Schizophrenia at the Crossroads:
A Blueprint for the 80's

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INTRODUCTION

It is a great honor to be doubly blessed by the Hoch Award. In my presidential address to this association in 1951 (a third of a century ago) at the birth of biometrics, I laid out the blueprint for the biometric approach to psychopathology. Seventeen years later in 1968, you honored me with the Paul Hoch Award and I then presented some of the achievements during those 17 years — our adolescent period. Now, today, 16 years later, as you honor me a second time the adult period has been reached — age 33. If you see fit to give me a third award, it would be in the year 2000, but you better not do so, because then I suppose I would get to keep it for good!

At the inception of our Biometrics Research Unit in 1956, we were practically alone, except for a few scattered centers in St. Louis and Iowa, and the Biometrics Branch at NIH headed by Morton Kramer. Since then, the biometric movement has spread so rapidly that we have had to run ahead fast in order not to get trampled by the crowd. We are especially pleased to note that some of our efforts, such as the vulnerability model and the work in information processing, especially the research in attention, has spread to many U.S. centers and even to European countries where the reception has been even more encouraging.

In contemplating whether to give another accounting covering the last 16 years of the biometric effort, I began to realize that we are still far from fulfilling the 1951 blueprint. For this reason, I decided not to talk of the past but of the future. Since moving to Pittsburgh to establish a new
Biometrics Unit, I decided that I would cut loose from the constraints of the past and invited Drs. van Kammen, Steinhauer and Day, members of the team that is now establishing a new multi-disciplinary approach to schizophrenia research at the Highland Drive VA Medical Center in Pittsburgh, to join me in the preparation of this presentation. I would like at this point to pay my respects to those who launched and supported the work of the old Biometrics Research Unit in New York and the new unit in Pittsburgh. In New York, the late Paul Hoch, then Commissioner of Mental Hygiene, launched the unit, and my debt to him is immeasurable. With the passage of time, his foresight in launching the Biometrics Research Unit is astounding and I believe it has exceeded even his expectations. Dr. Benjamin Passamanick, Director of Research of the Department of Mental Hygiene was most helpful in the expansion of the Unit. The heads of the Sections that carried out the mandate of the Unit over the last 30 years, and who now administer independent programs were, in alphabetical order:

1. Anthropology - Muriel Hammer
2. Biostatistics - Joseph Fleiss
3. Diagnosis - Barry Gurland and Larry Sharpe
4. Family Research and Drug Addiction - Denise Kandel
5. Evaluation Research - Robert L. Spitzer and Jean Endicott

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1 In addition to the schizophrenia research programs at the Highland Drive VA, there is another center of schizophrenia research at Western Psychiatric Institute and Clinic, including Gerard Hogarty's program involving expressed emotion, family therapy (with Carol Anderson), and attention parameters (with Diane Wagener), as well as the schizophrenia module headed by S. Charles Schulz, which covers research dealing with movement disorders, neuroleptic resistant patients, and various biological parameters.

8. Psychophysiology – Samuel Sutton, Gad Hakerem and Mitchell Kiizman

9. Sociology – Ruth Bennett and David Wilder

10. Vulnerability Project – Bonnie Spring

Drs. E. I. Burdock and Anne Hardesty, left the Biometrics Research Unit to establish a Biometrics Laboratory at New York University and Bonnie Spring transferred her vulnerability project to Harvard University. These researchers verified for me the sayings of the sages: "Much have I learned from my teachers, even more from my colleagues, but from my pupils more than from any of them."

I owe a great deal to Dr. Thomas Detre, Director of Western Psychiatric Institute & Clinic, for inviting me to Pittsburgh, to Dr. David Kupfer, our new chairman of the Department of Psychiatry and to Mr. Carl Cossu, Director, Dr. Peter Stajduhar, Chief of Staff, Dr. Gerhard Werner, Coordinator, Clinical Education and Dr. Gerald Goldstein, formerly Research Coordinator, at the VA Medical Center, Highland Drive; The Western Psychiatric Institute & Clinic staff have been most helpful, especially Drs. Evelyn Bremet, Nancy Day, Shirley Hill and J. R. Jennings. In a sense, the award is really being given to these collaborators, both past and present for without them, the work would have been impossible.

Our Biometrics Research Program is continuing at the Highland Drive
Veterans Administration Medical Center in Pittsburgh. While our major thrust during the past several years has been in the domain of psychophysiological research in schizophrenia, we have recently extended the program to the investigation of psychosocial factors and their impact on recidivism.

[NOTE TO PRINTER: END OF INTRODUCTION]

THE BIOMETRIC PERSPECTIVE

Each of the collaborators in the preparation of this blueprint has his own particular point of view and should in no way be held responsible for the inevitable distortion that may result in any attempt to lay them on the procrustean biometric bed I have provided. When their turn comes for the award they will call the tune and I will be glad to oblige.

Let me spell out the major biometric questions that face the student of schizophrenia today. This is no small task since asking the right question is perhaps the most important thing we can do. As John Tukey has said (called to my attention by Connie Duncan-Johnson): "Far better an approximate answer to the right question, which is often vague, than an exact answer to the wrong question, which can always be made precise." (pp. 13-14)

A review of the questions which I raised in 1951 indicates that they are still with us now. Unlike old soldiers they do not even fade. The primary questions are still 1) how can we further improve classification 2) how can we fathom etiology 3) how can we improve treatment and 4) how can we evaluate it.

Some of these questions have been around so long that they have become
chronic. However, several new revolutionary developments in the biometrics of psychopathology have occurred since 1968. Prognosis of schizophrenia seems to have changed for the better, the classification problem has been revolutionized, a search for biological, neurophysiological and behavioral indicators of vulnerability to schizophrenia - markers as they have come to be called - has begun; biochemical and psychosocial treatment regimens have undergone clinical trials for their evaluation. Space does not permit to review them all. Following Medawar's injunction we shall limit ourselves to the soluble.

In order to indicate what to expect in this presentation, I want to make a confession. After a lifetime of working in schizophrenia and living through the various revolutions that the concept has undergone, I feel that I have become a heretic with regard to some of the current views of the psychiatric establishment, and since confession is supposed to be good for the soul, I want to list my heresies:

1. Schizophrenia is far more benign in outcome than what we have been led to believe.

2. It is an episodic disorder and not the persistent chronic condition that DSM-III makes it out to be - the only persistent quality it has is vulnerability on the part of the patient to the development of one or more episodes.

