers useful for our purposes. Schmale (44) suggests that giving in to feelings of helplessness and hopelessness is the earmark of a beginning episode. Luborsky and Auerbach (36) have derived another potential mini-episode index by examining speech samples of patients in psychoanalysis taken just before instances of momentary forgetting or just prior to reports of migraine headaches or stomach pain. When these passages are rated for expression of content, hopelessness ratings are found to be much higher than for samples taken at other times during therapy sessions. It is not entirely outside the realm of possibility that mild transient mini-episodes might also be provoked experimentally by psychological or biochemical challenges. The ethics of such experimental procedures must be carefully investigated so as not to interfere with the civil rights and freedom of the patient, but under skilled personnel, mindful of the ethical issues involved, perhaps some salutary solution can be found. It should be no more hazardous than a challenge with a glucose tolerance test in diabetes.

Internal Environment Markers

Janowsky et al. (24) have shown that if methylphenidate (Ritalin®) is injected in a patient undergoing an episode of schizophrenia, an exacerbation of the episode will occur briefly, but if the episode is ended, no exacerbation is induced. Thus, challenging a patient with methylphenidate can be used as a probe for determining the state of the episode.
Another strategy may be to monitor mini-episodes or acute periods of symptom exacerbation in patients during their hospital stay. These may, in microcosm, reveal some properties of onset and offset of maxi-episodes. Some progress has been made in this area. Although most of it has concerned a search for indicators of the onset and offset of mini-episodes in depressed patients, it is likely that comparable indexes can be found for schizophrenic mini-episodes induced by visitors, peer conflicts, and so on. In a study of the rise and fall of corticosteroid levels in reactive depression by Sachar, MacKenzie, Binsback, and Mack (43), it was observed that hormonal stress levels rise when the patient actively struggles with the confrontation of the loss of a love object or when his defense mechanisms falter temporarily. On the other hand, when his defenses are operating adequately and he seems clinically comfortable and adjusted, the hormonal level drops to normal. After the patient has adjusted to the hospital regime and achieved stable hormonal levels, perturbations in corticosteroid levels may therefore index the eruption of mini-episodes.

**Neurophysiological Markers**

Just as the beginning and end of episodes of epilepsy can be indexed by electroencephalographic characteristics before and after seizure, so in depression there have been findings indicating that changes in sleep characteristics (30) and motility (32) serve to mark the beginning and end of episodes. In schizophrenia, too, a reduction in rapid-eye-movement sleep accompanies acute episodes (31).

**VULNERABILITY: RECOMMENDATIONS FOR ITS STUDY IN SCHIZOPHRENIA RESEARCH**

As a result of the research work now going on in various laboratories, it is expected that we will have available in the not too distant future a series of vulnerability and episode markers together with a group of triggering contingencies which elicit episodes in the vulnerable. Some of these may turn out to be predictors of episodes in the vulnerable.

It would thus be possible to detect individuals in the general population who stand in high risk of developing episodes. As a first step, it would be advantageous to study a group of siblings of schizophrenics because of the increased risk they represent, to determine which of them exhibit the markers. These siblings could then be followed for several years to determine who succumbs to an episode. The circumstances which surround developing episodes, the life events, and the social networks that surround the individuals could be analyzed to determine the triggering events leading to the episode. The siblings who do not show the markers can also be followed for control purposes and their development compared with those who have markers. A comparison of those who show the markers with those who do not, and a comparison of those with
markers who develop episodes with those who do not, ought to shed light on the question of what kind of intervention may be possible.

