Diagnosis and Classification of Schizophrenia

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Abstract

Schizophrenia is a clinical syndrome of both extraordinary importance and extraordinary complexity. Its conceptual history contains many perspectives on the "essential" nature of the illness. For example, Kraepelin in 1919 emphasized primarily onset and course, although he also stressed the importance of some symptoms such as changes in affect and volition. Bleuler in 1911 took a more cross-sectional approach and attempted to identify fundamental characteristic symptoms, especially stressing fragmenting of thought processes. Schneider's (1959) approach was cross-sectional, stressing a group of "first-rank symptoms." *DSM–III* and its successors attempted to achieve a synthesis of these concepts. Nevertheless, heterogeneity in the clinical presentation of schizophrenia is certain, and heterogeneity in pathophysiology and etiology is likely. Although we can now define a particular construct of schizophrenia with reasonable agreement, the construct must be recognized as provisional and based on a need to achieve consensus about definitions rather than on an understanding of pathophysiology and etiology. The major challenge confronting the student of schizophrenia is to identify its mechanisms and causes in order to develop improved strategies for treatment and prevention. Several different approaches have been proposed to achieve this goal. Early attempts to explore and validate the construct of schizophrenia stressed descriptive and epidemiological techniques; the "validity" of a given construct of schizophrenia would be determined by evaluation of familial aggregation, course and outcome, response to treatment, and laboratory tests. This earlier approach to validation is now complemented by one that draws on techniques from neuroscience and attempts to understand schizophrenia in terms of underlying neural mechanisms. While the earlier approach conceptualized schizophrenia primarily in terms of a single disease entity, the second approach is particularly useful for the exploration of subtypes or dimensions. Research strategies for the study of schizophrenia have been developed to explore its heterogeneity. Three different competing models are discussed: (1) A single etiopathological process leading to diverse manifestations, similar to multiple sclerosis; (2) multiple disease entities leading to schizophrenia by different etiopathological processes, similar to the syndrome of mental retardation; and (3) specific symptom clusters within schizophrenia reflecting different disease processes that come together in different ways in different patients. Each of these models has strengths and weaknesses for the identification of etiology and pathophysiology.

Schizophrenia is a clinical syndrome that is extraordinarily com-

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plex. The care and study of persons afflicted with schizophrenia is challenging, fascinating, and frustrating. Some facts about diagnosis and classification are noteworthy. Schizophrenia is a leading public health problem. The lifetime prevalence rate is high (0.5%–1%, depending on the definition), morbidity is severe, and mortality is significant. Schizophrenia often begins relatively early in life, frequently leads to social and economic impairment, and typically leaves traces on its victims for the remainder of their lives. Schizophrenia results in great suffering for both patients and their families. Its cost to society is also great, exceeding the financial burden of cancer (National Foundation for Brain Research 1992).

Schizophrenia can be recognized and defined with reasonable agreement, but its etiologies and pathophysiologies are not yet known. Subdivisions within schizophrenia and boundaries between this syndrome and other disorders are also unclear.

Heterogeneity in clinical presentation is certain, and heterogeneity in pathophysiology and etiology is likely. The signs and symptoms of schizophrenia are diverse, encompassing almost every aspect of cognition and behavior: perception, inferential thinking, speech and language, motor behavior, attention, volition, emotion, and executive functions. Yet not every patient manifests signs and symptoms in all these areas, nor does the clinical presentation remain stable throughout the course of illness. The student of schizophrenia pursues a moving target. Manifestations of this disorder are varied, ranging from apathy, emotional remoteness, and mental impoverishment to florid delusions, hallucinations, and disordered thought. Both these extremes of presentation help define schizophrenia. Bleuler (1911/1950) spoke of the "group of schizophrenias," and the plural reminds us of this heterogeneity. Regarding schizophrenia in the singular leads to cohorts in research studies that are not comparable among studies and that may include subjects who do not manifest the features central to the specific study hypothesis.

Schizophrenia's history is replete with efforts to identify homogeneous subtypes. Traditional approaches include subtypes such as paranoid, catatonic, and hebephrenic and course distinctions such as good prognosis/poor prognosis, reactive/process, and acute/chronic (Vaillant 1964; Stephens et al. 1966; Tsuang and Winokur 1974; Carpenter et al. 1976; Carpenter and Stephens 1979; Kendler et al. 1984, 1985, 1988; Gruenberg et al. 1985; Fenton and McGlashan 1991). More recently, investigators have also focused on specific symptom clusters such as positive and negative or have established typologies such as Type I versus Type II, positive versus mixed versus negative, and deficit versus nondeficit (Strauss et al. 1974; Crow 1980; Andreasen 1982, 1984*a*, 1984*b*, 1989, 1990; Andreasen and Olson 1982; Carpenter and Stephens 1982; Lewine et al. 1983; Bilder et al. 1985; Carpenter et al. 1985*a*, 1985*b*, 1988; Pogue-Geile and Harrow 1985; Liddle 1987; Lenzenweger et al. 1991; Carpenter 1992). These approaches are particularly suited for clinicopathologic correlations with neural processes and for defining response criteria in treatment studies and putative phenotypes (Carpenter and Buchanan 1989).