3. Chronicity is not an essential part of its natural history but reflects either the persistence of premorbid personality or iatrogenic, ecogenic or nosocomial artifacts. This also holds true of the negative symptoms which go along with chronicity.

4. It is a unitary rather than a multiple disorder, but may arise in a variety of ways.

It must be remembered that the heresies of today often become the dogmas of tomorrow which in turn give way to the heresies of the day after tomorrow.
Luckily, there are no more burnings at the stake!

What are the reasons for optimism about the outcome of Schizophrenia?

There is ample reason to be more optimistic today, but the dire nature of schizophrenia, during the episode, dampens our enthusiasm. It is difficult to demonstrate the change for the better in this country, because of the absence of life-time follow-up studies, but data from such studies in Europe give overwhelming evidence for a better outcome than is generally believed. Several follow-back studies of shorter duration in so-called chronic or long term cohorts in this country show surprisingly somewhat similar results, as reported by Courtney Harding. It is clear from these studies that schizophrenia, far from being a persistent chronic deteriorating state is actually an episodic illness. As shown in Table 1, the proportion of the first admissions in Bleuler's study having only one episode with remission was 30.9% and the proportion having an episodic course with final remission was 47.1%. Thus fully 78% were episodic.

Insert Table (1)

Although rehospitalization is conventionally regarded as an exacerbation of an ongoing illness, the vulnerability hypothesis postulates that many rehospitalizations are often related to the onset of a new episode following a period of recovery and freedom from symptomatology.

While there are quite a number of other studies which demonstrate the episodic nature of schizophrenia they were not all as well controlled as Bleuler's, who made a personal follow-up of each of his probands. We shall, therefore, limit our consideration to only those that give evidence of careful
follow-up and only to first admissions, since they give a clearer picture of outcome.

The five year follow-up of the WHO patients in a still incomplete study (personal communication) reports that the proportion of total follow-up time during which the patients were in psychotic episodes varied between 66.9% in Aarhus to 18.8% in Ibadan. Ibadan and Agra were the two centers in which the highest proportion of patients were found to have had a single psychotic episode followed by a remission without further relapses over the five year period. An average of 21% of the patients in the developed countries were continuously ill throughout the five year period compared to only 12% in the developing countries. Thus, there seems to be a tendency for more episodic courses in patients in developing countries.

Another study confirming the episodic nature of schizophrenia is the 6 Bucksinghamshire County Study. This was a five-year follow-up of all the schizophrenics admitted from the catchment area of this county of approximately 500,000 individuals feeding into a single mental hospital. This study is more epidemiologically representative of the course of schizophrenic illness. Table 2 shows the course of illness for the first admissions.

Insert Table (2) Here

Considering the total column only, 23% had only one episode, 35% had more than one episode with a final remission or a total of 58% with an episodic course. It is interesting to note that the females had a much better episodic outcome than the males, with 31.8% having only one episode and 36.4% having more than one episode with final remission or a total of 68.2% with an episodic
The superior outcome for the females is even more striking as shown in Figure 1 which shows the percentage of first admission schizophrenics discharged and not readmitted during the last few decades.

Insert Figure (1)

While the proportion of males vacillated around 35%, the corresponding proportion for females increased during the last four decades from 33% to 60%. This superior outcome for females should be investigated more thoroughly since the sources of recidivism may be revealed in such an analysis.

Further evidence of the episodic course of schizophrenia even in patients whose duration of illness extended for 15 or more years after the initial episode is given in the study of Smaonova et al. Some 30% had only one episode, 25% two episodes, 16% three episodes, and the rest had from four to eleven episodes in decreasing frequencies. It is not clear whether these data represent exacerbations of an ongoing episode, "attacks", or new episodes.

The revolution in descriptive psychopathology.

This revolution had many causes. Its early beginnings can be traced to Adolf Meyer and later to Nolan D.C. Lewis who recruited me to help in the revision of the Mental Status Examination Handbook in 1944. This work was interrupted by military service, but on my return from the war Eugene Burdick and later Anne Hardesty and Gad Hakerem helped to launch an attack on improving the psychiatric interview in the form of a Ward Behavior Interview. They in turn initiated Robert L. Spitzer and later Jean Endicott into the
preparation of items for structured clinical interviews in which Joseph Fleiss and Jacob Cohen also participated. At the same time, with the help of Morton Kramer, the now classic US-UK Project was organized. This project demonstrated the usefulness of systematic interviewing and its potential for clarifying diagnoses both here and abroad. This was accomplished by Barry Gurland with the collaboration of Lawrence Sharpe and Joseph Fleiss and a team of devoted assistants in the US, and by John Cooper, Robert Kendell and John Copeland and their associates in the UK. This study together with the WHO Pilot Study of Schizophrenia and the pioneering work of the St. Louis school under Eli Robbins laid the foundation for the revolution in diagnosis which culminated in a series of interview instruments, and finally in DSM-III and the Research Diagnostic Criteria under the direction of Spitzer and Endicott.

The reception of the SADS and DSM-III by the profession indicates what a great need has been filled. There are a few issues that have been raised regarding this revolution. First is the question regarding the definition of schizophrenia. It is high time we realized that rigorous mathematically tight definitions do not hold for nature, only for abstract mathematics. If we tried to introduce such rigor into psychopathology we would end up with rigor mortis. If it were necessary that a category be defined rigidly, such widely useful concepts as "species" would go by the board. Julian Huxley has pointed out that: "...there is no single criterion of species. Morphological difference; failure to interbreed; infertility of offspring; ecological, geographical, or genetical distinctness - all those must be taken into account, but none of them singly is decisive. Failure to interbreed or to produce fertile offspring is the nearest approach to a positive criterion. It is, however, meaningless in apogamous forms, and as a negative criterion it is
not applicable, many obviously distinct species, especially of plants, yielding fertile offspring, often with free Mendelian recombination in crossing. A combination of criteria is needed, together with some sort of flair." (p.11).

