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Advances in the Diagnosis and Treatment of Schizophrenic Disorders

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Table of Contents

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Robert Cancro

All of medicine has been profoundly influenced by the work of Koch, who demonstrated the bacterial origin of tuberculosis. In 1882, Koch presented a series of elegant experiments that proved the etiologic role of the tubercle bacillus in the origin and transmission of a disease. This monumental achievement made it possible to exclude other pulmonary infections, which previously had been misdiagnosed as tuberculosis, and to include those infections that belonged there but that had previously been excluded. In this way, the category was restricted to a biologically more homogeneous population. The powerful promise of this work for meaningful classification and nosology was not lost upon Kraepelin. He recognized that the protean manifestations of tuberculosis could now be understood and classified within a single disease entity conception. Kraepelin attempted to translate and apply the work of Koch to psychiatry. Obviously, it was not possible to fulfill the requirements of Koch's postulates to obtain the bacterium and have it infect a new host, in mental disorders. Kraepelin attempted, therefore, to translate the postulates into a form more appropriate for psychiatry and to create, on the basis of clinical features, entities that shared a specific etiology, presented with a consistent picture, and followed a predictable course over time. In this

way, he hoped to create diagnostic categories of mental disease that would be comparable in their clinical unity to Koch's explanation of tuberculosis.

As early as 1883, Kraepelin began to use the course of illness as a classificatory variable. This attempt to use the outcome of patients suffering from mental disorders as a means to group them into different diseases achieved its fullest expression in 1899 when he separated dementia praecox from manic-depressive psychosis. This separation, while enormously helpful clinically, failed to create distinct and genuine entities. In the more than eight decades that have passed since Kraepelin's historic division, the problems of categorizing schizophrenic disorders have remained both baffling and frustrating.

This chapter will attempt to summarize selectively some of the more recent developments in the conceptualization, diagnosis, and etiology of the schizophrenias. These developments do offer some direction and help guide the explorations of those interested in achieving greater familiarity with the many features and facets of the problem. No chapter can hope to be an accurate nor even an adequate Baedeker for those who strive to achieve certainty in matters psychiatric. This very lack of certainty may contribute to the excitement of the activity.

Conceptualization

There have been a variety of positions taken concerning schizophrenia: It has been conceptualized as a disease of the brain to a mythology developed in the name of political repression. Griesinger's theories were representative of the approach that mental disorders are diseases of the brain. This conceptualization can be characterized by the slogan: "For every twisted thought there must be a twisted molecule." Conversely, observers such as Szasz have argued that there is no such thing as mental illness, only socially unacceptable behaviors. This chapter will initially utilize certain assumptions that are best made explicit, particularly since not all of them are demonstrably true. It is assumed that the schizophrenic disorders represent a syndrome. This syndrome is heterogeneous in its etiology, pathogenesis, presenting picture, course, response to treatment, and outcome. In other words, the syndrome consists of multiple disorders rather than a single entity. It will also be assumed that the schizophrenias represent illnesses and not alternative life styles. The schizophrenias are seen as pathological adaptations to a highly altered sense of inner and outer reality. They are seen as pathologic adaptations because of the psychotic features that impair the quality of the person's life. Finally, the schizophrenic disorders are diagnosed on the basis of their clinical features, independent of the route of origin of these features.

Diagnosis

General Comments

The careful diagnosis of a patient is important for many reasons, although it has not always been in fashion. It is important not only for the care of the individual patient but for the progress of the field. It must be understood that any clinical population labeled schizophrenic has been arrived at through the process of diagnosis. Research studies done on such populations are not more reliable than the diagnostic criteria that produced the groups studied. There are different strategies for diagnosing the disorder. Perhaps the most basic diagnostic question is whether a single criterion or multiple criteria will be used. The single-criterion approach, of course, offers greater simplicity of application. More important, it can also increase the homogeneity of the population labeled schizophrenic. Nevertheless, the multiple-symptom approach has become the dominant nosologic fashion in recent years. Some of the multiple symptoms are nonspecific, while other symptoms are treated in an egalitarian manner; that is, every symptom is equal to every other for diagnostic purposes. It does not matter in this approach which symptoms or signs the patient has from the given list as long as the patient obtains the correct number of such items. Recently, diagnostic practices have also shifted to an emphasis on symptoms and signs requiring low levels of inference. This emphasis allows for greater reliability, although it suffers from a lack of clinical sophistication. The conceptualization of schizophrenia has narrowed in the last decade, and the diagnostic emphases today are on chronicity and phenomenologic manifestations of low inference

and, therefore, high reliability.

