The Diagnosis of Schizophrenia

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Abstract

Diagnosis refers to developing the best methods for classifying disorders and for identifying their characteristic symptoms. Most importantly, however, diagnosis refers to the identification of particular disorders that differ in their underlying mechanisms and causes, and therefore defines them as discrete diseases. Most current work on schizophrenia attempts to identify the best ways to classify it and the best ways to identify and define its characteristic symptoms to improve the ongoing search for mechanisms and causes. One idea that is currently widely discussed is the distinction between positive or florid symptoms and negative or defect symptoms. Much more research needs to be done on this model, however, and we need many more studies that attempt to integrate biological research with the careful work that has been done to date on clinical description. The astute modern investigator must be able to move freely between the biotype and the phenomenotype if he or she is to understand fully the clinical picture and ultimately the cause of schizophrenia.

In 1987, a time when both American diagnostic nomenclature as embodied in *DSM-III* and international nomenclature as embodied in ICD-10 are in the process of changing, it seems appropriate to begin this essay on the diagnosis of schizophrenia by discussing both the concept of diagnosis and the concept of schizophrenia. If one is to think about the diagnosis of schizophrenia very deeply, one cannot discuss one concept without discussing the other.

The Concept of Diagnosis

The study of diagnosis has three aspects: nosology (or the classification of disorders), phenomenology (or the identification of defining features of disorders), and pathophysiology and etiology (or the identification of the mechanisms and causes that separate one disorder from another and define each as a discrete disease). These three aspects of diagnosis are intimately intertwined with one another, particularly in the case of disorders not yet fully understood, as is the case with schizophrenia. The discovery of a discrete pathophysiology or etiology for a disorder usually crystallizes our understanding and is frequently tied to the evolution of technology. In a presurgical era, for example, doctors could only identify abdominal distention and pain, with very inchoate attempts to link these phenomena to various organ systems. Postsurgically, we have a large differential diagnosis for acute abdomen, ranging from cholelithiasis through appendicitis to ruptured ovarian cysts. What could once be described only phenomenologically can now be described nosologically by organ systems and pathophysiologically and etiologically by mechanisms and causes.

For schizophrenia, as well as for many other major mental disorders, we are now reaching some consensus that the organ system involved is the brain, tempered with the recognition that cerebral function is mediated by a broad range of social and environmental factors.

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Because the technology of brain research is evolving so rapidly in the 1980's, we anticipate that our understanding of the nosology and phenomenology of schizophrenia must be flexible, utilitarian, and adaptable. Our concept of the best way to identify defining features of the illness or the best method for classifying and subtyping it will change and vary as new techniques develop for studying pathophysiology and etiology. Likewise, as we learn more about mechanisms and causes, our perceptions of phenomenology and nosology will change. Interaction between these three aspects of diagnosis during the 1980's is likely to be a true "inter-action"—a working back and forth as new ideas and findings emerge.

The Concept of Schizophrenia

The concept of schizophrenia is almost universally accepted, but also ill-defined. Almost anyone who works carefully with patients suffering from this illness will concur that it is a "real disease," but will be hard pressed to define it in a way likely to lead to universal consensus. There is debate about the best methods for defining it; some clinicians stress the importance of longitudinal course and outcome, while others emphasize cross-sectional phenomenology. Controversy swirls about the boundaries of the concept. Should it include acute as well as chronic cases (acute or good premorbid schizophrenia), cases with affective features in addition to psychotic features (schizoaffective disorders), or cases that have prominent negative symptoms but lack psychotic features (simple schizophrenia, schizotypal personality, latent schizophrenia)? Clinicians also disagree about the core or characteristic symptoms of this illness; some emphasize traditional Bleulerian thought disorder, while others stress the importance of psychotic features such as delusions or hallucinations.

These controversies are neither academic nor trivial. The boundaries of the concept of schizophrenia have expanded and contracted over time, and the changing boundaries make previous research more difficult to interpret. The first definition of schizophrenia, put forth by Kraepelin (1919), was relatively narrow and defined this illness as one characterized by an early age of onset and a deteriorating course with significant cognitive impairment ("dementia praecox"). Kraepelin's definition stressed course and outcome as the basic defining features. Bleuler (1950) broadened the concept enormously by introducing the term "schizophrenia" and emphasizing cross-sectional phenomenology as more important than course and outcome. Kraepelin was never sure whether dementia praecox represented a single illness or many, but Bleuler was quite explicit about the heterogeneity of schizophrenia, referring to it as the "group of schizophrenias." For Bleuler this group of illnesses encompassed both severe and mild forms, ranging from individuals who were highly impaired to those with mild nonpsychotic forms ("simple schizophrenia"). He saw associative loosening as the core defining feature, followed closely by affective blunting, autism, ambivalence, avolition, and disordered attention. Research conducted during the 1950's and 1960's relied heavily on relatively broad Bleulerian concepts.