Eventually, with the results of such a study in hand, it will be possible to sample the general population for the vulnerable individuals and institute possible therapeutic interventions for preventing the development of episodes. A beginning in screening the general population by Haier, Buchsbaum, and Murphy (18) has already been described. Similarly, the Chapmans (11) found that individuals with high scores on their anhedonia scale and on their body-image scale (two standard deviations above the mean) reported symptoms of rather severe psychopathology. It is important to develop such techniques for screening out individuals with deviant characteristics in order to provide them with prophylactic intervention against the development of episodes and to eliminate such individuals in selecting control groups in studying schizophrenics. Among the specific gains that the discovery of markers can achieve are the following:

1. **Aid to diagnosis**: The availability of objective markers of psychopathology for the various mental disorders can help validate the diagnostic categories into which patients are placed.

2. **Differential diagnosis**: One of the perennial problems facing the diagnostician is how to separate affective disorders from schizophrenia. The availability of specific markers can help in their differentiation.

Individual differences in the behavioral, physiological, or biochemical indicators within the psychiatric population may themselves become the basis for delineating more specific patient subgroupings. Sutton has emphasized the possible advantages of utilizing such an iterative approach (51,52) in which the independent variables are interchanged. Individuals who exhibit similar patterns or profiles of behavioral, physiological, and biochemical responses can constitute a new subgroup. These subgroups may be identified by cluster analysis. Subgroups can then be compared for their clinical characteristics as determined by the clinical assessment procedures. That is, response differentiation in the laboratory test profiles is assumed to reflect some characteristic difference between the patient groups which can be verified by examining their clinical profiles. The newly found clinical profile which characterizes these subgroups can now become the independent variable for classification. The profile of laboratory test performance becomes the dependent variable to see how clearly the new clinical subgroups live up to the expected laboratory profile differentiation.

This iterative process can continue until a stable set of subgroups is established and replicated on new data. For example, the iterative approach can be applied to the study of EEG patterns to distinguish psychiatric subgroups, much as they have been used for identification of individuals prone to seizures or having localized neural pathology (14).

3. **Objective indicators of episodes**: Objective episode markers can provide indicators of the beginning and end of episodes and provide objective indications for initiating and terminating treatment, and thus avoid errors in delay of treat-
ment or in prolonging it unduly with the danger of incurring unnecessary side effects.

4. Avoiding the stigma of mental illness: If we can alter the public image of schizophrenia from that of being a persistent deteriorative disease to that of being a vulnerable state, the stigma of schizophrenia, which now attaches to former patients and which prevents the majority of them from resuming their place in society, can be mitigated.

5. Prophylaxis for the vulnerable: Individuals who belong to the vulnerable group can be educated to deal with their vulnerability in the same way that diabetics or hypertension cases can be educated to live more normal lives by preventing or avoiding situations which may catapult them into an episode. Furthermore, if the staff could be taught to regard the patient as vulnerable rather than as sick, and proceed to relieve him of the stressors which elicit his vulnerability, there would be no need to label him as ill and induce him to accept the label. The label of vulnerability is probably much easier to take and live with since it presages a brief episode from which the patient will soon recover without being labeled schizophrenic the rest of his life. Furthermore, the episode could hopefully be prevented by proper intervention.

6. Other advantages: There are several other baffling problems which the vulnerability hypothesis can help explain. The apparently spontaneous recovery of long-standing patients falls into this category. The patient may have emerged from his episode much earlier but the recognition of this fact may occur suddenly and the recovery consequently may be regarded as miraculous. Some patients develop and mature in the hospital and increase competence and coping efforts under its protective environment. These too fit into the vulnerability hypothesis since it is often reported that suddenly, patients who have been hospitalized for many years make a miraculous recovery. As a matter of fact, the episode has long since passed and the primary change has been not in the disease process but in further development of coping skills. The observation of Manfred Bleuler (5) that as decades passed, there was a tendency toward improvement, rather than deterioration, falls into this category.