Finally, it should be made clear that there is no independent test for validating the diagnosis. In the absence of such independent validation, any diagnosis must be arbitrary. This arbitrariness does not reflect lack of care on the part of the practitioner, but rather an exclusive reliance on clinical criteria. Until the time when independent diagnostic procedures are available, the diagnosis of the schizophrenic disorders will remain a clinical activity with all of the inherent unreliability of such a practice.

Strategies

There have been a number of strategies utilized through the years in making the diagnosis of schizophrenia. Kraepelin followed the classical clinical method. He described patients in meticulous detail. In this way, the student could learn the descriptions of typical cases and compare his patient against a mental template of the disorder. Obviously, there are many deficiencies in such an approach, not the least of which is poor reliability.

Bleuler moved away from the disease-entity approach of Kraepelin and introduced the concept of schizophrenia as a syndrome, or group of disorders, that contained certain clinical features in common. He identified the essential common features that were necessary for the diagnosis of the syndrome. Bleuler deemphasized delusions and hallucinations as diagnostic criteria, and

relegated them to a relatively minor or accessory role. He placed major emphasis on what he considered to be characteristic disorganizations of thinking and the loss of harmony between various mental functions, in particular thinking and affect. The diagnostic advantage of this approach was that there were specific admission criteria to the category. The patient had to demonstrate particular altered fundamental signs of the disorder before the diagnosis could be made. No pathognomonic delusions or hallucinations were sufficient to diagnose the illness. While this increased reliability considerably over the Kraepelinian approach, it still was not sufficiently reliable. Bleuler's diagnostic method required clinical judgment, which reduces reliability.

Langfeldt in many ways bridged and combined the diagnostic preferences of Kraepelin and Bleuler. He recognized the multiplicity of illnesses in the category by separating true schizophrenia from schizophreniform psychosis, while continuing to utilize, as did Kraepelin, a long list of typical symptoms. In the Kraepelinian tradition, he attempted to separate the schizophrenias into those with good and poor outcomes, with only the latter representing the true disorder.

In the last decade, the diagnostic approach of Schneider has received increasing attention. He developed his criteria empirically by identifying the most common signs and symptoms in patients about whom there was diagnostic consensus. These were referred to as symptoms of the first rank.

They included audible thoughts, voices heard arguing, voices commenting on the person's actions, somatic passivity experiences, thought withdrawal, diffusion of thought, delusional perception, and all feelings that are experienced as a result of the influence of others. The use of Schneiderian criteria tends to create a somewhat more homogeneous population with a tendency toward a chronic form of illness.

The *Diagnostic and Statistical Manual of Mental Health,* 3rd edition (DSM-III) has been profoundly influenced by the Schneiderian approach. It uses a multiaxial system of diagnosis, which includes an effort to assess personality structure, other medical conditions, and the highest level of recent social functioning. The essential requirements for a diagnosis of a schizophrenic disorder are evidence of disorganization from the previous level of daily functioning, the presence of at least one symptom from a list of six during the active phase of the illness, and at least a six-month duration of symptoms (including the prodromal, active, and residual phases of the illness) during which the symptom or symptoms necessary for making the diagnosis are present. This list of required symptoms for diagnosis of the active phase of the illness includes three that are delusional in nature and two that are hallucinatory. It is obvious, therefore, that, unlike Bleuler, DSM-III places great diagnostic significance on the presence of delusions and hallucinations. Nevertheless, it recognizes the syndrome nature of the category and acknowledges that it is a group rather than a single disorder.