The introduction of Schneiderian concepts to Great Britain in the late 1960's tightened up and narrowed British ideas, leading to a divergence between British and American thinking (Mellor 1970; Cooper et al. 1972; Wing, Cooper, and Sartorius 1974). By the 1980's, the pendulum in America had swung back to a narrower definition, largely through the influence of the St. Louis criteria, and American concepts are now narrower than British concepts (Feighner et al. 1972; American Psychiatric Association 1980). Adding to the confusion, until the introduction of diagnostic criteria or computerized diagnostic systems in the late 1960's and early 1970's, investigators usually did not specify how they identified a particular cohort of patients as "schizophrenic."

Many of the debates in lecture halls and journals about whether schizophrenics respond to treatment, have identifiable biological correlates, or have a poor prognosis are at least partly explicable on the basis of variability of the concept across time and space. American psychiatrists in 1960 were identifying very different patients as schizophrenic from those so identified in 1985, and a cross-national study conducted in 1985 would almost certainly indicate that Americans are using narrower concepts than are the British. Changing concepts make past research more difficult to interpret and require that we exercise caution in grouping studies together and generalizing from them (sometimes referred to as the "box score" approach). More importantly, these problems also have implications for our study of schizophrenia in the present and the future. We still do not agree on the best way to define it, but we have made great progress in at least recognizing that we *must* define it. Depending on the questions to be answered, strategies for definition will vary, a point that subsequent sections of this article will amplify further.

Phenomenotype vs. Biotype

Traditionally, investigators have resolved issues concerning the identification and definition of disorders by examining various aspects of the clinical picture. It may be useful to refer to these by a single general term, the "phenomenotype." Various aspects of the phenomenotype are summarized in table 1. Broadly defined, the phenomenotype includes both longitudinal and cross-sectional features. Ignoring longitudinal aspects probably wastes information, although one must recognize that in cases with acute onset or brief duration, very little longitudinal information will be available. Is the mode of onset acute or insidious? Does the illness begin relatively early in life, or is the age of onset widely distributed throughout life? What kinds of symptoms tend to occur together? Do all patients have all symptoms, or only some? How many symptoms should be present? Is there a single characteristic symptom, or is the disorder characterized by a clustering of symptoms? Are cases with mild symptoms the same as cases with more severe symptoms? Is the course of the illness episodic, chronic, or deteriorating? Is there any characteristic long-term outcome, such as recovery, mild social impairment, or inevitable severe handicap and even death?

Using a clustering of these variables originally led to the identification of dementia praecox and its differentiation from manic-depressive illness by Kraepelin (1919). Kraepelin's phenomenotype stressed the importance of course and outcome in particular, and dementia praecox was by definition a disorder characterized by deterioration over time.

One of the major purposes of diagnosis is to achieve prediction. Given a diagnosis of a particular disorder in a particular patient, what can one say about the future? Will the disease be acute and remitting or chronic and progressive? Will it respond to treatment? Because Kraepelin's use of the phenomenotype included outcome in its definition of schizophrenia, it had innate predictive validity. Many continue to object, however, that approaches to the phenomenotype that include both cross-sectional and longitudinal features within a single definition also have inherent circularity. If one defines poor outcome as a characteristic feature of schizophrenia, then it becomes difficult or impossible to include cases with good outcome within the boundaries of the disorder. It is difficult indeed to meet the needs of a diagnostic system for predictive validity and yet avoid circularity and premature closure about basic concepts and boundaries.

Some approaches to the phenomenotype would reduce it simply to types of symptoms and perhaps severity of symptoms, ignoring longitudinal features except as dependent variables. This is the approach of Bleuler and many who have followed him. While emphasis on cross-sectional symptoms has a certain economy and simplicity, it also has certain limitations. The history of medicine is replete with disorders that have similar cross-sectional symptoms and yet are quite different diseases—disorders characterized by coughing, or by frequency of urination, or by fever and confusion. Usually the science of diagnosis has advanced as expert clinicians and scientists have recognized that particular symptoms tend to have a variable outcome and are therefore ultimately discrete illnesses.