It should be borne in mind that certain dangers may lurk in the standardization of interviewing and diagnosis. In the course of their training, researchers and clinicians have to develop certain required skills such as interviewing, apparatus handling, research design and statistics. Unfortunately, in the course of this onerous training, they often let their imagination lag. "But skill without imagination is craftsmanship and gives us many useful objects such as wickerwork picnic baskets...," says Tom Stoppard, 13 but it is not creative. There is a great need for reviving the imagination of our researchers. For example, the skill in interviewing and diagnosis has reached a point where it is now considered by some that it is possible to determine the diagnosis by following blindly the skills learned in the training process. This routine interviewing, good as it is for meeting daily clinical needs, is not sufficient for research and diagnosis and may stultify our knowledge as of 1984. We need to reintroduce the curiosity and creativity which developed the current available skills in the first place in order to permit innovations to occur. Standardized craftsmanship leads to sterility, as has been the case with intelligence testing. Only with the development of the information processing approach and the rise of cognitive psychology have the shackles of standardized tests been removed as an obstacle for further research in intelligence. Looking at the patient, listening to his style, developing empathic relationships instead of merely noting the answers to the items on the interview becomes a prerequisite for the improvement of
interviewing techniques and diagnosis. For diagnosis is, in fact, a mini-experiment in which a series of hypotheses are examined for their tenability until the most tenable hypothesis regarding the diagnosis is reached.

But why, despite the improvement in our techniques is it still so difficult to determine the presence of a schizophrenic syndrome? Despite the advances made in descriptive psychopathology, genetics, biochemistry, and biophysics, we have not yet found the etiology of any of the mental disorders and must still depend on behavioral syndromes. But the behavior of the patient is determined not only by his current mental disorder but also by his underlying premorbid personality, and it is this mixture which he presents at the time of admission. If we could dissect the behavior due to the mental disorder from the behavior due to premorbid personality and to their interaction, we could recognize the focal disorder in isolation from its surround—and probably find this factor characteristic of all similarly afflicted patients. What we perceive, however, is not the effect of the focal disorder alone, but the effect of the illness, which reflects the premorbid personality, and the focal disorder, and their interaction. This is why no two schizophrenics are alike—their focal disorder may be the same but their illness is different. The relation between premorbid personality and psychopathology is still moot and involves such thorny issues as the distinction between "trait" and "state."

The Search for Markers

Another new direction that has developed during the last 16 years is the investigation of markers for the various scientific etiological models that
have been suggested for schizophrenia. These include the biologically based
genetic, internal environment, neurophysiological and neuroanatomical models
on the one hand, and the environmentally based ecological, developmental and
learning models on the other hand.

In view of the multiplicity of models, an interdisciplinary supermodel
had to be developed in order to encompass them as submodels for an
understanding of etiology. This gave rise to the vulnerability model, as
depicted in Figure 2.

Insert Figure (2)

Briefly stated, the vulnerability model assumes that schizophrenia is
essentially episodic, developing in a vulnerable individual when subjected to
exogenous or endogenous stressors. When the episode terminates the patient
returns to his premorbid level of adjustment. For the good premorbid patients
we consider the ending of the episode and the return of the patients to their
premorbid niche, a recovery, or at least a remission. For the poor
premorbid, it is difficult to know whether the episode has ended since a
return to the premorbid level still does not enable them to function and they
are often mistakenly considered as persisting in their episode. However, not
all the vulnerable who undergo stressors necessarily develop episodes. The
moderating variables of premorbid personality, social networks, and ecological
niches, if favorable, may cushion the impact of the stressor and the episode
is aborted.

One of the obstacles to accepting the vulnerability model is the problem
presented by the so-called chronic or long-term patients. Is chronicity an essential part of the natural development of an episode, a side effect, or is it an artifact? It is generally agreed today by what might be called the psychiatric establishment that schizophrenia is a chronic disorder or even a disease which persists throughout the life of the individual bearing that diagnosis, that it is essentially genetically transmitted, and complete recovery is rather rare, since residual symptoms of the disorder develop which characterize the person throughout life and prevent a return to society to the fullest degree.

The thesis presented here challenges the established view and will present the tentative evidence for a newly emerging view of this disorder which might be summarized as follows: while the established view maintains that the person diagnosed as schizophrenic is essentially sick but may have intermittent periods of wellness, the new view maintains that this person is essentially well but may have one or more intermittent episodes of illness.

This view challenges chronicity as a natural part of the disorder. It maintains that the persistent feature of this disorder is not its continued presence, but the presence of a vulnerability which may or may not develop into an episode. It considers genetics not to be a sufficient nor a necessary etiological agent, nor the only possible etiological agent. Many of the residual symptoms masquerading as chronicity may be artifacts produced by the reaction of the individual himself, the peer group, and society as a whole to the acute episode that had developed. It may also reflect the return to the poor premorbid personality at the end of the episode, or the toxic niche to which the patient returns.
In view of the fact that chronicity is generally regarded as an expected stage in the course of schizophrenia, it is well to examine the evidence for and against the proposition that chronicity is indigenous to schizophrenia.

Against this proposition are the following arguments:

Arguments Against Chronicity as an Indigenous Component of Schizophrenia

1. Not Universal: Not all schizophrenics develop chronic states. M. Bleuler found no more than 10% continuously hospitalized after first admission in his follow-up study.

2. Prevalence is Exaggerated: The apparent prevalence of chronicity is due to the accumulation of a small proportion of chronic patients, but even of these, in M. Bleuler's follow-up, 30% remain in the hospital for lack of any other home.

3. General Trend in Outcome is Remission Rather than Chronicity: Long term follow-up studies (Bleuler, Ciompi, Huber) indicate that the general trend is towards improvement rather than deterioration. Sporadic recovery can occur even after a lifetime of chronicity.

4. Environment Rather than Heredity is Associated with Chronicity: Long term outcome is often independent of family history of schizophrenia - environment rather than heredity may influence the appearance of chronicity. Such moderating variables as social networks, ecological niches and premorbid personality, if favorable, may mitigate the impact of stressors, but if unfavorable, may exacerbate the impact leading to chronicity.

5. Chronicity is Associated with Psychosocial Factors:
   a. Life events play a triggering role in recidivism and in maintenance of chronic episodes.
   b. Labelling impact prevents readjustment, especially occupationally.
   c. Highly critical families play a role in the prolongation and resumption of schizophrenia episodes.