The third edition of the *Diagnostic and Statistical Manual* deviates very sharply from the second, and it is important that the field understand the new nosology. The multiaxial approach, while new in psychiatry, has been used previously in much of medicine. Five axes are included in the new diagnostic manual. The first is the *diagnosis of the clinical syndrome.* The second is the *diagnosis of the personality.* It is possible for the clinician to specify two or more diagnoses on either of these axes. The third axis is the *diagnosis of any coexisting physical condition.* The final two axes are the *presence of psychosocial stressors and the highest level of adaptation achieved in the past year.* Obviously, this multiaxial approach gives a much richer picture of the patient than does a single diagnostic label.

The essential diagnostic features of a schizophrenic disorder are listed in DSM-III as disorganization from a previous level of functioning, the presence of characteristic symptoms, the absence of an affective disorder, the absence of an organic brain syndrome that can explain the clinical picture, a tendency toward chronicity, onset before the age of forty-five, and a duration of continuous symptoms in excess of six months. To diagnose the active phase of the illness, it is necessary for the patient to show disorganization from previous functional levels in two or more areas of daily living. These areas include work, social relationships, self-care, and so on. At least one symptom from a list of six must be present for diagnosis of the active phase of the illness to be made. The symptoms are:

1. Bizarre delusions that are obviously absurd. (Typical delusions include the belief that one's thoughts are being broadcast so that other people can hear them, the belief that thoughts are being put into the mind by external forces, the experience of thought withdrawal, or the delusion of being controlled.)

2. The presence of religious, grandiose, nihilistic, somatic, or other delusions without persecutory or jealous content. (This group of delusions need not be bizarre, but cannot be accompanied by either persecutory or jealous ideation.)

3. Delusions with a persecutory or jealous content if they are accompanied by hallucinations of any type.

4. The presence of two or more hallucinatory voices conversing with each other, or auditory hallucinations in which a voice keeps up a running commentary on the person's behaviors or thoughts as they occur.

5. Auditory hallucinations on several occasions, which are not related to either the presence of depression or elation and which are not limited to one or two words.

6. Marked loosening of associations, incoherence, illogicality, or marked poverty of speech if associated with at least one of the following: (a) blunted, flat, or inappropriate affect; (b) delusions or hallucinations; (c) catatonic or grossly disorganized behavior.

In addition to the active phase of the illness, there may be a prodromal

and/or a residual phase. The prodromal precedes the active phase and the residual follows it. The prodromal and residual phases also must not be secondary to an affective disorder. In order to diagnose either a prodromal or residual phase, the patient must show at least two symptoms from a list of eight. The symptom list for the diagnosing of prodromal and residual phases includes: (1) withdrawal or social isolation; (2) marked impairment in role functioning; (3) markedly eccentric, odd, or peculiar behavior; (4) impairment of personal hygiene and grooming; (5) blunted, flat, or inappropriate affect; (6) speech that is tangential, digressive, vague, overelaborate, circumstantial, or metaphorical; (7) odd or bizarre ideation, magical thinking, overvalued ideas, ideas of reference, or suspected delusions; and (8) unusual perceptual experiences, suspected hallucinations, and sensing the presence of a force or person not actually there.

DSM-III recognizes several phenomenologic subtypes of the schizophrenic disorders: disorganized, catatonic, paranoid, undifferentiated, and residual. These subtypes reflect cross-sectional syndromes and are not assumed to be stable over time within a given person. The subtypes are descriptive of the symptoms as they appear in an individual at a given moment in time.

The disorganized category is closest to the classical concept of hebephrenia. The major clinical features required for the diagnosis of this

subtype are severe incongruence and the presence of flat, incongruous, or silly affect. The delusions and hallucinations, when present, tend to be fragmentary and not organized into extended or coherent themes. A number of features associated with this category are less central than those already cited. They include the presence of grimaces, mannerisms, hypochondriacal complaints, social withdrawal, and peculiarities of behavior. The premorbid personality tends to be withdrawn and inclined toward the schizoid end of the spectrum. Onset usually is at an early age and insidious in nature. As would be expected, these patients tend to run a chronic course with few if any significant spontaneous remissions, let alone restitution to the premorbid state of the personality.