Perhaps the most trenchant reason for investigating the vulnerability hypothesis stems from the fact that advances in health are likely to come in the future, as in the past, from modification of conditions which lead to psychopathology rather than from therapeutic intervention after it has occurred. We need to tackle the conditions leading to the disorder, whether they be internal or external, before the disorder develops. Notable examples of such an approach are the “high-risk” studies of the offspring of the mentally ill. However, these “high-risk” studies are perforce longitudinal and the payoff in terms of actual cases is low. Only a minority of schizophrenics belong to families with a history of schizophrenia (46). Only about 5% of the parents of schizophrenics and about 9% of the siblings of schizophrenics suffer the same disorder. Whether they are representative of schizophrenia as a whole is highly debatable. Bleuler (5),
for example, has reported that those with family histories tend to have milder disorders. Another problem is the fact that “only” offspring of fertile, married, cooperative, and sustaining parents, often lodged in intact families, constitute the sample in high-risk studies. In our vulnerability study we are certain that the patients we study are diagnosed schizophrenic and any markers we discover can be used to detect individuals in the population and initiate effective intervention even before an episode develops.

**SUMMARY**

Schizophrenia today is no longer the deteriorative disorder which it appeared to be 40 years ago. The vast majority of schizophrenics seem to spend the majority of their lives in the community. If the community were to provide better facilities, Manfred Bleuler’s follow-up studies (5) suggest that probably only 6 to 10% would remain chronically ill.

Schizophrenia is not basically a continuous disorder. What is continuous is the vulnerability to the disorder. This vulnerability can remain latent for life, or be elicited by life event stressors of both the exogenous and endogenous variety. It resembles an allergy rather than a persistent disease.

The underlying causes of the vulnerability depend on the etiotype or types which characterize the person, and these range from ecotype to auxineotype (development), mathetotype (learning), genotypetype, chemotype, and neurophysiotype. The impact of a life event stressor produces a crisis in all of us. Depending on our degree of vulnerability, we can contain the crisis homeostatically, as long as the stress produced is below our threshold. If it exceeds our threshold of vulnerability, an episode of illness will develop. When the episode ends, and all of them are time limited, we return to our pre-episode coping level. If that was good to begin with, we are regarded as recovered. If it was on a poor premorbid level, we are often mistakenly regarded as still disordered even though the episode has ended. The primary therapeutic problem is not so much to cure the disorder—it is self-limiting—but to provide the means for preventing the initial occurrence or recurrence of the episode.

To accomplish this end we need to find markers of vulnerability for the various etiotypes, and markers for the beginning and end of episodes. Once these are available we can through the use of screening tests identify the vulnerable and provide them with techniques for preventing initial or recurrent episodes, through the use of therapeutic psychological and/or pharmacological or other somatic intervention.

What is preventing the discovery of the markers today and what is causing the logjam? It is unlikely that any one etiological model will provide pathognomonic markers by itself. Even the advocates of the most highly developed model—the genetic—seem to have given up such a claim. Only the patterning of the markers across the etiological models can break the current logjam. Whether such patterns will require the subdivision of schizophrenia into separate
subcategories or whether schizophrenia can remain polythetically defined even though it may lose its monothetic character remains an empirical though challenging question.

The implications of the vulnerability hypothesis for chronic schizophrenia are only vaguely discernible at this time because the hypothesis is still in the process of being tested. If the hypothesis proves tenable, only a small fraction of schizophrenia (some 6 to 10%) need ever become chronic. Even these cases need not remain in their chronic state for life (38). As for the recidivists to whom the revolving door pattern applies, a monitoring of their home atmosphere for its emotional quality can give the clues to the triggering events which initiate relapses or new episodes (34). As for those who are no longer in their episode but are still kept in the hospital mistakenly, the discovery of episode markers may hasten their delivery from overtreatment or prevent too early release.

But the most important implication of the vulnerability hypothesis is that the future discovery of the markers of vulnerability and of the beginning and end of episodes, as well as of the triggering contingencies which elicit episodes in the vulnerable, may halt the development of chronicity by providing means of identifying the vulnerable even before an episode develops. In this way the march toward chronicity can be halted even before it begins, just as it is now possible to abort episodes of diabetes by education and proper safeguards in the vulnerable.

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