3

The arguments pro and con chronicity follow the paradigm presented by 17

Ciompi.
6. Negative symptoms do improve with neuroleptic treatment and do respond to amphetamines

Arguments in Favor of Indigenous Nature of Chronicity

1. Irreversibility of Negative Symptoms:
   a. It has been claimed that the presence of irreversible negative symptoms characterizes chronic schizophrenia, but negative symptoms may be associated with chronicity because they may have been premorbidly present, and when the episode ends, the patients return to their premorbid level including their negative symptoms. As evidence for this possibility, 70% of Bleuler's probands had deviant premorbid personalities including negative symptoms, and about 58% of these poor premorbid were regarded as attaining a moderately severe or severe end state (chronic). Furthermore, deviant behavior can develop due to institutionalization and isolation and may be mistakenly regarded as a natural consequence of schizophrenia. For example, negative symptoms are also seen in long-term prisoners, neglected residents of old age homes, nursing homes, etc.
   b. It is often difficult to distinguish chronic schizophrenics from other chronic patients in the back wards of institutions, but these symptoms often disappear under social stimulation.

2. Biochemical or Organic Basis: No generally accepted evidence is available for any specific somatic, biochemical or other organic basis for chronic schizophrenia. Chemical intervention, though effective in the acute phase against positive symptoms, is not generally effective in the chronic phase against negative symptoms; the latter may be more amenable to psychosocial intervention.

3. Ubiquity of Chronicity: It has been claimed that chronicity is ubiquitous and that it transcends differences in environments. However, cross-cultural studies indicate that developing countries have better outcomes and hence less chronicity than developed countries.

Thus, it may be concluded that the proposition that chronicity is not an indigenous part of the course of schizophrenia (except in a small proportion...
The Future Perspective

Diagnosis

While it is not always easy to discern the trend of the future, some of the trends cast their shadows before them. With regard to descriptive psychopathology, it is quite clear that diagnosis has made tremendous strides. In contrast with the 20's and 30's when it was primarily an academic exercise without any significance for treatment or outcome it has now become one of the most important single activities of the clinician. The wholesale acceptance of diagnosis by the law and agencies dealing with third party payments is sometimes a frightening spectacle. Witness the problem in PKU where a certain titre of phenylalanine makes it incumbent upon the clinician to intervene in certain of our states, or the shift from the criminal court to the clinic in such cases as compulsive gambling and even embezzlement to support the habit - changing a crime into an illness! There will no doubt be attempts to curb the law from running ahead of science or even keeping up with it. The law and third party payments need to be handicapped by at least a decade behind science in order to permit the tentative findings of science to be verified.

Another problem in descriptive psychopathology is the need to objectify the individual symptoms which form the basis of our syndromic diagnoses. Just as we have developed research criteria for diagnoses, we need desperately research criteria for the definition of anxiety, depersonalization, thought disorder, etc.
It will become necessary to separate diagnoses — an everyday clinical service — from classification — a scientific endeavor free from marketplace considerations and local social-cultural implications. There is need for an Academy of Scholars to study the problem of taxonomy in psychopathology. Perhaps it would be necessary to establish first, an academy for the taxonomy of human behavior to lay a foundation for the classification of normative behavior before entering the arena of deviant behavior. Another trend of the future is the development of approaches to the study of the validity of diagnosis as opposed to its reliability. We have gone as far as we can go with the latter, and further polishing of reliability independently of validity would turn us into craftsmen rather than scientists. There are signs that construct validity approaches are beginning to develop which may provide a DSM of the future with objective indicators for at least some of the diagnostic categories. Elsewhere, I have laid out a blueprint for the study of vulnerability consisting of 1) discovery of markers to identify the vulnerable 2) development of techniques for investigating the life-event triggers necessary to elicit the vulnerability and 3) determining the moderating variables which prevent an episode from developing even when a life event trigger strikes a vulnerable individual.

Markers

In future tests of the vulnerability hypothesis it will become necessary to find means of identifying the vulnerable, regardless of whether they exhibit their vulnerability in the form of an episode. These indicators of vulnerability have generally gone under the name of vulnerability markers. These refer to specific types of performance or characteristics that identify individuals who either had schizophrenic episodes in the past, are having one
presently or have a higher risk of developing an episode in the future.

The ideal marker is one that occurs only in schizophrenics and not in normal controls nor in non-schizophrenic mental patients.

At the present time, there are no such ideal markers. What we presently mean by a marker is a characteristic or behavior which discriminates (occurs significantly more frequently) schizophrenic from normal controls or non-schizophrenic mental patients. In order to simplify our discussion we shall tentatively refer only to the discrimination between schizophrenics and normal controls and not deal with the discrimination between schizophrenics and non-schizophrenic mental patients.

Because of the heterogeneity of schizophrenia, it is not likely that pathognomonic markers will be found. More often these markers will also be found, albeit less frequently, in normals and in non-schizophrenic mental patients. Consequently, we may have to depend upon patterns across several markers to identify individuals vulnerable to schizophrenia. In analyzing the nature of the marker, i.e., whether it is a vulnerability marker or episode marker, we have to determine the pattern it presents across the three time periods of pre-episode, episode and post-episode, and whether or not it exists significantly more frequently or less frequently in first degree relatives.

Table 3 shows the various types of markers in accordance with their pre-episode, episode, post-episode status and their familial frequency in siblings or other first degree relatives.

Insert Table 3 Here
Since the starting point is usually a patient in the hospital with an episode, it is difficult to determine without suitable follow-up or follow-back, whether the marker under investigation is an episode marker or a vulnerability marker. To differentiate between the several types of markers, the status of the marker must be known in the pre-episode period, during the episode, and post-episode.

**Vulnerability Markers:**

A vulnerability marker should be present in the pre-episode, episode, and post-episode periods, and in accordance with the seven etiological models discussed previously, should also be present in greater frequency than chance in unaffected first degree relatives. We distinguish two types of vulnerability markers: 1) familial, which characterizes first degree relatives with a frequency exceeding chance expectancy, and 2) non-familial, which does not exceed chance. Thus, marker A satisfies all the requirements for a vulnerability marker. AA is present during all the three specified periods but is not characteristic of first degree relatives, and hence is probably non-familial. D is a vulnerability marker that disappears after the episode ends but nevertheless is found in first degree relatives. Apparently the episode extinguishes the marker. Once a marker is established it can be applied to screen the general population for the presence of vulnerable individuals.