At preliminary stages of study, it may be quite useful scientifically and statistically to identify a group of patients with a common set of symptoms, to describe them carefully, and then to determine long-term outcome. The next logical step, however, is to separate those with different outcomes and to determine whether any particular symptoms are more useful than others in predicting outcome. The various studies of good versus poor prognosis schizophrenia conducted during the past several decades exemplify this approach well. Consistently, they have suggested that acute onset, good premorbid functioning, presence of affective features, and presence of a family history of affective disorder are suggestive of a good outcome among the large group of patients characterized by psychotic symptoms. On the other hand, insidious onset, poor premorbid functioning, affective blunting, and a family history of schizophrenia are associated with poor outcome (Vaillant 1962; Stephens 1978). Indeed, some have argued that the results of this research are so conclusive that acute schizophrenia or schizoaffective disorder is a distinct illness or perhaps not even a type of schizophrenia at all, but rather a subtype of affective disorder. (See discussion of schizoaffective disorder below.)

As the above discussion indicates, although approaches to identifying diagnostic categories have generally begun with the phenomenotype, the results of this approach have often been controversial, largely because investigators cannot agree on how much of the phenomenotype should be included in definitions. The debate about *DSM-III* (American Psychiatric Association 1980) is a typical example. Although the criteria include longitudinal features (6 months of illness), many have ob-

jected that this approach is too narrow or too circular. Since the ultimate goal of a diagnostic system is to identify pathophysiology and etiology, an alternate approach is to begin with important and significant biological features of an illness and then to attempt to identify the symptoms associated with a particular biological feature (or group of biological features), hoping in this manner to identify a discrete disorder.

As indicated in table 1, the biotype can be defined through the use of neuroanatomy and neuropathology, brain imaging, genetics, neurophysiology, neuroendocrinology, and neuropharmacology. A simple (and indeed oversimplified) approach to using the biotype as a way to identify a discrete disorder is to subtype a group of patients with shared phenomenology (e.g., psychotic symptoms such as delusions and hallucinations and the absence of prominent affective symptoms) into two dichotomous groups based on the presence or absence of some biological feature. For example, one could use the presence of a family history of schizophrenia as a dividing factor, or presence versus absence of abnormalities on computed tomography (CT scan), or diminution of psychotic symptoms through the use of drugs that selectively block dopamine$_2$ receptors, or differences in patterns of brain electrical activity, or differences in patterns of prolactin response to growth hormone challenge, etc. The strength of this approach is that it places our most important goal, the identification of pathophysiology and etiology, at the forefront of investigation by stressing the use of various biological probes. The weakness of this approach is that we are not as yet certain which biological probes are really relevant or specific, and whether various biological factors operate in isolation or whether they interact with one another in a multifactorial way. If the latter is the case, as seems likely, then multiple biological factors must be incorporated into a single study.

Table 1. The phenomenotype and the biotype

Phenomenotype	Biotype
Types of symptoms	Neuroanatomy, both gross and histologic (computed tomography, magnetic resonance imaging, neuropathology)
Severity of symptoms	
Cognitive function	
Mode of onset	Dynamic brain function (topographic mapping of brain electrical activity, positron emission tomography)
Age of onset	
Duration of symptoms	Genetic factors
Course of illness	Neurophysiological variables (electroencephalogram, eye tracking)
Outcome	
Response to treatment	Biochemical measures
	Neuroendocrine measures
	Biochemical response to pharmacologic manipulation

Recent Developments and Research

Within this context of increasing awareness about the complexity of diagnostic issues, it seems clear that the major problems facing investigators have been (and are) to define the boundaries of the concept of schizophrenia, to determine the extent to which it represents a heterogeneous set of disorders, to identify the most characteristic symptoms, and to develop complex models that integrate the phenomenotype and the biotype.

The Boundaries of the Concept. As has been described above, schizophrenia was originally narrowly defined within the Kraepelinian system. The concept broadened for a time, particularly in the United States, and more recently was narrowed again through the influence of *DSM-III*. Various international studies such as the International Pilot Study of Schizophrenia or the U.S./U.K. Study have indicated that the American concept was too broad in comparison with the rest of the world (Cooper et al. 1972; Wing, Cooper, and Sartorius 1974). Further, clinicians and researchers concurred that the concept had often become so ill-defined that it was almost meaningless, impairing both the selection of treatment and the conduct of research. More recently, however, some have begun to wonder if the American pendulum has swung too far. Thus, in recent years, investigators have begun to assess the implications, both pro and con, of the narrowing of the concept of schizophrenia.