Heterogeneity in clinical presentation may reflect heterogeneity in etiology and pathophysiology. Although efforts have been made to link a particular pathophysiology to a particular clinical presentation (e.g., structural brain abnormalities and the negative syndrome, dopaminergic hyperactivity and psychotic symptoms; Crow 1980), such straightforward relationships are heuristic and do not mirror the complexity of the brain itself. This issue of *Schizophrenia Bulletin* will review current developments in this context.

If this clinical heterogeneity does indeed reflect different pathophysiology or etiology, it would account for the difficulty in replicating research studies in this disorder. Even samples defined by relatively narrow diagnostic schema such as *DSM–III–R* (American Psychiatric Association 1987) contain substantial clinical heterogeneity. For example, a patient who spends every day in the library working on an elaborate delusionally based thesis may be typical of one cohort, but underrepresented in a cohort skewed toward patients who rarely get out of bed and seem devoid of interest and motivation. These two cohorts may lead to very different inferences concerning the relationship between schizophrenia and ventricular enlargement, familial aggregation, history of birth injuries, and other potentially informative correlates.

History of the Concept: Attempts to Define Features

Dementia Praecox: Course and Outcome. Kraepelin (1919/1971) was the first clinician/scientist to develop a comprehensive definition of schizophrenia that gained wide acceptance. Using the term "dementia praecox," he identified a

syndrome that tended to begin relatively early in life ("praecox") and produce a pervasive and persistent impairment in many different aspects of cognitive and behavioral function ("dementia"). While Kraepelin repeatedly stressed the diversity of signs and symptoms occurring in dementia praecox, he found a chronic course and a poor outcome to be the characteristic defining features. In later dialog with Bleuler he conceded that some patients with dementia praecox could recover, although both pioneers observed poor outcome in the vast majority of cases.

The Group of Schizophrenias: Fundamental Symptoms. Kraepelin's initial formulation was rapidly complemented through the work of Bleuler (1911/1950), who suggested that the term "dementia praecox" should be superseded by the term "the group of schizophrenias." Bleuler emphasized a different aspect of this large syndrome. Surveying the various patients who seemed to have dementia praecox and attempting to identify the most fundamental aspect of its presentation, he focused primarily on signs and symptoms rather than on course and outcome. He attempted to identify symptoms that were relatively specific; that is, they tended to occur in patients from the group of schizophrenias, but not other disorders. These defining symptoms tended to be present throughout the course of the disorder (though sometimes in mild form) and to be present in all patients who had the disorder. For Bleuler, the most important and fundamental symptom was a fragmentation in the formulation and expression of thought, which he interpreted in the light of the associational psychology prevailing at the time and referred to as "loosening of associations." He renamed the disorder "schizophrenia" to emphasize splitting of associations as the most fundamental feature of the disorder.

Bleuler also identified a variety of other signs and symptoms as fundamental: ambivalence, autism, avolition, affective blunting, and attentional impairment. He believed that the dissociative thought process tended to occur only in the group of schizophrenias, so he contrasted this process with various psychotic symptoms, such as delusions and hallucinations, which also occurred in other disorders, including manic-depressive illness. Within the context of the group of schizophrenias, these psychotic symptoms also tended to wax and wane and were referred to as "accessory," while the fundamental signs and symptoms tended to remain throughout the course of the disorder. In fact, accessory symptoms were seen as derivative from the fundamental disorder.

Schneiderian First-Rank Symptoms: Characteristic Psychotic Symptoms. Another influential perspective on the defining features of schizophrenia was provided by Kurt Schneider (1959, 1974). Like Bleuler, Schneider attempted to identify features that were highly specific to schizophrenia. Attempting an atheoretical approach, Schneider emphasized diagnostically discriminating symptoms that could be reliably observed and occurred often enough to be useful in differential diagnosis. Jaspers (1963, 1968) had, in fact, provided a theoretical context by assigning primacy to the difficulty others experienced in empathetic comprehension of the schizophrenia psychosis ("non-understandability") as the distinguishing feature of schizophrenia. This term refers obliquely to impairment in social interactions and to extreme oddity of inner experiences and perceptions, a field now defined as social cognition (Brothers 1989). Certain very specific psychotic symptoms were considered of first-rank importance in diagnosing schizophrenia. While Kraepelin and Bleuler emphasized dissociative and avolitional processes, Schneider identified a group of delusions and hallucinations that were implausible and bizarre: for example, experiences of thought withdrawal, thought insertion, thought broadcasting, voices conversing about the patient in third person or making a running commentary on the patient's behavior, and externally controlled thought, movement, and impulse (Schneider 1959; Fish 1962; Mellor 1970; Carpenter et al. 1973*a*, 1973*b*). Schneider believed these specific types of psychotic experiences occurred only in schizophrenia and toxic psychotic syndromes, while the more general forms of hallucinations and delusions could occur in a broader range of disorders. This concept formed the basis for the British Glossary (Great Britain General Registrar's Office Subcommittee on Classification of Mental Diseases 1968) and was the most influential approach in Great Britain and parts of Germany until *DSM–III* (American Psychiatric Association 1980).