**Episode Markers**

The starting point in the search for episode markers are the individuals who are presently having an episode. B is such an episode marker because it
waxes and wanes with the episode but does not characterize unaffected first degree relatives. Once the marker is found, it may be applied to patients to determine whether the episode is still present or to the general population to identify those who are undergoing an undetected episode.

Residual Markers

E and G are markers that make their appearance during the episode, but persist after the episode. It is still to be determined whether they are indigenous to the disorder or result from iatrogenic, nosocomial or ecogenic factors.

Prodromal and Early Signs of Incipient Episodes

There are also certain prodromal characteristics which usually appear when an episode is imminent. These harbingers are not invariably followed by an episode and therefore, are not regarded as markers, but as predictors of a possibly approaching episode.

Invulnerability Markers

The H̄ marker, which is present in excess only in unaffected first degree relatives of schizophrenics but not in the probands themselves presents an interesting possibility. Perhaps an H̄ marker is an indicator of invulnerability, a characteristic which is antithetical to schizophrenia even as Meduna thought epilepsy was. Thus, though the first degree relatives may share other vulnerability markers with their probands, the presence of the H̄ marker may prevent the expression of the episode. Similarly, the AA marker which is absent in first degree relatives in a proportion significantly below
that in the general population, but is present in the probands in pre-episode, episode, and post-episode intervals, may identify the individuals who are resistant to schizophrenia. Had this marker been present in the probands, they too may not have developed an episode. A search for such markers would indeed be a worthwhile endeavor.

**BIOLOGICAL PERSPECTIVE**

Out of the many aspects which the biological approach provides we have selected two which will be our chief guides in thinking about biological aspects of schizophrenia in the coming years: 1) the multiple biological roots of the disorder and 2) the role of the changing homeostasis of the internal environment of the patient.

We shall make the following assumptions: 1) That even though schizophrenia may be a phenomenologically unitary disorder, the etiology of schizophrenia is heterogeneous and or multifactorial as was described in the seven scientific models earlier. 2) That the homeostatic disturbances observed in the incipient stage of the disorder can serve as an early indication of the imminence of an episode, an exacerbation of an ongoing episode, or even as an early indication of the therapeutic response to treatment.

**Heterogeneous Etiology**

There seems to be increasing evidence that not all schizophrenia is genetically based. The recent evidence of brain atrophy in some schizophrenic patients, as reported by the Maudsley group, indicates that CT Scan
abnormalities occur more frequently in patients without schizophrenic relatives. Although normal lateral ventricle size is largely genetically controlled, the schizophrenic probands in pairs of discordant identical twins have the larger ventricles. If some environmental event can cause this discrepancy in ventricular size, then a viral etiology becomes a tenable hypothesis for non-familial schizophrenia. The most recent data on seasonality of schizophrenic births support this notion. It is very intriguing that certain viruses have a preference for specific neuro-transmitter systems such as dopamine, norepinephrine, or serotonin. Lycke and Roos proposed that dopamine receptors could regulate viral entrance into the cell. Shaskan et al. hypothesized that MAO may act as a virus receptor. Low platelet MAO activity has been proposed as a vulnerability marker for schizophrenia, and found to be associated with long-term hospitalization, neuroleptic treatment, and, ironically, with good premorbid functioning and extraversion. It also seems to correlate with severity of psychosis.

Solomon Goldberg addressed the differences between sporadic and genetic schizophrenia in great detail. It will be important in future studies of platelet MAO activity and cognate studies to separate the patients with genetic loading from those without. Platelet MAO activity may turn out to be a moderating variable modifying the illness once it sets in.

Brain atrophy such as enlarged ventricle size and cortical atrophy has been shown to be present in a substantial number of schizophrenic patients. This brain atrophy, which may be caused by brain damage raises the possibility of pre- or peri-natal trauma or anoxia or viral infection. Recently,
Schulsinger et al. reported that obstetric complications in schizophrenic mothers led to wider ventricles in those of their children who became schizophrenic. This finding supports the concept that the CT scan abnormalities are associated with neuronal injury. Schulsinger et al. also proposed that perinatal trauma or anoxia may be necessary to bring out psychosis in patients with schizotypal personalities. Since 10% of schizophrenics have a familial history of the disorder and there is an excess of winter births among schizophrenic patients, the prenatal infection may be an etiological agent. However, the absence of epidemics or higher rates of schizophrenia in the staff of mental hospitals, militates against this possibility.

Brain atrophy in schizophrenic patients is associated with decreased CSF dopamine turnover. Other findings include cognitive impairment and negative symptoms in patients with brain atrophy. This suggests that a subgroup of schizophrenic patients can now be identified by biological means.

Episodic Instability in Internal Environment as an Early Warning Sign Preceeding Psychotic Behavior

The leading biological hypothesis of schizophrenia of the decade is the dopamine hypothesis. In reality, this appears to be a hypothesis of psychotic decompensation. Because psychotic decompensation is a dynamic process which develops over time, biological markers of impending relapse could perhaps be found. Close scrutiny of the pharmacological evidence for the dopamine hypothesis implicates the norepinephrine (NE) system as well. Both neurotransmitter systems interact with each other and are involved with the autonomic nervous system. Autonomic arousal seems to increase prior to
relapse. Rather than a trait marker, increased CSF NE may be a state dependent early warning sign of psychotic decompensation. However, the state of the internal environment may not be synonymous here with clinical status and changes in the former precede changes in the latter.

Other evidence supporting the possibility of identifying biochemical early warning signs comes from the amphetamine challenge test. In 50 patients treated with neuroleptics, the response to the test identified beforehand those who would relapse following withdrawal from neuroleptics, an identification which could not be made clinically. The concept of instability or episodic dysregulation in the internal environment preceding psychosis is consistent with the stress diathesis or vulnerability model of schizophrenia. Environmental stress can sensitize the internal environment or make it stress-tolerant. The amphetamine challenge test exposes the sensitivity to stress in the patients.