The essential clinical feature of the catatonic subtype is the marked involvement of the motor system either in the direction of over- or underactivity. There can be a relatively rapid alternation between over-activity (excitement) and underactivity (stupor). There are a number of associated features for this subtype, which include negativism, stereotypies, mannerisms, posturing, and waxy flexibility. An interesting feature that is sometimes found is mutism. The diagnosis of this category requires that the clinical picture be dominated by one of the following symptoms during the active phase of the illness: (1) catatonic stupor or mutism; (2) catatonic rigidity; (3) catatonic excitement; or (4) catatonic posturing.

The paranoid subtype should be diagnosed when the clinical picture is dominated by a persecutory or grandiose symptom complex. These symptoms can take the form of persistent delusions and/or persistent hallucinations. The critical diagnostic issues are the nature of the symptom, that is, delusion and / or hallucination; and the nature of the content, that is, persecutory and/or grandiose. Delusions of jealousy are also acceptable as one of the diagnostic criteria. During the active period of the illness, the clinical picture must be dominated by the persistence of at least one of the following symptoms in order to diagnose this subtype: (1) persecutory delusions; (2) grandiose delusions; (3) delusions of jealousy; and (4) hallucinations with a persecutory or grandiose content. The clinical features associated with, but not diagnostic of, this subtype include anger, argumentativeness, violence, fearfulness, ideas of reference, concerns about autonomy, concerns about gender identity, and preoccupation with sexual preference. These patients may show very little social impairment, particularly in the workplace. At times the delusional concerns are relatively encapsulated and do not intrude into the person's day-today life. The age of onset of the schizophrenic disorder tends to be at a later age in this subtype, and the likelihood of cognitive deterioration is less.

The so-called undifferentiated subtype tends to be less of a subtype than a "wastebasket" category. Patients who meet the criteria for a diagnosis of a schizophrenic disorder and cannot be placed in any of the three previous

classes, or who manifest criteria for more than one of those subtypes, should be categorized in this grouping.

The remaining subtype is the residual. This category is utilized for individuals who have had a clear-cut episode of a schizophrenic illness, but whose clinical picture does not, at the time of examination, contain prominent psychotic symptoms. The person must show evidence of a persistent mental disorder, otherwise the diagnosis of no mental disorder must be entertained. The common manifestations of persistence that would require the use of this category include: emotional blunting, social withdrawal, eccentric behavior, and mild communication difficulties. Delusions or hallucinations may be present if they are not prominent and have lost their affective intensity. This subcategory is quite similar to the concept of partial clinical remission. An individual can be categorized as being in full remission if there are no signs of clinical illness with or without medication. If the person is free of medication and clinical symptoms for five or more years, the diagnosis is changed to no mental disorder.

General Comments on Diagnosis

The concept of acute schizophrenia has been eliminated from DSM-III. The disorder can be chronic, which is defined as in excess of two years, or sub-chronic, which is defined as more than six months but less than two

years. DSM-III does recognize the possibility of acute exacerbations, particularly in residual phases of the disorder. During these acute exacerbations, prominent psychotic symptoms can reemerge and dominate the picture. Nevertheless, disorders that remit in six months or less must be classified elsewhere. The diagnosis of a schizophrenic disorder requires the exclusion of both organic mental disorders and affective disorders. It is not unusual for organic mental disorders to present with symptoms such as delusions, hallucinations, incoherence, and affective changes—all of which are suggestive of a schizophrenic disorder. This is particularly true in syndromes associated with substances such as phencyclidine and amphetamines. A proper differential diagnosis frequently requires the passage of a period of time; it should not place an exclusive reliance on the cross-sectional picture at a single moment. However, it is an excellent clinical rule of thumb to suspect organic mental disorder whenever confusion, disorientation, or memory impairment are significantly present in the clinical picture. The clinician must also remember that it is possible for a person to have simultaneously both an organic mental disorder and a schizophrenic disorder.

The differential diagnosis of affective disorders from schizophrenic disorders is clinically very important and is based on the presence or absence of a full affective syndrome. If a full affective syndrome is present and the disorder of mood is a prominent and relatively persistent part of the illness, the diagnosis of an affective disorder should be made. An affective syndrome

may be present in a schizophrenic disorder but it must occur after the development of the psychotic symptoms. In order to diagnose mania, it is necessary for the person to show one or more distinct periods with a predominantly elevated, expansive, or irritable mood. In order to diagnose depression, the person must show a dysphoric mood or loss of interest or pleasure in most, if not all, of his usual life activities.