Kraepelin's and Bleuler's ideas continue to be preeminent at the conceptual level. However, Schneider's work has been espe-

cially important at the operational level of diagnosis, partly because his conceptualizations were incorporated in the influential interview structure and diagnostic algorithm of the Present State Examination (PSE; Wing 1970; Wing et al. 1974). The PSE time frame is the past month, so the diagnostic approach is oriented toward cross-sectional patterns of signs and symptoms. The presence of Schneiderian first-rank symptoms makes the diagnosis of schizophrenia certain, according to the PSE algorithm, and defines the nuclear syndrome. The PSE was developed by John Wing of the Maudsley Hospital, a diagnostic mecca for world psychiatry for many decades, and thousands of psychiatrists throughout the world have been trained to conceptualize schizophrenia from the perspective of the PSE algorithm. The PSE had a powerful influence on the first comprehensive structured interview and diagnostic system developed in the United States, the Schedule for Affective Disorders and Schizophrenia (SADS; Endicott and Spitzer 1978) and the Research Diagnostic Criteria (RDC; Spitzer et al. 1975). Orientation toward the past month, a cross-sectional evaluation, and an emphasis on psychotic symptoms for a diagnosis of schizophrenia were all part of the SADS and the RDC. *DSM–III* was subsequently developed within this context and also incorporated many ideas from the PSE and the Schneiderian tradition, particularly the emphasis on the cross-sectional assessment and on the importance of psychotic features.

Much was accomplished in the Schneiderian era of cross-sectional differential diagnosis based on pathognomonic or highly discriminating symptoms. In particular, the gap between North American and European definitions of schizophrenia was narrowed by a new emphasis on reliable differential diagnosis in the United States (Cooper et al. 1972; Feighner et al. 1972; McGlashan 1984). However, first-rank symptoms were proven not to be pathognomonic (Carpenter et al. 1973*a*; Carpenter and Strauss 1974), and the construct of poor-prognosis nuclear schizophrenia defined by highly discriminating symptoms was not validated by a later generation of followup studies (Strauss and Carpenter 1974*a*, 1974*b*; Hawk et al. 1975). Nor were more recently and empirically derived cross-sectional approaches (Helzer et al. 1981, 1983; Cloninger et al. 1985) especially robust in defining poor-outcome schizophrenia, except where these approaches were confounded with longitudinal data such as premorbid history and duration of illness criteria (Taylor 1972; Abrams and Taylor 1973). Premorbid and early morbid features have proven most effective in predicting outcome (Strauss and Carpenter 1979), and longitudinal pattern has regained emphasis together with specific cross-sectional symptom manifestations in present-day diagnostic developments (Carpenter et al. 1978; Stephens et al. 1980, 1982; Strauss et al. 1981; Andreasen 1982, 1990; Andreasen and Olson 1982; Helzer et al. 1983; Cloninger et al. 1985; Endicott et al. 1986).

Diagnostic and Statistical Manuals: *DSM–III*, *DSM–III–R*, and *DSM–IV*. The Diagnostic and Statistical Manual of the American Psychiatric Association currently provides the most widely used system for diagnosing and classifying schizophrenia spectrum conditions in North America and in the international research community. Given the emphasis on the *DSM* approach, it is crucial that clinicians and investigators recognize it for what it is: an effort to create an arbitrary but well-informed consensus on the definition of schizophrenia so that clinicians and investigators can communicate with one another, achieve an acceptable level of reliability, and refer to approximately the same set of disorders when considering data from different sites.

***DSM–III* and *DSM–III–R*.** The rationale behind the development of these criteria has been widely discussed (Frances et al. 1989; Kendler et al. 1989; Andreasen and Flaum 1991; Flaum et al. 1991). The criteria that define schizophrenia in *DSM–III* were the product of a particular environment in the United States in the early 1970s. They were developed in the context of several important clinical and research developments. The US/UK study (Kendell et al. 1971; Cooper et al. 1972) and the *International Pilot Study of Schizophrenia* (World Health Organization 1973) had recently indicated that the American concept of schizophrenia was far broader than that prevailing in Europe, suggesting a need to narrow the concept. This narrowing involved eliminating nonpsychotic forms of schizophrenia and recognizing that other disorders, especially affective disorders, may present with psychotic features. In addition, clinical realities such as a developing awareness of the risks of tardive dyskinesia, the efficacy of lithium, and the availability of effective antidepressants led to a recognition that placing affective disorders high on the differential diagnostic

hierarchy was beneficial to patient care.

Two criteria sets that preceded *DSM–III*, the Washington University Criteria (Feighner et al. 1972) and the successor RDC, had introduced the use of a 6-month duration criterion and an emphasis on psychotic symptoms, particularly Schneiderian first-rank symptoms, as defining features (Spitzer et al. 1975). Because concerns had been raised about the reliability of Bleulerian fundamental symptoms and the fact that they had contributed importantly to excessive breadth of the construct, psychopathologic manifestations such as ambivalence, autistic withdrawal, and affective blunting were deemphasized in the criteria.

The utility of the *DSM–III* approach has been well-documented in a variety of studies that demonstrate good reliability, a relatively narrow concept, and traditional validity (Johnstone et al. 1979; Tsuang et al. 1979; Helzer et al. 1981, 1983; Kendler and Davis 1981; Coryell et al. 1982; Stephens et al. 1982; Guze et al. 1983; McGlashan 1984; McGuffin et al. 1984, 1987; Coryell and Tsuang 1985; Loyd and Tsuang 1985; Coryell and Zimmerman 1987; Harris and Jeste 1988; Harris et al. 1988; Jeste et al. 1988; Pearlson and Rabins 1988; Kendler et al. 1989; Fenton and McGlashan 1991). Relatively modest changes were made in the development of *DSM–III–R*, primarily to clarify the boundary between schizophrenia and delusional disorder and to strengthen the traditional approach to subtyping (Kendler et al. 1989).