Schizoaffective disorder. Clinicians have recognized for many years that some patients with schizophrenia also have affective symptoms such as depression, es-

pecially relatively early in the illness (Kasanin 1933). Early work indicated, in fact, that the presence of affective symptoms was a good prognostic sign, particularly when tied to other important indicators such as acute onset, good premorbid adjustment, and family history of affective disorder. When lithium became widely available as a treatment for mania, it was only natural that conscientious and caring clinicians would also attempt to use it as a treatment for schizoaffective disorder. When many patients with schizoaffective disorder were found to respond well to lithium, the whole concept of schizoaffective disorder was reevaluated through a broad range of data-based research.

This research has now been summarized in a large number of review articles (Welner, Croughan, and Robins 1974; Pope and Lipinski 1978; Clayton 1984; Coryell 1986). Many of these are flawed, however, by the fact that they pool many different definitions of schizoaffective disorder—some of them emphasizing acuteness of onset; others, response to treatment; and others, mixed phenomenology. Brockington, Wainwright, and Kendell (1979) have summarized the many different criteria that have been applied to define schizoaffective disorder.

In general, most of the recent studies and summaries have concluded either that schizoaffective disorder is a variant of affective disorder, or that it represents some type of syndrome that is intermediate between affective disorder and schizophrenia. The emphasis varies depending on the external validator used. Those explored most commonly include family history, response to treatment, and outcome. In a recent review, Coryell (1986) concludes that most of the 17 studies that look at outcome find that schizoaffective patients do less well than patients with pure affective disorder, but better than patients with schizophrenia. Studies of treatment response appear to indicate that patients with schizoaffective disorder are less likely to respond to lithium alone, but do respond relatively well to combinations of lithium and antipsychotics, and show an overall better response than patients with pure schizophrenia (Pope and Lipinski 1978). The family history studies indicate that patients with schizoaffective disorder have higher rates of schizophrenia in their families than do patients with pure schizophrenia. Family studies do seem to indicate, however, that schizoaffective patients with manic features (schizo-bipolars or schizo-manics) may be much more closely allied to the affective disorders than are schizoaffectives who manifest only depression (Clayton 1984).

Most of these findings can be explained by the assumption that the current definitions of schizoaffective disorder probably identify a mixture of atypical patients with schizophrenia and with affective disorder. As research progresses further, we may be more successful in identifying the best criteria for classifying these atypical patients. At present, the term schizoaffective disorder, as it is usually used, probably refers to a "mixed bag."

In this context, the boundary between schizophrenia and affective disorders must remain flexible, depending on whether the goal is research or patient care. A narrow definition of schizophrenia, as manifested by *DSM-III* and *DSM-IIIR*, is well suited to patient care, since it minimizes the chance that a patient who might respond well to lithium or electroconvulsive therapy will be denied such treatment because of being prematurely diagnosed as having an illness (schizophrenia) that does not usually call for such treatment. For research purposes, a narrow definition allows for minimum contamination of schizophrenic cohorts by patients with affective disorder, although it may produce contamination of samples of patients with affective disorder by including some patients who in fact have schizophrenia. While this might seem a desirable situation for investigators interested in studying schizophrenia, since it identifies a relatively pure sample of schizophrenics, it may be inappropriate for some types of studies. In particular, genetic and family studies might benefit from a broader concept of schizophrenia. Studies of diagnostic concordance among twins, or individual patients over time, could be subject to falsely elevated estimates of discordance if further research supports that the full range of pathology in schizophrenia is in fact broader.

Schizotypal personality. The concept of schizoaffective disorder requires that we consider the bounds of schizophrenia with respect to affective symptoms, while the concept of schizotypal personality asks that we consider the bounds of schizophrenia with respect to severity.

In the preneuroleptic era, mild nonpsychotic forms of schizophrenia were gradually added to the concept under a variety of different names: latent, pseudoneurotic, and simple schizophrenia. It was frequently observed that these patients did not respond particularly well to psychotherapy. Neuroleptics, when they became available, did not seem particularly efficacious either. As the risk of tardive dyskinesia became more apparent, pressure mounted to narrow the concept of schizophrenia to prevent the excessive or inappropriate use of neuroleptics.

The impetus to use severity criteria to narrow the concept of schizophrenia thus also arose for a psychopharmacological reason—in this instance, to prevent a particular somatic treatment rather than to suggest a specific one.