Etiology

Of those people who are diagnosed as having a schizophrenic disorder, there is no single personality type that is pre-morbidly present. While no personality type is spared being vulnerable to the disorder, those premorbid personalities that are schizoid and those that show autistic tendencies have a relatively poor prognosis. And just as there has been no single personality type, there has been no universal biologic pattern pre-morbidly, not even a genetic one. At least 90 percent of the patients diagnosed as having a schizophrenic disorder fail to show any first-degree relatives with such an illness.

The premorbid history of individuals with this diagnosis frequently shows one or more episodes of a neurotic-like illness. These episodes of illness are unlike a true neurosis in that they are transient, sudden in onset, and last only four to six weeks. The symptoms include anxiety, phobias, and

obsessional preoccupations. These neurotic-like episodes do not show apparent sequelae and clear completely. These premorbid micro-episodes mirror, in a nonpsychotic fashion, elements of the future psychotic decompensation. They are not always present in the history and do not appear to have any particular prognostic significance. They raise, however, an important theoretical question: Are there environmental experiences that may help to suppress or exaggerate these micro-episodes? It is certainly possible that the progression from a micro-episode to a full-blown decompensation is influenced by a variety of fortuitous life events, some of which may be deleterious while others are healing.

Stress

There are major methodologic problems facing investigators who wish to study the role of stress in the schizophrenic disorders. Different definitions of stress will produce different findings. There is no universal definition, and the concept itself is in many ways ambiguous. Investigators have usually chosen to rate events that are externally caused and that are experienced most often as either unpleasant or undesirable. It has been shown that people at the lower end of the socioeconomic scale have more of these negative life events; for example, unemployment, job insecurity, physical illness, and inadequate housing.

The literature does not answer the question of the role of stress in the etiopathogenesis of a schizophrenic disorder. The most cited studies- do suggest a relationship between the frequency of the illness and stress. However, there is a relationship between class differences and coping abilities, such that lower-class individuals are less able to cope with stress effectively. It may be, therefore, necessary to conceive of a dynamic equilibrium between stress and the adaptive resources of the individual. Despite the many limitations of the studies, there is a suggestion that an acute episode of a schizophrenic disorder is preceded by an increase in stressful events and that these events are more likely to occur among the lower socioeconomic classes. It is very difficult to study life events rigorously. The more recent of the case control studies done by Jacobs and Myers found that first-admission schizophrenics reported more current life events than did controls. In addition, more of these events were classified as undesirable. These data must be interpreted cautiously, but they do suggest that a precipitating role may be played by current life events.

The classic studies on the contribution of stress as a predisposing rather than a precipitating factor were done many years ago. The Faris and Dunham study found that the inner or central city, and in particular the transitional zones, had the highest rates for hospital admissions. Work done by Clark showed that the highest rates of schizophrenia were in the lowest status occupations. This finding of a disproportionate concentration of

schizophrenics in the lowest social class was replicated in a number of cities in the United States and abroad. The relationship between social class and prevalence rate is a complex one. It is linear in cities of over one million in population. There is no relationship between social class and the prevalence rate of schizophrenia in cities of less than one hundred thousand population. Cities of an intermediate size—between one hundred to five hundred thousand—do not show a linear relationship but rather a clustering of schizophrenic patients in the lowest social class.

There have been several interesting reports describing a relationship between season of birth and the schizophrenic disorders. These reports, from two Scandinavian countries and Great Britain, describe a disproportionate number of schizophrenics born between January and April in the northern hemisphere. While it is possible that a winter birth may constitute some as yet undefined stress, it is more likely that there is a relationship between intrauterine development and the environmental demands of the winter.