The two concepts of etiological heterogeneity and episodic instability are not in contradiction with each other; they support and compliment each other. They also promise a better methodological testing of, for instance, the dopamine hypothesis by taking different etiologies and state dependency into account. These concepts do not identify a specific dopamine disorder, but provide for the possibility of several dopamine related disturbances be they supersensitivity of dopamine receptors, overactive regulator protein, different dopamine receptors, impaired dopamine release or utilization, impaired peptidergic, serotoninergic, gabaergic or noradrenergic activity. Conversely, the same etiologies could be involved with different disorders including sporadic schizophrenia, affective disorders, and impulse disorders.
These concepts also suggest that we should not expect to find a specific diagnostic marker applicable to all schizophrenic patients. So far that seems to hold true.

In summary, we see the next decade as breaking new ground in the following areas:

1. Defining the state dependent dopamine and norepinephrine disturbances which precede an episode.

2. Identifying relapse prone and neuroleptic responsive patients which will allow us to treat patients pharmacologically only as needed, something which Marvin Herz has also proposed.

3. Identifying patients who should be treated with lithium, propanolol, clonidine or other non-neuroleptic treatments.

4. Understanding the PET, brain blood flow and CT Scan findings in relationship to specific subgroups of patients and clinical states.

5. Separating and identifying different genetic and sporadic forms of schizophrenia.

6. Development of anti-psychotic drugs without risk of extra-pyramidal side-effects or tardive dyskinesia. (D receptor antagonists)

NEUROPHYSIOLOGICAL PERSPECTIVE

One of the more exciting approaches to research in schizophrenia during the past decade has been the application of information processing theory to psychopathology. In reviewing such activities, it is clear that much of the neurophysiological and other psychophysiological data are closely related to some purely behavioral techniques, such as reaction time, dichotic listening, and span of apprehension.

Significantly different performance for schizophrenics compared to
normals have been reported so frequently and consistently, that we tend to attribute any poorer performance on the patients' part to a "generalized performance deficit," rather than to a specific deviation characteristic of schizophrenia only.

Triggered by the incisive criticisms of the Chapmans' more careful research designs have been employed in attempts to control for such generalized deficits. For example, we had originally demonstrated that in a reaction time task, schizophrenics not only performed more slowly than normals, but also had an unusually prolonged response to cross-modal stimuli, that is, stimuli which differed in sensory modality from the immediately preceding stimulus . A recent dissertation by Salvatore Manuzza in the Department of Psychophysiology laboratories at New York State Psychiatric Institute has re-evaluated cross-modal retardation in schizophrenics from the perspective of the Chapmans' argument, and has demonstrated that the cross-modality retardation in schizophrenia is neither artifactual nor due to generalized deficit. Where does one go to next with such data? The logical step seems to be a determination of whether the findings are only meaningful across groups of subjects, or whether they can be applied to patients individually. Currently, it appears that the Shakow cross-over technique in reaction time studies, while providing indications of group differences, is less likely to provide easily discernible individual classification than the cross-modality technique.

There are several important reasons for emphasizing a search for discriminating measures that can be used to characterize individuals rather than groups. One of the primary reasons is to establish new criteria for
diagnostic subgroups. The iterative technique, advocated by Sutton, suggests that the finding of identifiable differences which discriminate sub-groups of schizophrenic patients on the basis of an experimental variable can be used as the stepping-off point for re-examining the confluence of symptomatology in such patients. Thus, the laboratory differences may provide a guide for directing the clinician to search more carefully for features that identify different types of patients.

Differences on experimental variables within the patient group may ultimately be used as a clinical tool to predict the type of therapeutic regimen which is most effective for each patient. An extension of this approach is to observe the reaction of patients to different pharmacotherapies, using a favorable reaction to assist in establishing diagnosis. This is an approach which currently seems to have gained greater headway in classification of depressive illnesses. A comparable type of discrimination which has been studied somewhat more among schizophrenics is the use of pharmacologic challenges which exacerbate symptoms among those who are apparently still within their episodes.

An example of the beginning of an evolution from overall group differences to individual characterization is the study of event-related potentials in schizophrenics. I take considerable pride in my participation in the "discovery" by Dr. Samuel Sutton of the P300 component in our

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The discovery of P300, the cross-modality effect in reaction time, the findings of the US-UK project, and the development of semi-structured interviewing, DSM-III, and RDC, and the development of the "immediacy hypothesis" are the high water marks of our biometric endeavors.
laboratories in 1964. P300 refers to a scalp positive wave that occurs with a latency of approximately 300 msec, and is most closely related to the informational significance associated with an event, rather than primarily the physical characteristics of the event. As detailed elsewhere, P300 was found while we were looking for evoked potential correlates of the effect of certainty and uncertainty in the cross-modality reaction time phenomena. Only the response of normal subjects had been recorded 17 years ago, and we still did not know whether P300 had any relevance for the study of schizophrenia. Not until 1972 did Roth and Cannon and then Levit in our own laboratories report that greatly diminished P300 amplitudes occur among schizophrenics. Since that time, decreased P300 amplitude in schizophrenia has been one of the most robustly reported phenomena, replicated in laboratories all over the world, notably the work of Shagass in Philadelphia, and Roth, Pfefferbaum and Kopell in Palo Alto, among others. A more comprehensive survey of this literature is provided by Zubin et al. In addition, P300 has been reported to be significantly attenuated in the high-risk offspring of schizophrenics by David Friedman, working with the high-risk sample of Erlenmayer-Kimling.

In our current studies in Pittsburgh, we have been examining P300 during a modified counting task. Not only do we find that P300 amplitudes are reduced, but we also find a difference in the pattern of responses across experimental conditions which suggests that many of the patients are utilizing information primarily from only immediately preceding trials, a phenomenon reflective of Salzinger's immediacy hypothesis, rather than responding to more complex aspects of sequential probabilities which normal subjects seem to do quite naturally. Having observed these effects in the grouped data, we
looked more closely at the responses of individual subjects, and realized that the pattern across conditions could be specified for individual subjects. There is increased confidence in the use of these patterns because parallel findings are observed in the pupillary dilation response and, to some degree, in cardiac changes, which are recorded simultaneously with the event-related potential. Thus, we may begin to classify patients on the basis of either amplitude alone, or patterning of this amplitude across experimental conditions. We can now indicate even for smaller amplitude responses, whether the patient shows a pattern like that of normals or one of several identifiable different patterns not found in normals. As a result, we may consider using the laboratory findings for fractionating the schizophrenia group into subtypes.