While this narrowing has been important because of its implications for treatment, more recent genetic and family data suggest that the boundaries may have been set too narrow. From an etiological or pathophysiological perspective, schizophrenia may exist as a spectrum of disorders including milder personality disorders (Kety et al. 1971). Differences in genetic loading or the exposure to other etiological factors may simply lead to a milder schizophrenic syndrome in some individuals.

There are a number of studies that examine schizoid or schizotypal traits in twins, adopted offspring, or first-degree relatives of schizophrenic probands. In a reanalysis of the Danish adoption study of schizophrenia, Kendler and Gruenberg (1984) found that biological relatives of adoptees with schizophrenia were at higher risk for schizotypal personality than were relatives of adoptees without schizophrenic psychoses (14.3 percent vs. 0 percent). An increased incidence of schizotypal personality in the first-degree relatives of schizophrenics has also been reported (Kendler et al. 1984).

Schizotypal features are also linked phenomenologically to schizophrenia. In fact, five of the eight criteria for schizotypal personality in *DSM-III* are nearly identical to the criteria for prodromal schizophrenia. The possible etiological link between schizotypal traits and schizophrenia certainly merits further research using a variety of paradigms, including genetics, neurochemistry, and brain imaging. At present, it may be necessary at least to consider the possibility that simple schizophrenia or schizotypal personality *do* belong within a broadly defined schizophrenia spectrum. Indeed, the emerging importance of negative or defect symptoms (which are closely allied phenomenologically with schizotypal features) may suggest that the schizotype is closer to "core" schizophrenia than is the "predominantly affective" schizoaffective.

Characteristic Symptoms. Schizophrenia is complex in its clinical presentation. We use the word "schizophrenia" to refer to patients ranging from the severely socially withdrawn and apathetic person with occasional auditory hallucinations to individuals who are relatively socially and cognitively intact but who suffer from persistent delusional thinking. In the past investigators have sought for the "core" or pathognomonic symptom that would serve as the single defining feature of the illness, since such a symptom would reduce the perplexing complexity of this illness to satisfying simplicity. Thought disorder (Bleuler 1950) and Schneiderian symptoms (Mellor 1970) have both been proposed to fill this role. Recently, however, we have grown to recognize that we must learn to live with a complex approach, since this provides the best description of clinical realities.

Most investigators are now finally confirming the fact that, at our present level of understanding, schizophrenia is characterized by a multiplicity of symptoms that reflect a broad range of cognitive and emotional dysfunctions. Patients with schizophrenia suffer from abnormalities in perception, attention, communication, volition, affective modulation, cognition, and motor function. We refer to these abnormalities as hallucinations, delusions, thought disorder, avolition, affective blunting, catatonia, etc. While these signs and symptoms occur in the broad range of patients suffering from schizophrenia and characterize it as a disease, no single patient manifests all of these symptoms at a given time or even during the entire course of his illness. In fact, a given patient may have only one or two, such as delusions with mild social impairment. The clinical picture of schizophrenia is very diverse when it is observed over a broad range of patients. This illness has many defining features, none of which is pathognomonic. Stated conceptually, the definition of schizophrenia is polythetic rather than monothetic: it is defined by a characteristic clustering of a variety of symptoms, no single one of which is specific to the disorder. (The affective disorders, by contrast, are monothetic, since they have the single defining feature of a disorder in mood.)

In an era that is confronting the fact that schizophrenia lacks "pathognomonic symptoms," investigators have turned instead to signs and symptoms that are descriptively useful (Carpenter and Strauss 1973). In an effort to bring some coherence to the broad range of schizophrenic symptoms, during recent years investigators have begun to divide them into two major groups: positive or florid symptoms and negative or defect symptoms (Strauss, Carpenter, and Bartko 1974; Andreasen 1979*a*, 1979*b*, 1979*c*, 1982*a*, 1982*b*, 1983, 1984, 1985*a*, 1985*b*; Crow 1980). As a group, positive symptoms tend to represent a distortion or exaggeration of normal functions. They include a variety of

delusions and hallucinations and abnormalities in language and behavior. Negative symptoms, on the other hand, represent a diminution or loss of function and include such features as poverty of speech and content of speech (alogia), affective blunting, asociality-anhedonia, and avolition. Some evidence suggests that positive symptoms may occur more frequently during the early stages of schizophrenia, whereas negative symptoms are prominent during later phases. Further, once they occur, negative symptoms tend to persist (Pfohl and Winokur 1982, 1983). There is also some evidence suggesting that negative symptoms respond less well to treatment with neuroleptics than do positive symptoms. This latter point is a matter of some controversy, however, and is likely to be a topic of research during the next few years.

