Models for the Etiology of Schizophrenia

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Introduction

In the search for the scientific etiology of schizophrenia we too often narrowly associate science with the application of experimental techniques in the laboratory and in the field and forget about the long scientific process of observing, identifying and classifying behavior which must precede any experimental approaches (Hunt, 1980).

However, the complete understanding of scientific entities involves not only their identification, description and classification, but also the development of the causes giving rise to the entity in question. Though we have made some progress in the former, progress in the etiology of the disorder has not kept pace. In order to further the search for etiology despite our ignorance, we must entertain a variety of potential etiologies and seek the evidence for each. We shall leave the question of what is meant by "cause" to philosophers of science and accept the proposition that when the cause is unknown, it is necessary to invent potential causes and test them for their tenability through observation. This procedure is usually referred to as model making and testing, and in the course of the last few decades some seven scientific models of etiology for schizophrenia have been formulated (Zubin, 1972, Zubin and Steinhauer, 1981). Each of these has given rise to a series of hypotheses which have been subjected to experimental and observational testing. Thus far, not one of the prevailing models has demonstrated its necessity and sufficiency for acceptance as a single cause of schizophrenia, but each of them has a devoted school of followers who expect to find its validation just around the corner.
Why we have this multiplicity of potential causes can be explained in several ways. First, until recently, the lack of objective diagnostic criteria for identifying schizophrenia may have resulted in such a conglomeration of individuals included in this category that the heterogeneity of causes could not be reduced. Fortunately, this source of heterogeneity has been considerably reduced by the provision of systematic structured interviews, DSM-III, and Research Diagnostic Criteria (RDC) (Spitzer, Endicott and Robins, 1978). Second, it is possible that schizophrenia is in reality a multifactorial disorder and each of the proposed scientific models may be true. Despite this multicausality, the end result in the form of the schizophrenic episode may be the same. A third possibility is that there may be only one etiology producing a focal or core disorder, but because the disorder is mounted on an existing premorbid personality and in a specific ecological niche, the form and content of the disorder varies accordingly. That is why no two schizophrenics look alike (Zubin and Steinhauer, 1981).

The various formal models of the etiology of schizophrenia provide a framework in which the hypotheses arising from each model are matched against the data available for testing the tenability of the model. In this way the various lists of facts, hunches, and hypotheses are organized for scientific scrutiny, and it becomes possible to judge the isomorphism between observed fact and hypothesis, and its cogency. The explanation of the causes of schizophrenia must, however, transcend the models and be based instead on some theoretical structure usually referred to as a theory which encompasses all the models. After the presentation of the seven models, an attempt will be made to provide such a theory for explaining the isomorphism between observations and hypotheses for each of the models and their integration into
a common framework or tapestry into which the facts and hypotheses can be woven.

Historically, schizophrenia-like behavior can perhaps be traced to the description of aberrant behavior found in the sacred books of the ancient Hindus Ayurveda (Haldipur, 1984) some 34 centuries ago. Since then a vast amount of clinical observation has given rise to a plethora of symptoms and signs which form the warp and woof of psychopathology (Lehmann, 1980). This accumulation of signs and symptoms has served generations of psychopathologists and has formed the basis for such classification schemes as those provided by DSM-III, ICD 10, and other national and international classification systems in various countries (Zubin, J., et al., 1965).

Each age had its own models for the etiology of mental disorders, including schizophrenia, even before they were identified as separate entities. It is interesting to note that these models seemed to reflect the ideology and technology of the period. Thus, primitive man, whose conceptual models of the world consisted of spirits producing the natural changes in his daily experience, blamed mental disorder on spirits and demons; treatment consisted of exorcism. During the Middle Ages, belief in possession by the devil was the accepted etiology, although according to Neugebauer (Neugebauer, 19--), this was not the only alleged cause. The models of the universe postulated by ancient man, medieval man and modern man each made their impact on the etiology of psychopathology. Thus, during the ancient Greek period, mental disorder was regarded as due to either perversity, being possessed or being drugged. The treatments of these causes were to counter perversity with physical force, leave the possessed to the priests or other spiritual healers,
and restore the imbalance in the humors of the drugged by physiological means. During the Moorish period in Spain, mysticism held sway and the behavior of the patient was interpreted in mystic terms rather than in terms of his needs and difficulties. The Western Caliphate, especially in Seville and Cordova, began to be concerned with mental disorder as a problem of personal responsibility and whether the mentally ill are culpable. This led to the speculation that mental disorder was not under the control of the individual but due to some external force (Zubin, J., et al., 1965).