The point of this brief discussion of the neurophysiological perspective has been not only to illustrate that it has been possible to change an emphasis from group differences to individual differences, but also to indicate the future of the information processing approach in the study of schizophrenia. As it appears now, our objective is to utilize techniques that tell us something about the manner in which processing activities differ in schizophrenics—the what, where, when, and how that we have described in other papers. We need to understand what is different about the use of information among (at least a subgroup of) schizophrenics, and whether the type of deviation in processing activity occurs consistently in different situations. It does little good to continue to find a difference in overall response level between normals and schizophrenics in our electrophysiological, positron emission, biochemical and behavioral measures unless we use the knowledge to lead to new approaches to classification, treatment, and
etiology.

Given the recent trend away from global research which looked only for evidence that some construct such as arousal or attention was different in schizophrenia, to the more specifically guided experiments that seek to delineate stages of processing activity, there seems every reason to be optimistic about what the near future will reveal about the bases of schizophrenia. An exemplary model in the experimental psychopathology domain is the meta-like analysis of the skin conductance orienting response undertaken by researchers from six different laboratories in Great Britain, West Germany and the United States in attempting to bring order to previously divergent findings.

PSYCHOSOCIAL PERSPECTIVE

The term "psychosocial factors" presently covers a diverse spectrum of studies, including research on the personality factors antedating the onset of schizophrenic psychoses, studies of the effects of stress and the familial environment on the course and outcome of the illness, as well as the work that focuses on how socioeconomic and cultural factors are related to the frequency and phenomenology of schizophrenic disorders. It covers a significant part of the research being done by psychologists, social psychiatrists, epidemiologists, sociologists, and anthropologists. I wish to take note of some of the more exciting work being carried on in this field and direct our attention towards what I consider to be some of the most interesting areas of future inquiry.

Many of the earlier hypotheses, such as those having to do with social
class position and the effects of poverty, have not proved to be as helpful as may have been initially expected. Yet, there remain significant findings in this area that we need to address. For example, there is much evidence to indicate that schizophrenic patients have a better course and outcome in the less developed and non-Western countries... This has been documented in several studies by very reputable transcultural investigators (e.g., Lambo in Nigeria, Rin and Lin in Taiwan, Murphy in Mauritius, WHO in India, Waxler in Sri Lanka) and we are still lacking an adequate explanation for these international differences.

In the past, the international work has focused on the development of a common language designed to facilitate communication across different cultural and theoretical traditions. A necessary part of this movement has been an emphasis on the aspects of schizophrenic disorders that are universal across cultures and time. Given the situation in the late 1950's when we were designing the US-UK Project, such a bias was understandable. Yet, a careful reading of the literature that has emerged from all of these large scale international studies indicates that the cross-cultural variations in the schizophrenic syndrome are just as obvious and striking as are the commonalities. It is also my impression that a renewed interest is developing in the careful study of the degree and types of variation found in schizophrenia cross-culturally. Interestingly enough, much of the impetus for this direction of work seems to be a product of the new generation of psychiatrists emerging in the developing countries. Many of these investigators are saying that our established classification systems fail to adequately describe what they see in their own clinical practice. In summary, it is my feeling that a renewed interest in and sensitivity to the influence
of sociocultural factors on the genesis, phenomenology, course, and outcome of schizophrenic disorders is one of the really exciting areas of theoretical and empirical work in the immediate future.

Closer to home, psychosocial research over the past ten years has shown a growing emphasis on the application of biometric methods to the study of the social environment and its implications for the basic vulnerability to episodes of schizophrenia. Perhaps the most exciting work that has taken place in the past ten years has occurred in the arena of the family. The research on the expressed emotion (EE) of family members and its relationship to schizophrenic relapse immediately comes to mind. Research in this area started out in Great Britain and has now spread to the United States, (see ) as well as to a number of non-English speaking and non-Western countries, respectively. Gerard Hogarty and Michael Goldstein describe some of the work going on in Pittsburgh and Los Angeles, respectively. The EE data reported so far have been striking, and I think that it is safe to assume that the work done in this area is going to have a substantial and permanent impact on the way we think about and treat the schizophrenias. In addition to EE measures, research into communication deviance, CD, in the families of schizophrenic patients has also made significant progress in recent years. Of particular interest are the data suggesting that EE and CD may be independent measures that interact together to determine the probability of a negative outcome in specific cases. It may well be that communication deviance in the family is associated more with the etiology of the condition, i.e., a vulnerability marker, whereas expressed emotion variables affect the short-term course of the illness, i.e., may only serve as triggers. In the area of acute stressors such as life events, there has been an ongoing
interest in their roles as triggers for specific episodes of the disorder 61, 62 I have seen the early drafts of some new international research carried out by the World Health Organization that support the involvement of life events in the onset of a majority of acute schizophrenic episodes.

All of this work is just a beginning, and it will be a long time before the data are available that will permit the construction of a fully elaborated theory of the effects of psychosocial variables on the schizophrenias. I do believe, however, that such a theory is possible and represents a worthwhile goal for our future research. In this connection, it is valuable to give some thought to the areas that are most in need of study and which would make the greatest contribution to the elaboration of our current knowledge.

It should be recalled that the greatest proportion of the work discussed above has involved schizophrenic patients and their families. It is also clear that the vast majority of so-called chronic or long-term schizophrenic patients do not live in family settings. We need to branch out and take advantage of the new concepts we have developed in order to increase the breadth and depth of our generalizations. In brief, the chronically long-term psychotic patient living outside of the family requires renewed attention in light of the data that have been collected over the past ten years.

A second area where much work still remains to be done concerns the buffering factors that act to mitigate the effects of toxic factors such as expressed emotion and life events. The buffering factor about which we have the greatest knowledge is, of course, neuroleptic medications. Still, a large percentage of patients relapse while actively taking their medications and it
is vital that we discover the role played by other exacerbating or buffering factors such as the social network, ecological niche and premorbid personality. Here we should emphasize the implications of social support and social network systems for the continuing health of patients with a schizophrenic vulnerability. There is a great need to expand our current knowledge to include systems that operate outside the immediate family milieu such as the extended non-kinfolk system and the peripheral members of the network. If we consider the entire social network in which the proximate social network is imbedded, we can better understand the entire social matrix in which the individual lives - i.e., the microcosm which represents the portion of the macrocosm. It is this matrix that determines health and well being, illness and even mortality.