Table 2 summarizes many of the signs and symptoms currently considered to be manifestations of schizophrenia as defined in two widely used rating scales for positive and negative symptoms. The reliability of these symptoms in different cultural settings has been documented in several recent studies (Ohta, Okazaki, and Anzai 1984; Moscarelli, Maffel, and Cazzullo 1985; Humbert et al. 1986). Table 2 shows the base rate of each of these symptoms, as observed in a sample of 111 consecutive admissions to the University of Iowa Psychiatric Hospital.

Heterogeneity of Schizophrenia. Given the breadth and diversity of the symptoms that characterize schizophrenia, it is only natural to wonder whether this disorder is truly homogeneous or whether it represents a related group of different disorders. Identifying possible subtypes is of great importance in the search for the underlying pathophysiology and etiology. If a diverse group of disorders is pooled together in studies of biological correlates, important findings may be lost because fundamental differences have been averaged out. Only a broad spread of variance is left behind as a clue to suggest the possible heterogeneity of schizophrenia. This variance is perhaps one of the most consistent observations in research on schizophrenia.

Methods for subtyping schizophrenia have been in existence since the disorder was originally identified. Kraepelin and Bleuler identified subtypes such as paranoid, hebephrenic, catatonic, and mixed or undifferentiated; Bleuler also added the concept of simple, or nonpsychotic, schizophrenia. A few studies have suggested some differences between these subtypes and other external validators (e.g., age of onset, family history, long-term outcome, and a variety of biological parameters), but most studies are plagued by problems in replication and lack of specificity (Tsuang and Winokur 1974; Potkin et al. 1978; Tsuang, Woolson, and Fleming 1979; Wyatt, Potkin, and Kleinman 1981).

Dissatisfaction with traditional subtypes defined on the basis of phenomenology has led some investigators to explore subtyping based on biological measures instead. For example, Weinberger et al. (1980) divided a sample of schizophrenics into those with prominent ventricular enlargement and those without evidence of structural brain abnormality. The responsiveness to treatment of these two groups was then examined, revealing that patients with prominent ventricular enlargement were less likely to respond to treatment with neuroleptics. Weinberger et al. did not observe any difference in clinical phenomenology among the groups with large versus small ventricles, although an association between ventricular enlargement and negative symptoms has been observed in other studies. Ventricular enlargement or cortical atrophy also appears to be associated with other phenomenological variables such as poor premorbid functioning, poor social adjustment, and impaired cognition (Johnstone et al. 1976; Rieder et al. 1979; Andreasen 1982*a*, 1982*b*; Owens et al. 1985).

Another new approach has involved replacing Kraepelinian subtypes with a subtyping scheme that uses positive and negative symptoms to identify separate diagnostic classes. This approach has clear heuristic and theoretical appeal, since it unites the phenomenotype and biotype into a single comprehensive hypothesis. According to this model, schizophrenia can be divided into extreme subtypes, possibly with a mixed or traditional subtype in between (Crow 1980; Andreasen 1982*a*, 1982*b*). One subtype is characterized by prominent negative symptoms, in association with poor premorbid functioning, cognitive impairment, evidence of structural brain abnormality (e.g., enlarged ventricles on CT scan), poor response to treatment, and an underlying pathophysiology and etiology suggestive of neuronal loss. The second subtype is characterized by prominent positive symptoms in association with good premorbid adjustment, normal cognitive functioning, good response to treatment, and an underlying pathophysiology and etiology due to increased dopamine transmission, perhaps in the limbic system. This model has received some validation in several studies, but others have failed to support it. It has considerable intrinsic appeal, since it permits the test-

Table 2. Base rate of negative and positive symptoms using the SANS and SAPS for 111 consecutively admitted schizophrenic patients in Iowa