With the rise of modern science and technology, each new technological discovery had its impact on psychopathology. Thus, the invention of the clock opened up the road to the development of the machine age that provided the machine model for understanding the behavior of man and its deviations. Though no specific models for psychopathology based on mechanics had been proposed, it is likely that mental illness was regarded as due to the malfunctioning of the human machinery, giving rise to the layman's designation of mental illness as a "screw loose somewhere". Descartes' doctrine of dualism of mind and body seems to have been based on the analogy between two independent clocks, one of which points to the hour while the other strikes. If one did not know about their machinery, one might mistakenly assume that the movements of the one caused the other to strike (Boorstein, 1983). As the anatomy of the body was laid open through dissection, the brain began to be the focus of mental disorders. As the microscope developed, bacterial infection became the standard model for etiology and the concept of disease entities each produced by a single etiological agent became the norm. The application of this model to general paresis became the paradigm which Kraepelin adopted for dementia praecox. With the discovery of diet as a
factor in health and illness, pellagra with psychosis finally yielded its etiology. With the development of genetics, biochemistry and biophysics, the models provided by sciences were seized on by researchers in psychopathology. Thus, cellular pathology, electrophoresis, chromosome analysis, electron microscopy, CAT scans, PET scans, nuclear magnetic resonance, all were harnessed in the search for the sources of psychopathology. As Derek J. de Solla Prince (1984, 1984) has pointed out, science and discovery move forward not so much through the insights of great men of genius as because of more mundane things like improved techniques and tools.

The scientific revolution was largely due to the improvement, invention, and use of instruments that expanded the reach of science. Perhaps one of the greatest impacts on psychopathological theorizing has come from the mechanics of the computer. The analogy between computer processing of data with information processing in the human brain has led to a new approach to the search for markers of vulnerability and episodes (Zubin and Steinhauer, 1981). As the psychosocial field developed, such factors as the role of the ecological niche the person occupied (psychosocial - cultural - physical characteristics of the niche), premorbid personality, social network, life event stressors, family structure, communication deviance, emotional expression of the family, all were investigated for their impact as potential sources of psychopathology. Because no single agent has been found necessary and/or sufficient as a cause, we had to fall back on behavioral syndromes for the identification and study of schizophrenia. Fortunately, advances in descriptive psychopathology have recently been quite rapid. We now have systematic structured interviews and objective criteria on which to base diagnosis, but despite the reliability of these descriptive methods, the
problem of validity remains and will remain until etiology is clarified.

The current models of etiology have been described elsewhere (Zubin and Steinhauer, 1981). Here we can indicate briefly their nature as follows:

Insert Figure 1 About Here

As shown in Figure 1, there are at least 7 scientific models of etiology ranging from the molecular biological type, exemplified by the genetic model, to the field theory type, exemplified by the ecological (social-cultural physical) model. Between these two extremes lie the internal environment (including infectious disease or viral), neurophysiological and neuroanatomical models leaning towards the biological pole, whereas the learning theory, developmental and ecological models lean towards the environmental pole.