Side effects of *DSM–III* and *DSM–III–R*. The salutary effects of these documents have not been without some adverse effects. First, although *DSM–III* and *DSM–III–R* provide only brief descriptions and use arbitrary criteria that are useful for defining schizophrenia for certain purposes, the field often treats them as comprehensive statements. *DSM–III* and *DSM–III–R* were the products of an evolution that stretched from Kraepelin through Schneider and from the PSE through the RDC. The historical traditions that flow into the concept of schizophrenia are rich and diverse, and are far larger and more complex than is suggested by the *DSM–III* or the *DSM–III–R* criteria. Somehow, the existence of such criteria gives the sense that we know what schizophrenia is when in fact we do not. Schizophrenia remains a clinical syndrome comprising an unknown number of disease entities or pathologic domains.

Second, the concept of schizophrenia has been somewhat distorted to emphasize psychotic features at the expense of other defining features. In the effort to narrow the concept, duration of illness and psychotic features have been required. This is desirable for clinical purposes, but many important aspects of the disorder are deemphasized in the *DSM–III* and *DSM–III–R* criteria. In particular, negative or deficit symptoms are given little prominence. Yet, a substantial literature exists, beginning with the work of both Kraepelin and Bleuler, that suggests that these may be the most important defining features of schizophrenia. In addition, these symptoms are often the ones that prevent patients with schizophrenia from holding a job, forming normal interpersonal relationships, or leading happy and productive lives. In the economic and social spheres, emphasis on these signs and symptoms is also needed. If the symptoms are not given prominence in the official definition, then third-party payers or compensation agencies may look askance at clinical care focused on these symptoms. In the scientific domain, failure to emphasize nonpsychotic symptoms can lead to ignoring the search for neural substrates of core phenomenologic components of schizophrenia that may be quite different from psychosis. As one emphatic illustration of this problem, contrast the effort in pharmacology to develop antipsychotic treatment with the effort to develop antideficit treatment.

Third, schizophrenia-like psychotic disorders excluded from schizophrenia have a rudimentary and generally unsatisfactory classification scheme (e.g., schizophreniform, schizoaffective, atypical psychosis, brief reactive psychoses). Definitions deviate significantly from historical concepts for these terms, are not validated with compelling data, and do not recruit adequate clinical and scientific attention to the "psychoses not elsewhere classified."

Development of *DSM–IV*. *DSM–IV* is being developed in a three-stage process: systematic literature reviews to identify issues and problems in the existing definitions and criteria; attempts to address these issues and problems through analysis of existing unpublished data sets (McArthur project); and exploration and resolutions of the issues and problems in multisite field trials (Frances et al. 1989). The criteria for schizophrenia and related conditions for *DSM–IV* are being completed by a small work group of five senior clinician/investigators, assisted by a panel of national and international advisers, as well as a group of younger investigators involved

in the McArthur analyses and field trials.

DSM–III–R criteria for schizophrenia have been evaluated to determine whether they are reliable, have a high enough base rate to be useful, and serve a useful gate-keeping function (i.e., are relatively specific). These issues were addressed through literature reviews and analysis of existing data sets and are discussed elsewhere (Andreasen and Flaum 1991).

Field trials to develop *DSM–IV* criteria have been completed recently. Six different criteria sets were compared in these field trials: the 10th International Classification of Disease (World Health Organization 1992), *DSM–III*, *DSM–III–R*, and three new options developed by work group members. Although *DSM–III* and *DSM–III–R* definitions are recognized as the narrowest in the world, the work group agreed that introducing changes that might increase the epidemiological base rate of schizophrenia would be detrimental to research and confusing to clinicians. Therefore, the new criteria will not change the prevalence of schizophrenia in a significant way. A consensus also exists among work group members, however, that the criteria for schizophrenia may be unnecessarily complex, that they lack an adequate coverage of negative/deficit symptoms, and that some components of the criteria may be unreliable or presumptive (i.e., their presence is recognized clearly only after concluding that schizophrenia is present, as with prodromal or residual symptoms). The overall goal has been to produce a new set of criteria that provide a more complete coverage of symptoms, to reemphasize the breadth of the characteristic symptoms of schizophrenia, and to simplify the criteria to enhance user friendliness.

The criteria for schizophrenia have not yet been finalized. For purposes of illustration, a provisional set of *DSM–IV* criteria appear in table 1. The goals of increased simplicity and improved

Table 1. *DSM–IV* draft criteria for schizophrenia

A. Characteristic symptoms: At least two of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated):
(1) delusions
(2) hallucinations
(3) disorganized speech (e.g., frequent derailment or incoherence)
(4) grossly disorganized or catatonic behavior
(5) negative symptoms, that is, affective flattening, alogia, or avolition
Note:—Only one A symptom is required if delusions are bizarre or hallucinations consist of a voice keeping up a running commentary on the person's behavior or thought, or two or more voices conversing with each other.

B. Social/occupational dysfunction: For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations, or self-care is markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, failure to achieve expected level of interpersonal, academic, or occupational achievement).

C. Duration: Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms that meet criterion A (i.e., active phase symptoms), and may include prodromal and/or residual periods when the A criterion is not fully met. During these periods, signs of the disturbance may be manifested by negative symptoms or two or more symptoms listed in criterion A present in an attenuated form (e.g., blunted affect, unusual perceptual experiences).