	Absent		Questionable		Mild		Moderate		Severe		Extreme	
Symptoms	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Negative symptoms												
Affective flattening												
Unchanging facial expression	5	4	9	8	28	25	32	29	30	27	7	6
Decreased spontaneous movements	38	34	12	11	25	23	21	14	11	10	4	4
Paucity of expressive gestures	21	19	25	23	20	18	18	16	19	17	8	7
Poor eye contact	32	29	17	15	26	23	18	16	10	9	8	7
Affective nonresponsivity	40	36	20	18	17	15	14	13	13	12	7	6
Inappropriate affect	41	37	14	13	13	12	19	17	21	19	3	3
Lack of vocal inflections	30	27	26	23	19	17	26	23	6	5	4	4
Global rating	3	3	10	9	25	23	36	32	26	23	11	10
Alogia												
Poverty of speech	52	47	15	14	7	6	15	14	11	10	11	10
Poverty of content of speech	55	49	12	11	18	16	19	17	5	4	2	2
Blocking	85	77	10	9	11	10	2	2	2	2	1	1
Increased response latency	77	69	10	9	15	14	3	3	3	3	3	3
Global rating	33	30	20	18	25	23	13	12	13	12	7	6
Avolition-apathy												
Grooming and hygiene	15	13	14	13	15	14	21	19	30	27	16	14
Impersistence at work or school	6	5	7	6	7	6	8	7	26	23	57	51
Physical anergia	20	18	16	14	10	9	30	27	27	24	8	7
Global rating	5	5	6	5	6	5	21	19	51	46	22	20
Anhedonia-asociality												
Recreational interests, activities	5	5	18	16	11	10	31	28	26	23	20	18
Sexual interest, activity	31	28	41	37	5	4	8	7	18	16	8	7
Intimacy, closeness	16	14	29	26	11	10	16	14	26	23	13	12
Relationships with friends, peers	4	4	10	9	10	9	18	16	35	32	34	31
Global rating	2	2	12	11	11	10	23	21	41	37	22	20
Attention												
Social inattentiveness	24	22	24	22	9	8	19	17	22	20	13	12
Inattentiveness during testing	40	36	13	12	19	17	18	16	13	12	8	7
Global rating	18	16	20	18	18	16	31	28	13	12	11	10

Positive symptoms												
Hallucinations												
Auditory	28	25	5	4	8	7	13	12	27	24	30	27
Voices commenting	47	42	27	24	12	11	12	11	10	9	3	3
Voices conversing	48	43	29	26	11	10	9	17	8	7	6	5
Somatic-tactile	88	80	6	5	6	5	6	5	3	3	3	3
Olfactory	104	94	1	1	3	3	2	2	1	1	0	0
Visual	57	51	20	18	10	9	8	7	12	11	4	4
Global rating	26	23	8	7	11	10	11	10	28	25	27	24
Delusions												
Persecutory	21	19	15	14	6	5	16	14	27	24	26	23
Jealousy	107	96	1	1	1	1	1	1	0	0	1	1
Guilt, sin	82	74	8	7	7	6	11	10	2	2	0	0
Grandiose	68	61	8	7	5	4	12	11	9	8	8	7
Religious	77	69	7	6	7	6	7	6	8	7	5	4
Somatic	80	72	5	4	7	6	6	5	8	7	5	4
Delusions of reference	57	51	15	14	8	7	7	6	14	13	9	8
Delusions of being controlled	60	54	10	9	13	12	14	13	10	9	4	3
Delusions of mind reading	58	52	16	14	8	7	13	12	10	9	5	5
Thought broadcasting	85	77	10	9	5	4	8	7	1	1	1	1
Thought insertion	7	69	13	12	6	5	11	10	4	4	0	0
Thought withdrawal	81	73	11	10	3	3	9	8	7	6	0	0
Global rating	9	8	8	7	5	4	17	15	47	42	25	23
Bizarre behavior												
Clothing, appearance	89	80	9	8	5	4	4	4	3	3	1	1
Social, sexual behavior	74	67	10	9	12	11	7	6	6	5	2	2
Aggressive-agitated behavior	81	73	9	8	11	10	4	4	4	4	2	2
Repetitive-stereotyped behavior	91	82	8	7	6	5	2	2	1	1	3	3
Global rating	67	60	15	14	11	10	7	6	8	7	3	3
Positive formal thought disorder												
Derailment	61	55	13	12	19	17	14	13	4	4	0	0
Tangentiality	56	50	19	17	16	14	16	14	4	4	0	0
Incoherence	85	77	15	14	6	5	4	4	0	0	1	1
Illogicality	85	77	14	13	8	7	3	3	1	1	0	0
Circumstantiality	72	65	23	21	11	10	5	4	0	0	0	0
Pressure of speech	84	76	12	11	11	10	4	4	0	0	0	0
Distractible speech	86	77	11	10	9	8	4	4	1	1	0	0
Clanging	108	97	2	2	1	1	0	0	0	0	0	0
Global rating	45	41	19	17	25	23	14	13	7	6	1	1

SANS = Scale for the Assessment of Negative Symptoms.
SAPS = Scale for the Assessment of Positive Symptoms.

ing of models about the interrelationship between clinical picture and underlying biology and since it gives an important position to the negative or deficit syndrome which has been too often ignored in the past. It also has some conceptual problems that must be addressed, such as the mixture of positive and negative symptoms in some patients, variations in symptom pattern over time in some patients, and variations in cerebral specialization and localization (Andreasen 1985*b*).