The genetic model is perhaps the most highly developed, yet has not explained the complete etiology of schizophrenia because of the high degree of discordance in identical twins (60%), and the presence of phenocopies as evidenced by probands who have no affected relatives. The ecological model, on the other hand, though not as generally accepted as the genetic, nevertheless points to such factors as low socioeconomic status, physical and social deficiencies in the milieu, minority or marginal status, ghetto niche, and educational and vocational limitations, characterizing individuals who have a high risk of developing schizophrenic episodes. The advantages that the genetic model has over the ecological inheres in the use of consanguinity for identifying individuals of high risk for developing a schizophrenic episode. Consanguinity with an individual who has suffered a schizophrenic
episode is one of the best indices for identifying this risk, since the risk rises from 1% in unrelated individuals to about 10% in first degree relatives and 40% in identical twins. There is no comparable measure for identifying risk on the basis of ecological similarity or for assessing similarity in ecological niches. It is possible, however, that with the development of knowledge of social networks, we may establish that characteristics of the network serve as the mediators of ecological forces impinging on the individual, and provide the ecological model with an underlying measure similar to the manner in which consanguinity functions for genetics. Just as the vascular system nourishes the body physical, the social network nourishes the body social and deviations in the latter may lead to higher risks of developing episodes of the disorder (Hammer, Makiesky-Barrow and Gutwirth, 1978).

The developmental model, based on individual developmental history, has not yielded as definitive evidence as that for the first two models in the etiology of schizophrenia, though earmarks of maldevelopment are beginning to be reported in the studies of high risk children of schizophrenic patients. Piaget's hypotheses of developmental stages and the patterning of attachment, socialization, and moral behavior may in the future provide normative baselines from which abnormal behavior could deviate. Meantime, we can postulate that as the fertilized ovum develops through the life cycle to a fetus, neonate, child, adolescent, adult and senescent, certain environmental supplies and maturational progress need to be provided to lift the individual from one stage to the next. It is in these interstitial contingencies that the source of malfunctioning is to be sought. Such interferences as prenatal and perinatal complications, nutritional deprivations, life-event stressors
during pregnancy, season of birth and cerebral injury after birth, many provide the matrix for the development of schizophrenia on a non-genetic developmental basis (Zubin and Steinhauer, 1981). The absence of intimacy in the friendship pattern during adolescence has also been found to characterize high risk (Kreisman, 1970).

The learning theory model stresses the reinforcement history of the individual as the source of his maldevelopment. Following Adolf Meyer's thesis that the accumulation of faulty habits in reaction to life's exigencies is a formative factor in dementia praecox, the negative and positive reinforcement schedules in the learning theory paradigm may provide a learning theory approach to etiology. Ineffectual social and interpersonal relationships, developed either actively in maladaptive situations or passively through inappropriate modeling, may serve either as causes of the behavioral disorder we denote as schizophrenia, or may prevent the development of good coping strategies, which could absorb the stress which otherwise would lead to an episode. It should be noted that some learning theorists deny the existence of an underlying schizophrenic disorder, but maintain that the disorder consists of the specific symptoms which can be targeted for elimination by behavior modification techniques.

The internal environment model has provided such hypotheses as the dopamine hypothesis as a cause of the disorder. Metabolic rates, hormonal activities, and neurotransmitters affect the psychological processes (perception, cognition, attention, motivation, mood, etc.) mediated through the synapses and deviations from the norm in the supplies of these substances and their activities may contribute to the cause of schizophrenia according to
this model. As to the viral infection hypothesis, the fact that 10% of the families of schizophrenic probands tend to have some first degree relative suffering from the disorder lends some credence to this model. The fact that the staffs of mental hospitals do not seem to "catch" the disorder may militate against the hypothesis but no data on this question are now available. Perhaps long continuous exposure is required if a slow developing virus is involved (Zubin, Steinhauer, Day and van Kammen, ress).

The neurophysiological model postulates that information processing by the brain is different in schizophrenics than in normals. These deviations may occur anywhere in the sequence of processing between the receptor on which the informational stimulus impinges, through the encoding and decoding by the higher centers of the brain, interaction with memories of previous experience and established neural network patterns, leading to the final emission of the response.