D. Boundary with schizoaffective disorder: The disturbance is not better accounted for by schizoaffective disorder (i.e., to diagnose schizophrenia, symptoms meeting criteria for an episode of mood disorder should not be present for a substantial portion of the disturbance).

E. Boundary with mood disorder with psychotic features: The disturbance is not better accounted for by a mood disorder with psychotic features (i.e., to diagnosis mood disorder with psychotic features, delusions or hallucinations have not been present for more than 2 weeks in the absence of prominent mood symptoms, i.e., immediately before the mood symptoms developed or right after they remitted).

F. Substance/secondary exclusion: The disturbance is not due to a substance-induced or secondary psychotic disorder.

coverage have been achieved, and field trials have indicated that the new criteria do not significantly change prevalence rates.

History of the Concept: Attempts to Identify Methods for Validation

When he identified dementia praecox at the turn of the century, it was evident to Emil Kraepelin that it would be validated through the study of cognitive science and neuropathology, the two leading disciplines of the era. Kraepelin was trained in the Würzburg School of Wilhelm Wundt, and he devoted his own career to clinical description and experimental cognitive psychology. The study of postmortem brain tissue, which could potentially identify the nature and site of the defining brain lesions, was his other main emphasis. Unfortunately, despite several decades of diligent effort, no characteristic lesions could be found in schizophrenia, which led to the conclusion that schizophrenia was the "graveyard of neuropathology." In the absence of clinicopathologic correlates, it was not clear how best to validate diagnostic constructs.

"Traditional" Validators. In a seminal article, Robins and Guze 1970 proposed a systematic approach for the validation of diagnostic constructs. These investigators suggested that psychiatric disorders could represent discrete syndromes on the basis of four validators: outcome, familial aggregation, response to treatment, and laboratory tests. Since the publication of that article, this strategy has been applied to the examination of schizophrenia in hundreds of studies. These studies have addressed a variety of problems, such as the boundary between schizophrenia and schizoaffective disorder, the relationship of schizotypal disorder to schizophrenia, and the relative validity of different diagnostic algorithms such as RDC versus *DSM–III* or *DSM–III–R* (Hawk et al. 1975; Bland and Orn 1979; Tsuang et al. 1979; Stephens et al. 1980, 1982; Cloninger et al. 1985; Cornblatt et al. 1985; Endicott et al. 1986; Fenton et al. 1988; Marneros et al. 1991). These validators have been evoked to support the separation of schizoaffective disorder and mood incongruent affective disorder from schizophrenia, to support traditional approaches to subtyping (particularly a distinction between paranoid and hebephrenic), and to support inclusion of late-onset cases within schizophrenia, to mention only a few examples (Johnstone et al. 1979; Tsuang et al. 1979; Helzer et al. 1981, 1983; Kendler and Davis 1981; Coryell et al. 1982; Guze et al. 1983; McGlashan 1984; McGuffin et al. 1984, 1987; Coryell and Tsuang 1985; Loyd and Tsuang 1985; Coryell and Zimmerman 1987; Harris et al. 1988; Harris and Jeste 1988; Jeste et al. 1988; Pearlson and Rabins 1988; Kendler et al. 1989; Fenton and McGlashan 1991).

While it has served its purpose well, this approach to validation also has several problems. First, the various individual validators have tended to be applied piecemeal. Investigators interested in description have used followup data, those interested in genetics have used familial aggregation, psychopharmacologists have examined response to treatment, and others have used laboratory data. Results from the various validators typically have not been integrated either conceptually or within specific cohorts. Inevitably, the application of different validators can lead to different conclusions. Schizotypal disorder may, for example, have a familial aggregation similar to schizophrenia but a different course and treatment response. What does this tell us about the nosological relationship of these two disorders? The principal accomplishment of this approach has been to refine classification to a point where an emphasis on pathophysiology and etiologic mechanisms can be considered. It is at the latter level that diseases must ultimately be defined.

Newer Validators That Focus on Mechanisms. While the approach proposed by Robins and Guze drew heavily on the dominant psychiatric disciplines of the 1970s, psychopathology and epidemiology, the field is now returning to clinicopathologic correlational validation using the new techniques of neuroscience. This approach to validation stresses the search for underlying neural mechanisms that may explain clinical presentation, course of symptoms, or response to treatment (Andreasen et al. 1992). From this perspective, the major question is not one of whether schizophrenia and schizoaffective disorder differ in terms of familial aggregation or response to treatment. Rather, the question is how can one explain the neural substrates of hallucinations, which occur in both schizophrenia and schizoaffective disorder and which show a similar response to neuroleptic agents that block dopamine receptors. This approach to validation leads inevitably to a concep-

tualization that stresses dimensions of psychopathology, either in addition to or instead of traditional diagnostic categories.

Relationship Between Clinical Presentation and Underlying Mechanisms

Diagnosis, Phenomenology, and the Search for Underlying Mechanisms. The various diagnostic systems that are currently used in psychiatry represent a provisional agreement to use the word "schizophrenia" to refer to a group of patients in a consistent way. Achieving consistency in the nomenclature has improved reliability, and, as a consequence, communication at both clinical and research levels has improved as well. Nonetheless, it is improbable that current approaches to the classification of schizophrenia have identified a group of individuals who are homogeneous in etiology, as in Huntington's disease. Nor do these approaches identify a group of individuals who have a uniform clinical presentation, as in Korsakoff's syndrome.