Family Studies

The early family studies, particularly in the United States, stressed the search for noxious parental interactions in the childhood of the schizophrenic patient. A variety of such destructive family interaction patterns were described by Lidz and colleagues, Wynne and colleagues, Wynne and Singer,

and Jackson. These early studies suffered from major methodologic problems including the absence of normal control families. In addition, the studies were retrospective, lacking adequate controls for the effects of early peculiarities of the child on the parenting style. However, the quality and rigor of the studies have continued to improve, and currently there is more emphasis on family communication patterns, particularly the way families solve problems and arrive at closure. It seems reasonable to conclude that the families of schizophrenic patients show more communication deviancies than do nonschizophrenic families. It also appears reasonable to conclude that the communication deviance precedes the onset of the actual illness.

Relapse rates in young schizophrenic males living in their parental home have been studied as a function of the emotional climate of that home. It has been shown that homes in which there was a tendency for the parents to make critical comments, express hostility, and show emotional over-involvement with the schizophrenic son were more likely to have relapses. Homes in which the parents were more tolerant of their offspring's deviance were much less likely to be associated with relapses.

Genetic Studies

The genetic studies of the past decade have focused on twin and adoptive strategies. Nevertheless, six major recent consanguinity studies

found that the prevalence rate in the siblings of schizophrenic patients was 10 percent. This does not differ significantly from the prevalence rate for other first-degree relatives and, therefore, this figure suggests that rearing practices do not have as direct an effect on the prevalence rate as do other factors.

A very important twin study was reported by Fischer in 1973. She followed her population of twins for a sufficient period of time so that virtually no age correction was required in her sample. She reported a monozygotic concordance rate of 56 percent in the twins she studied. This is in many ways the best estimate of the true concordance rate because it does not rely on age correction. Fischer found that monozygotic twins who were concordant for schizophrenia were not at an increased risk when compared to discordant monozygotic twins. She studied the offspring of her twin sample and found that the children of the discordant pairs were at an equally high risk for schizophrenia, as were the children of the concordant twin pairs. Perhaps the most striking finding in her study was that the nonschizophrenic twin was as likely to produce a schizophrenic child as was the schizophrenic twin. The concordance results of Fischer are quite consistent with the better earlier twin studies, which consistently showed that the concordance rate for schizophrenia was significantly higher in monozygotes as compared by dizygotes. If one examines the five best twin studies, the average monozygotic concordance rate is 47 percent compared to an average dizygotic concordance rate of 15 percent, f In other words, the average monozygotic

concordance rate is three times as high as the average dizygotic concordance rate.

The initial findings of the Danish adoption studies were that the adopted offspring of schizophrenic parents were more likely to develop the illness and that the biological relatives of the schizophrenic offspring were more likely to show a schizophrenia spectrum disorder.- This sample is particularly important because the majority of the off-spring of schizophrenic parents were adopted prior to the parental psychotic episode. This fact controls for the effect of possible adoptive agency bias in placement and/or the effect of the prior knowledge of a family history of mental illness on the parenting style in the adoptive home. The more recent results obtained from this sample are based on extensive psychiatric interviews of over 90 percent of the available relatives. The findings consistently support the conclusion that those who bear the child are more important for the prevalence rate of schizophrenia than those who rear the child.

Vulnerability

A complex and heterogeneous group of illnesses such as the schizophrenic disorders cannot be directly transmitted genetically. What can be transmitted is a diathesis toward the development of the necessary phenotype. The current literature tends to think of this diathesis as a

vulnerability to the schizophrenic disorder. The data do not suggest that the phenotype involved in the transmission of the schizophrenic disorder predisposes to psychosis, but rather predisposes to a schizophrenic form of illness should one become psychotic. Vulnerability most likely means that a given individual has the capacity to develop specific behaviors under certain conditions, which might lead a psychiatrist to make a particular diagnosis. The transmitted vulnerability need not be abnormal nor inherently pathogenic, but rather plays a role in the etiopathogenesis of the symptoms that are used for the diagnosis of the illness.