The neuroanatomical model, which has been rescued from oblivion by the recent development of brain-scanning techniques, is beginning to provide evidence that at least some schizophrenics have enlarged ventricles and exhibit other types of anatomical atrophy and other deviations (Zubin, Steinhauer, Day and van Kammen, ress).

Since each of these models has been postulated as a causal agent in the development of schizophrenic episodes, we can now apply a suitably named ectype to each of these models even as the term genotype is applied to the genetic model. Thus, the ecological model would have a corresponding etctype, the developmental model an auxonotype (Greek word for development) the
learning theory model a mathetotype, the internal environment a chemotype (exclusive of DNA), the neurophysiological model a neurophysiotype, the neuroanatomical model a neuroanatomotype and the viral infection model a virottype (Zubin and Steinhauer, 1981).

The question now arises whether each of these etiotypes gives rise to a specific kind of schizophrenia or whether despite the differences in etiology, the final pathway is the same, leading to the same type of deviant behavior. As far as we can now determine, none of the etiotypes by themselves gives rise to a specific disorder, and the likelihood is that several of these etiotypes interact to produce the disorder. The apparent heterogeneity of schizophrenia may result not so much from the different individual etiological models, but from the variety of interaction between the postulated models. Another source of heterogeneity may arise from the fact that the deviant behavior characterizing the core is made up of two factors: (1) the effect of the focal core disorder itself, and (2) the interaction between the core disorder and the premorbid personality on which it impinges. The variations in premorbid personality may relate to the special kinds of psychopathological behavior noted, even though there is a basic focal core disorder underneath the cloak of the premorbid personality.

But since not one of the postulated models is in itself necessary and/or sufficient to develop a schizophrenic episode, we must find a theory based on the common denominator of these models if we are to maintain the singularity of the disorder (if indeed such singularity exists). This theoretical structure is an attempt to integrate the facts and hypotheses of the seven models into an explanatory framework for the etiology of the disorder.
The vulnerability theory is an attempt to provide proper weights for each of the underlying models in the causation of a schizophrenic episode. It is aimed at eliminating the dichotomy which has arisen in the field of schizophrenia. On the one side are those who regard it as essentially a biological disorder in which psychosocial factors play a minor or even trivial role, and on the other side are those who regard it as a psychosocial disorder in which biology plays a minor role. The vulnerability theory has been introduced as a compromise between these two extreme views. It assumes that schizophrenia occurs in a vulnerable individual for whom a time-limited episode is triggered by a life event stressor of either exogenous or endogenous origin. The sources of this vulnerability lie in the various etiological models that have been presented above. But vulnerability alone is not a sufficient cause for an episode to occur, it has to be triggered by a life event stressor (either exogenous or endogenous). Perhaps the greatest difference between the two extreme camps (biological and psychosocial) and the middle ground of vulnerability is the attitude towards recidivism. According to the biological, and to some extent, the psychosocial approaches, the periods of mental health of a vulnerable person are but temporary respites in a life of continuing disorder. According to the vulnerability model, the episodes of the disorder are but temporary interruptions of an essentially healthy life.

The vulnerability model also differs from the other two in the postulated cause of recidivism. According to the biological model, recidivism is brought about by either premature release which results in an exacerbation of the unterminated episode, failure of chemotherapy, non-compliance with the treatment regime, post-release drug intake, or natural undulation of the
course of the disorder.

According to the psychosocial model, recidivism is also due to premature release as in the case of the biological model, but it is also attributed to the return of the patients to their noxious, critical families, or to failure in the transference to real life outside of the hospital of the improved behavior instituted through psychosocial treatment in the hospital, failure in vocational readjustment, the demanding nature of the environment, and its intrusionary qualities.