The *DSM–III* system is essentially atheoretical. Although it has relied on a consistent process of literature review, with an effort to extract maximal validating data from the existing research literature, it does not take a formal position on other key issues in the definition and classification of schizophrenia, such as unity versus heterogeneity, models of disorder or disease, or the nature of the underlying pathophysiology and etiology.

Ultimately, disease categories within medicine are defined on the basis of their pathophysiology and etiology. The long-term goal in developing definitions for schizophrenia, or the group of schizophrenias, must be the identification of its underlying mechanisms and causes. In order to reach this goal, research strategies must ultimately go beyond syndrome definition and develop new approaches to conceptualizing the definition and classification of schizophrenia. A syndrome-level diagnosis would ensure relevance to schizophrenia while subcategorization may be more robust for studying mechanisms.

Conceptual Models of Schizophrenia. The heterogeneity of schizophrenia remains a most vexing problem. Regardless of diagnostic approach, there is substantial between-patient variation in age and pattern of onset, clusters of symptom manifestations, extent to which course of psychosis is episodic, nature of treatment response, presentation of associated features, observed risk factors, and long-term course and outcome. There are three general explanatory constructs or models for dealing with this observed heterogeneity: (1) a single etiopathologic process leading to diverse manifestations; (2) multiple disease entities leading to schizophrenia by different etiopathologic processes, similar to the syndrome of mental retardation 50 years ago; and (3) specific symptom clusters within schizophrenia reflecting different disease processes that combine in different ways in different patients.

The first construct was used by Bleuler despite his introduction of "the group of schizophrenias." He believed that fundamental flaws (especially loosening of the associative threads) explained the disorder and that the various accessory symptoms of schizophrenia were secondary to a basic change in cognitive/emotional processes. Schneider also approached schizophrenia as a single disease. Most workers have adhered to this position, at least as reflected in study designs that select subjects according to syndromal criteria rather than criteria for a specified subgroup. Studies that examine schizophrenia versus comparison cohorts for some relevant variable (e.g., ventricular size) or that compare treatment A versus treatment B in schizophrenia are typical, although recent studies tend to perform secondary analyses correlating findings with severity and pattern of symptoms. The diagnostic and statistical manuals also encourage the use of this approach, since the system is atheoretical concerning etiology, refers to schizophrenia by a single name, and treats the subtypes as variants within a single category. This approach is robust if construct no. 1 is correct, since each subject will have the central pathologic process despite differences in symptom manifestation. However, if construct no. 2 or no. 3 holds, the unitary approach is compromised to the extent that the schizophrenia study cohort is diluted with subjects meeting schizophrenia criteria but not having the particular pathologic process in question.

The history of the second construct is traced to the proposed disease entities of paranoia, hebephrenia, and catatonia, which were defined before Kraepelin joined them in the dementia praecox syndrome. Traditional subtypes continue to constitute an approach to defining putative disease entities. Problems arise because patients often manifest symptoms of more

than one subtype (e.g., paranoid delusions are common to most forms of schizophrenia) (Carpenter et al. 1976), and patients may change subtypes in subsequent episodes (Guggenheim and Babigian 1974; Carpenter and Stephens 1979; Kendler et al. 1985). Nonetheless, paranoid and hebephrenic subtypes have extensive validation (Tsuang and Winokur 1974; Winokur 1975). Catatonia is sometimes considered to be a separate disease category because it is now seen infrequently in developed countries, and its periodic form has a strikingly different course from the other schizophrenias. Subtypes of simple, undifferentiated, residual, and other less compelling concepts have received less attention.

A series of newer dichotomous or trichotomous approaches to heterogeneity reduction have been introduced that have attempted to apply a form of the second construct. The acute/chronic, process/reactive, and good/poor prognosis schizophrenia subgroups have been robust in predicting course (albeit tautologic to varying degrees), but have not otherwise proven their heuristic value.

One recent effort to apply this approach was originally proposed by Crow, who suggested a Type I/II dichotomy (Crow 1980). The Type I/II dichotomy uses the concept of positive and negative symptoms but also includes other criteria (e.g., I.Q., treatment response, structural brain abnormalities). In its original presentation, this model did not distinguish between defining criteria and validating measures. Rather, all information was used to establish the defining criteria for Type I/II. Subsequent emphasis has been on the centrality of irreversible negative symptoms to the distinction between I and II (Crow 1985). However, if these discrete criteria are used as the sole basis for the distinction, this typology shifts to construct no. 3, in which specific domains of psychopathology are isolated for study.

An alternate adaptation is to include three groups: positive, negative, and mixed. This approach was designed to explore the possibility of discrete underlying disease processes linked to clinical presentation, using cross-sectional presenting symptoms as the defining criteria and treating other informative measures as potential validators (e.g., structural brain findings, neuropsychological performance) (Andreasen 1982; Andreasen et al. 1990). This strategy separates validating from defining criteria and recognizes ambiguity in clinical presentation by introducing a mixed category. Inherent limitations include the fact that the mixed group is often large, and patients tend to change class, especially as psychosis exacerbates and remits.