Mode of Gene Action

Even in the simplest of traits, the genotype does not immutably determine the phenotype in the absence of an environmental influence. The more steps involved between the genotype and the phenotype, the more room there is for individual variation in development. The genotype is one factor that accounts for individual differences, but it is certainly not the only factor. The gene is activated by the environment, and the phenotypic outcome is determined by the nature and timing of that gene-environment interaction. The gene-environment interaction is not a passive activation, but rather a union between the gene and the activating environment. The final phenotypic outcome is determined by the complex interplay of both genetic and environmental factors. The same gene activated in different environments

will produce variations in the phenotype. Any given phenotype represents only one of the possible outcomes inherent within that particular gene. The degree of freedom within the genotype is finite, and the differences in the final phenotypic characteristic may be small. Nevertheless, the difference may be of clinical significance, including the presence or absence of a pathologic trait. The amount of variability inherent within the genotype is not a theoretical question but rather an empirical one. It can only be determined by exposing the genotype to a range of environment-evoking stimuli. Having the appropriate genes necessary for a schizophrenic illness is not sufficient to produce it, as can be seen clearly from the identical twin studies.

A knowledge of the genotype does not allow a prediction of the phenotype and, similarly, a knowledge of the phenotype does not allow an inference of the underlying genotype. Any phenotype can be arrived at from different genotypes being activated in different environments. There is enormous plasticity in biologic systems, which contributes to the diversity that characterizes all species. Each individual is a unique biologic experiment in which the gene-environment interaction will never be reproduced identically again. The phenotypes that are necessary for a schizophrenic illness need not be sufficient to cause it. It is theoretically possible to have these phenotypes without becoming ill, particularly if the phenotypes represent normal variations of the trait. The phenotypes involved in the transmission of schizophrenia need not be pathogenic or inherently

pathologic. For example, if shyness were to represent a phenotypic trait, it may not be pathologically exaggerated in the premorbid personality of a person who might later become schizophrenic. But should that person become psychotic, it is highly likely that the character trait of shyness will become integrated into the symptom formation. Just as the identical twin studies clearly show that the presence of a genotype is not the single cause of a schizophrenic illness, so clinical experience demonstrates that there is as yet no identifiable phenotype that is a necessary and sufficient cause of the disorder.

Conclusions

The very complexity of the etiology of the schizophrenic disorders, which has become more apparent in recent years, has significant clinical implications. There are a number of different genotypes that can be involved in the production of the syndrome. And there are a number of different evoking environments that can combine with these different genotypes to produce the phenotypic characteristics that are important in the etiopathogenesis of the illness. The pathways that lead to the production of the necessary phenotypes will differ as a function of the differences in the gene-environment interactions. The clinical disorders that are called schizophrenia are, at best, modestly homogeneous syndromes deriving from different initial conditions through different biopsychosocial pathways. This

variability in etiology and pathogenesis is a reality and not a nosologic deficiency. The inherent heterogeneity results from the fact that there is no single genotype or single environmental experience that will inevitably lead to a schizophrenic disorder.

The heterogeneity manifests itself not only in etiology and pathogenesis, but in the presenting picture as well. The presenting picture varies enormously, with some patients showing rapid onsets, while others show more insidious onsets. In some patients the presenting symptoms are more florid, while in others they are not. The various clinical courses also reflect the heterogeneity inherent in this group of disorders. It follows then that the attempt to identify the correct or even preferred treatment for the schizophrenic disorders is futile. There can be no preferred treatment when the group consists of multiple illnesses. Treatment helpful for some people may be useless or even harmful for others. The range of treatments must reflect the variability inherent within the disorder. There are many schizophrenias and there must be many treatments. A wide range of useful treatments can be expected. Obviously, this insight must be tempered by judgment, lest worthless fads be inflicted upon these patients.

The goal of the treatment of the schizophrenic disorders is to attain a level of psychological rehabilitation in which the individuals afflicted with the disorder begin to feel better about themselves. It has come to be recognized

that psychotic symptom reduction is not enough. The patient with a schizophrenic disorder must be able to participate in the life of his or her community as a full adult member. This includes the ability to love, to work, to assume responsibilities, and so forth. While psychopharmacologic agents are very helpful in psychotic symptom reduction, they do not have a direct effect on social or personality development. There is need for social, vocational, and intrapsychic rehabilitation as well as symptom reduction. Despite our best therapeutic efforts, a significant percentage of these patients will be left with real deficits. It remains a task of psychiatry to maximize the residual assets of these patients so that they can lead as normal a life as possible.

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