According to the vulnerability model, recidivism is due primarily to the impact of a life event stressor which elicits a new episode unless some moderating variables intervene to prevent it. If it were not for the occurrence of the life event stressor, no new episode would occur. It does not deny the claims of the other two models, but challenges the possibility of natural undulation as a cause unless periodic recurring life event stressors bring it about. It also denies chronicity as an indigenous element in the natural history of the disorder, maintaining that it is largely an artifact due to iatrogenic, ecogenic and nosocomial factors. It also denies non-compliance with the treatment regime as a cause, since even when enforced compliance occurs as in depot treatment, new episodes still develop. If we regard the behavior of families high in expressed emotion as stressors, we can add this source of recidivism to the vulnerability approach. The schizotrope or vulnerable individual may or may not develop an episode, since 60% of identical twins are discordant though both twins are schizotropes. On the basis of a penetrance of .26 (Zubin and Steinhauer, 1981) it can be expected that if there are 2-3 million schizophrenics in the USA (1% of the population)
there are 6–9 million schizotropes who never develop an episode.

In order to test the tenability of the vulnerability theory we need to specify its parameters and assumptions, and subject these to experimental examination of the degree to which observed data interdigitate with expectation from the theory.

The parameters of the vulnerability theory are:

1. Degree of Vulnerability: The risk of developing an episode of schizophrenia depends upon the degree of vulnerability of the individual which can vary from zero to maximum of certainty, or inevitability of the development of an episode.

2. Etiotypes: This vulnerability depends upon the pattern of etiotypes which characterize the person. These etiotypes reflect the variety of scientific models of etiology which have been postulated: (ecotype, auxanotype, mathetotype, genotype, chemotype, neurophysiotype, and neuroanatomotype).

3. Life Event stressors: Life event stressors are required in order to elicit episodes in the vulnerable.

The assumptions of the theory are:

1. Episodes are time limited.

2. When an episode is terminated, individuals return to their premorbid level of coping.

The consequences of the interaction between the three parameters of the model and the two assumptions lead to the following expectations:

1. Schizophrenia is an episodic disorder.

2. Chronicity is an artifact due to iatrogenic, ecogenic and nosocomial factors.

3. Since not all the vulnerable etiotypes develop into phenotypes,
there must be some moderating factors that prevent this development. Prominent moderating factors are:

a. Premorbid personality
b. Ecological niche
c. Social network

4. Intervention to prevent development of episodes may be based on the manipulation and/or modifications of the three moderating factors.

In order to investigate the tenability of the vulnerability theory, research in the following areas is necessary.

1. The discovery of markers of vulnerability and markers of episodes
2. The development of measures of the three moderating factors
3. Determinations of the differences between those schizotropes (vulnerable individuals) who develop episodes and those who do not.

In our own laboratory and clinic we are pursuing several problems emanating from the postulates of the theory. Our investigations of markers of vulnerability are based on the assumption that the information processing operations in schizotropes differs from the processes in normals. To this end investigations of event-related brain potentials (especially P300), pupillography and heart rate are under way. By determining the presence of such markers premorbidly, morbidly and post-morbidly in probands as well as in unaffected first degree relatives, it becomes possible to decide whether the marker in question is a vulnerability marker, episode marker, residual markers or immunity (invulnerability marker) (Day, et al., 1984).

In a second investigation we are searching for the differences between
recidivists and non-recidivists. To this end, follow-up of released patients are conducted to determine the frequency of life event stressors and to measure the variations in social networks, ecological niches and coping abilities in the two contrasted groups.

Summary

The purpose of this chapter has been two fold: (1) to lay down the framework for considering the etiological models for schizophrenia and (2) to propose a theory of vulnerability to replace the currently dominant biological and psychosocial theories that preempt the field. While the vulnerability theory proposed here is not new, being based on the diathesis - stress model (Rosenthal) it nevertheless leads to a new synthesis of the available data that results in a much more optimistic outlook for the nature and outcome of schizophrenia.

Thus, by rejecting the view of schizophrenia as a persistent chronic disorder and substituting the vulnerability theory, it may become possible to discover the vulnerable even before an episode develops. By examining the factors differentiating the schizotropes who develop episodes from those who do not, perhaps suitable intervention methods for prevention may be found. By further examination of the recidivists in comparison with non-recidivists, it may become possible to abort recurrence of episodes.
REFERENCES