Explanatory construct no. 2, the multiple disease entities approach, puts its strongest foot forward when it avoids premature closure either concerning the nature of defining clinical features or the nature of underlying pathophysiology. At the present time, this approach is best conceptualized as one that posits heterogeneity at the etiologic level and uses data-driven exploratory approaches to identifying etiologies. Schizophrenia is conceptualized as similar to mental retardation. Genetic forms may exist (analogous to phenylketonuria), as well as environmental forms (analogous to fetal alcohol syndrome). Many forms may be multifactorial, combining both genetic (polygenetic) and a broad array of environmental factors. Although hypotheses may be explored that attempt to link particular types of presentations to involvement of specific brain regions (e.g., prominent hallucinations to temporolimbic regions), ultimately solutions or conclusions must also mirror the complexity of the brain itself. That is, although focal lesions can sometimes produce a relatively constrained clinical presentation (e.g., Broca's aphasia secondary to stroke), individuals may also be relatively intact with multiple small or large lesions (e.g., Hebb's study of memory [Hebb 1957], prefrontal leukotomy, some stages of multiple sclerosis or syphilis, and asymptomatic multiple infarctions in hypertensive encephalopathy). Contemporary models of brain structure and function postulate parallel distributed processes, suggesting the possibility that a single focal lesion can affect multiple aspects of cognition on the one hand, and on the other hand that sometimes multiple lesions may also be required to have a single effect.

Construct no. 2 can take a strong theoretical position and posit particular disease categories (e.g., Crow's [1980] typology), or it can take a more exploratory and hypothesis-generating approach. In one approach, a comprehensive data base concerning both clinical presentation and underlying biology—both broadly defined—is accumulated, and hypotheses are derived from exploratory data analysis. For example, a subtype of schizophrenia may be delineated in an analysis that reveals that patients with agenesis of the corpus callosum tend to present with treatment refractory delusions and hallucinations. This clinical presen-

tation may reflect a neurodevelopmental form of schizophrenia that is "hard wired" and involves aberrant connections in midline temporolimbic structures that form during the same neurodevelopmental stage as the corpus callosum (Andreasen 1988; Swayze et al. 1990). In this instance, recognition of a biological abnormality leads to identification of a clinical subtype. Although the findings do not identify an etiology, they suggest pathophysiologic homogeneity. This would provide the crucial ingredient for etiologic inquiry. If midline abnormalities provide a key to etiology, the design that selects patients with the abnormality is more powerful than the design that selects schizophrenia subjects without regard for midline abnormalities.

Construct no. 2 is conceptually and methodologically complex, with all the strengths and weaknesses inherent in such an approach. It lends itself best to an agnostic inductive approach that permits recognition of patterns by a "prepared mind." It permits maximal use of available data because it avoids premature closure concerning which characteristic presenting symptoms relate to which underlying neural mechanisms. Thus, it depends primarily on inductive integration from large data bases and is stronger for hypothesis generation than for hypothesis testing. On the other hand, the disease entity approach can be crisply defined for hypothesis testing when a priori criteria define subgroups such as paranoid and hebephrenic, or Type I and Type II.

The third construct is fundamentally different from the multiple disease entities approach (Carpenter and Buchanan 1989), which assumes discrete pathophysiologic processes underlying specific symptom domains. Disease process "A" leads to symptom complex "1," disease process "B" leads to symptom complex "2," and so forth. A given patient may have one or more of these disease processes, thereby contributing to heterogeneity.

Since Strauss and colleagues (1974) proposed three symptom clusters as central to schizophrenia, a number of studies have suggested the following clusters: positive psychotic symptoms involving delusions and hallucinations; disorganization and dissociative thinking involving positive thought disorder and bizarre or disorganized behavior; and negative symptoms involving poverty of speech, affective blunting, avolition, and anhedonia. The last are sometimes referred to as deficit symptoms to emphasize the primary and enduring trait pathology of schizophrenia, since patients often manifest secondary negative symptoms that confound any study of etiology, pathophysiology, or treatment if this distinction is not made in differential diagnosis. Eight different factor analytic studies collected from sites throughout the world have shown a convergence suggesting three domains of psychopathology in schizophrenia (Bilder et al. 1985; Andreasen 1986; Kulhara and Skotaka 1986; Liddle 1987; Moscarelli et al. 1987; Arndt et al. 1991; Gur et al. 1991; Lenzenweger et al. 1991). Occasional disagreement exists concerning interrelationships between signs and symptoms. For example, it is not yet clear how attentional impairment, incongruity of affect, and neurological signs relate to the primary clusters. However, the similarity of findings across studies is striking, suggesting the potential utility of these three domains in the study of etiology, pathophysiology, and treatment.

Study designs based on this approach may be particularly robust in that schizophrenia within a specified domain is compared to schizophrenia outside the domain. Each subject in each group is therefore ascertained around a single criterion for subgroup membership, and group differences are interpreted accordingly. This allows for more specific data interpretation and also reduces artifact as an explanation since comparison groups can be similar on key variables such as neuroleptic exposure and severity and duration of psychosis.