In our study of recidivism in schizophrenia at the Highland Drive VA Medical Center in Pittsburgh, we have been impressed by the large number of outpatients that never fully achieve a proper remission from illness. Instead, they remain actively psychotic while living in the community. How much of this chronic symptomatology can be explained by the fact that these people leave the hospital only to return to toxic community settings where they exist within alienating, lonely and, sometimes, downright frightening social circumstances? We believe that we can prove that more than just a negligible proportion of this chronic symptomatology is socially induced.

This raises a final point. Let us recall that schizophrenia, as we know it, involves a central or acute syndrome, as well as long-term states of impaired functioning. The studies we have reviewed today have focused almost exclusively on the problems of florid relapse and the appearance of positive
symptomatology. My new position in the VA system has made me acutely aware of the absence of new and exciting inroads into the problems of so-called chronic deficit states or long-term episodes. There are important theoretical and practical advances to be made in this area. The most recent data from long term European follow-up studies indicate that, contrary to general opinion, the majority of the schizophrenics need not have a disastrous outcome. I firmly believe that when we take the time to do the requisite research, we are going to find out that the greatest part of the iceberg of disability we face is actually a socially induced artifact and not an inherent part of the illness process itself. If I am correct in this, we may also speculate that it is in this area, the study of chronic states of disability and impairment, that psychosocial researchers have the greatest potential contribution to make. It is my position that schizophrenia, in the vast majority of cases, is an episodic condition and need not result in the chronic deficit states that we have come to both expect and to accept as a self-fulfilling prophecy.

SUMMARY

It is clear that the greatest advance in the 70's has been made in descriptive psychopathology and to prevent this success from becoming a failure in the 80's, we must encourage innovative imagination to overcome the drift toward rigid application of standardized procedures.

As for the improved outlook in outcome of schizophrenia, the evidence from long term follow-up studies in Europe indicates that a significant proportion of schizophrenics have only one episode from which they recover and that an even larger proportion show an episodic course of several episodes with final remission. Only a small proportion remain chronically ill
continuously but they are the ones who accumulate in our facilities and give schizophrenia its undeserved reputation for chronicity. The evidence has also shown that there is considerable doubt whether much of the chronicity that overwhelms our daily practitioners and engenders pessimism is indigenous to schizophrenia. There is reason to believe that it may be an artifact engendered by iatrogenic, ecogenic, and nosocomial factors.

As for vulnerability markers, there are several potential candidates which have been found in both probands and in their unaffected first degree relatives with frequencies greater than chance expectancy.

1. Cross-over index in reaction time (Shakow)
2. Smooth pursuit eye movement index (Holzman)
3. Continuous performance task (Kornetzky, Hirsky et al.)
4. Span of apprehension (Assarnow)
5. Dichotic listening with distraction (Spring)
6. Platelet MAO

We still have to determine whether these markers are vulnerability markers, episode markers, or residual markers.

While the specificity of each of these markers for schizophrenia is still to be established, the possibility exists that patterns across these markers may serve to identify subgroups of schizophrenia and thus reduce the apparent heterogeneity of global schizophrenia.

The availability of such markers, and the proposed behavioral and chemical challenges for eliciting episode markers as well as the possibility
of early warning signs of the imminence of an episode, indicate that the
future bodes well for supplementing the current clinical diagnoses and
treatment with objective indicators that may succeed in reducing the
heterogeneity of our nosological categories and reduce the excessive use of
neuroleptics and other treatment modalities. These, together with the
development of more knowledge about the role of the psychosocial factors in
the development of episodes or in their triggering, ought to provide more
efficient methods for therapeutic and preventive intervention.


10. Lewis, M.D.C., "Outlines for Psychiatric Examinations," New York State Department of Mental Hygiene, 1944.


14. Zubin, J., & Steinhauer, S.R., "How to break the logjam in


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Table 2. Clinical course of schizophrenic first admissions during 5-year follow-up (1975-80). (Adapted from Watt, Katz and Shepherd\textsuperscript{6}, Table 2, p. 667.)

Table 3. Types of markers by pre-episode, episode, and post-episode status, and presence in first degree relatives. (Adapted from Zubin and Steinhauer\textsuperscript{14}, Table 3, p. 484.)
Table 1. Frequency of hospitalization among first admissions during the total follow-up period.

<table>
<thead>
<tr>
<th>Category</th>
<th>No.</th>
<th>%</th>
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<tr>
<td>Never released</td>
<td>6</td>
<td>8.8</td>
</tr>
<tr>
<td>Released and rehospitalized and never released again</td>
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<td>13.2</td>
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<tr>
<td>Rehospitalized more than once followed by release</td>
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<td>Released and never rehospitalized</td>
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<td>Clinical course</td>
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<tr>
<td>(1) One episode only - no impairment</td>
<td>4 (15.4)</td>
<td>7 (31.8)</td>
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<tr>
<td>(2) More than one episode with no or minimal impairment</td>
<td>9 (34.6)</td>
<td>8 (36.4)</td>
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<tr>
<td>(3) Impairment after first episode with subsequent exacerbations and no return to normality</td>
<td>1 (3.8)</td>
<td>3 (13.6)</td>
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<tr>
<td>(4) Impairment increasing with each of several episodes and no return to normality</td>
<td>12 (46.2)</td>
<td>4 (18.2)</td>
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<tr>
<td>Total</td>
<td>26 (100)</td>
<td>22 (100)</td>
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<tr>
<td>Marker</td>
<td>Pre-Episode</td>
<td>Episode</td>
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**Legend:**
- + = marker significantly more frequent in schizophrenics than in normal controls during the designated period.
- - = marker significantly less frequent in schizophrenics than in normal controls during the period.
- - = marker not differential during the period.
- ? = doubt whether the pattern across the periods occurs in nature
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Fig. 1. Percentage of first admission schizophrenics discharged and not readmitted during the subsequent 5 years. striped = males; white = females; black = total. (Adapted from Watt, Katz and Shepherd⁵, Fig. 3, p. 668.)

Fig. 2. Relation between vulnerability and challenging life 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. (Adapted from Zubin and Steinhauer¹⁴, Fig. 2, p. 481.)
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