In the above discussion we considered implications for reducing heterogeneity using psychopathologic constructs. In seeking validation of classification in differential disease mechanisms, construct no. 1 is compromised if there is more than one disease process, and schizophrenia subjects vary on which is present. Construct no. 2 attempts to resolve this problem by proposing several disease entities, but the multiple criteria involved complicate interpretation of group differences in most study designs. For example, are the paranoid versus hebephrenic subtype differences caused by the difference in age at onset, the difference in personality deterioration, the difference in affect or thought disorder, or the difference in paranoia? Construct no. 3 speculates on which psychopathologic distinctions are crucial and establishes the experimental and comparative cohorts accordingly. Study questions address the domain per se rather than schizophrenia in general or a subtype defined by mul-

tiple criteria. The domains are conceptualized as nonmutually exclusive categories. Any given patient may be afflicted with one or more of these putative disease processes. As with other pathologic categories, afflicted individuals can be scaled on a severity dimension. Such scaling is most appropriate when asking state-dependent questions such as how the intensity of psychosis during positron emission tomography (PET) scan correlates to metabolism in a region of interest. For presumed trait variables (e.g., hippocampal size), psychosis rating on the day of magnetic resonance imaging is not as informative as some longitudinal assessment of severity.

This third construct also has the practical advantage of pointing out the possibility that there may be several core processes associated with specific aspects of schizophrenia rather than only one process or several processes leading to the same common pathway phenomenon. This concept has clear heuristic value in enriching our repository of research strategies and designs.

We have emphasized the difference between these three constructs since research design and data analysis are often weakened by uncritical selection of nonoptimal constructs. Choice of construct must be determined by the specific scientific question. The hypothesis that dorsolateral prefrontal cortical (DLPFC) dysfunction is associated with all schizophrenia is best tested in construct no. 1, although constructs no. 2 and no. 3 would work if comparison groups consisted of nonschizophrenia patients. However, if the DLPFC dysfunction is specifically relevant to negative or deficit symptom psychopathology, inclusion of nonnegative symptom patients undermines hypothesis testing. That such distinctions may be critical was recently demonstrated in a resting glucose metabolism PET study (Tamminga et al. 1992) in which frontal and parietal cortical metabolism was similar between schizophrenia subjects and controls, but robustly different in a small subset of deficit patients compared to nondeficit schizophrenia or normal control subjects. The DLPFC hypothesis was rejected using construct no. 1 and supporting using construct no. 3. The within-schizophrenia comparisons that can be accomplished with constructs no. 2 and no. 3, where each schizophrenia subgroup will have been exposed to common sources of artifact, lessen the likelihood that this result was due to artifact.

While constructs no. 1, no. 2, and no. 3 differ significantly at the level of concept and study design, they all make use of clinicopathologic correlation. In this regard, the data sets needed for hypothesis-generating analyses described with construct no. 2 are also the empirical base for no. 1 and no. 3. The example of a subset of patients with agenesis of the corpus callosum associated with treatment-resistant delusions and hallucinations discussed in construct no. 2 is illustrative. In construct no. 2 a putative disease entity defined by agenesis, treatment-refractory hallucinations and delusions, and other defining features would be contrasted with another schizophrenia subtype defined by, for example, small hippocampi and treatment-responsive thought disorder. Group differences may be due to defining features of either group. In construct no. 3, the process hypothesized to be central (e.g., agensis of the corpus callosum) would be used to divide schizophrenia patients into those with and those without agenesis. Differences between the two groups would be interpreted as related to the etiopathologic process associated with agenesis. Construct no. 1 is weakened to the extent that agenesis of the corpus callosum defines a unique subgroup.

Other Approaches. Psychopathology-based subgrouping of schizophrenia is not the only approach to heterogeneity reduction. Physiologic markers (Holzman 1985; Freedman et al. 1987; Geyer and Braff 1987) are also promising, although they are early in development. Information on other candidate markers is found elsewhere in this issue.

Risk factors may be another approach to identifying subtypes of schizophrenia. They provide an important opportunity to subdivide schizophrenia into etiologically relevant groups, but they are difficult to apply. Genetic loading, birth and pregnancy complications, and winter birth are associated with increased risk for schizophrenia, and study designs comparing subgroups defined by these risk factors are often reported. But no ascertainment procedure with adequate sensitivity and specificity is available. For example, negative family history does not confirm a case as nongenetic, and winter birth data simply indicate an increase of by about 8 percent in the chance of having an unknown risk factor. Date of birth can be determined accurately, but a patient born in January is only slightly more likely to have the winter-born risk factor than a June-born patient.

In principle, it is desirable to reduce heterogeneity at each func-

tional level of the individual. Theoretically, this can be done from the level of molecular genetics through neural systems to subjective experience and cultural setting. The domains of psychopathology or disease entity approaches can be applied together with any promising markers. If a marker is associated with a symptom complex rather than global schizophrenia, this clinicopathologic correlation approach will be the most robust in construct no. 3 if the symptom complex is known and in construct no. 2 if the subgroup is defined by multiple factors.

Summary

Schizophrenia is a clinical syndrome that involves disruptive psychotic experience as well as other core elements of psychopathology. Today's construct is quite similar to that developed by Kraepelin and Bleuler, but international agreement on definitions and criteria is more recent. Much is known about the manifestations and course of schizophrenia and the application of currently available treatment. Little is now specified regarding the etiology and pathophysiology of schizophrenia, and the number of disease processes within schizophrenia is yet to be determined. Therefore, present-day nosology is necessarily arbitrary and preliminary. It is, nonetheless, robustly valid for many clinical, research, and demographic purposes. The within-schizophrenia heterogeneity remains a vexing and limiting problem, but psychopathologic delineations are providing a more heuristic approach to its reduction. Validation at the level of neural mechanism is now plausible.

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