Phenomenology of Schizophrenia and Cerebral Localization. On a theoretical level, one can also develop models of how the symptoms of schizophrenia could be related to relatively specific abnormalities in brain function (Andreasen 1986). Negative symptoms in particular correspond quite closely to a diminution of functions normally thought to reside in the frontal lobes. A substantial body of evidence suggests that the frontal lobes regulate such capacities as abstract and creative thinking, fluency of thought and language, affective responsiveness and attachment, social judgment, volition, and attention (Fuster 1980). Neurochemically, these symptoms could represent a diminution or decrease in dopaminergic function (Chouinard and Jones 1978; Lecrubier et al. 1980; Mackay 1980). Positive symptoms do not lend themselves as readily to anatomical localization, although one can speculate that hallucinations could be due to irritative phenomena in the auditory cortex or in subcortical nuclei that encode perceptual memories such as the hippocampus. Delusions, positive thought disorder, and disorganized behavior all appear to represent hyperarousal, which could be explained anatomically in a variety of different ways, ranging from excessive activity in the reticular activating system through a "hyperconnection syndrome" in the corpus callosum. Neurochemically, hyperdopaminergic transmission is, of course, the most widely accepted explanation (Creese, Burt, and Snyder 1976; Seeman et al. 1976; Angrist, Rotrosen, and Gershon 1980).

Future Directions and Needs for Research

Future directions in diagnosis must stress integrative approaches. The introduction of diagnostic criteria, the emphasis on describing symptoms reliably, and cross-national comparative studies have already brought us a long way. This highly refined cross-sectional descriptive approach must be supplemented, however, through longitudinal studies that examine the course of this disorder over time and that relate diagnosis to other scientific domains.

Importance of Predictive Validity. Diagnosis is important only insofar as it assists clinicians and researchers in thinking and communicating about disorders in a clear, organized, and useful manner. It provides clinicians with a system for recognizing patterns or groups among patients and placing them in classes so that decisions about management or treatment can be made. The diagnostic concept of schizophrenia should be used clinically to assist in decisions about which medications to prescribe, what advice to give the family about long-term outcome, or what social management may be appropriate. The diagnosis may be used for genetic counseling, or for counseling about what long-term personal goals may be realistic for the patient. In other words, the diagnosis is useful only insofar as it has some predictive validity.

In the future, research on diagnostic aspects of schizophrenia must pursue predictive validity more carefully and in more detail. Early work on good versus poor prognosis schizophrenia has been useful in the past, but more studies of the prognostic implications of symptoms in schizophrenia are needed in the future, particularly in the light of new and fluctuating definitions of schizophrenia, the recent emphasis on negative symptoms, and the growing recognition that the various symptoms of schizophrenia vary in their response to treatment. We need a new series of studies that use both outcome and response to treatment as independent variables and attempt to determine which clusters of symptoms or which methods for nosologic subtyping are most useful in predicting response to treatment. Although much has been said and written, for example, about the possibility that negative symptoms are associated with a poor response to treatment, we have only a few recent studies that attempt to evaluate this population with a rigorous design and a well-thought-out definition of positive vs. negative symptoms (Johnstone et al. 1978; Angrist, Rotrosen, and Gershon 1980).

Landmark studies concerning the variable treatment responsivity of symptoms were done in the 1960's, when phenothiazines were first developed (Goldberg et al. 1967, 1972; Klein and Davis 1969). These are difficult to interpret due to the evolution and change in the concept of schizophrenia itself. We need studies of comparable quality in the 1980's and 1990's.

With the growing concern about tardive dyskinesia and about poor responsivity of some symptoms of schizophrenia, clinicians and phar-

maceutical companies are searching for new treatments and new types of drugs. Atypical or energizing neuroleptics and benzodiazepines have both been proposed as useful adjuncts to the treatment of schizophrenia, for example (Lecrubier et al. 1980). As these new treatment strategies are applied, it will be important to determine whether particular symptoms do respond differentially to particular types of treatment. Just as positive symptoms may be more responsive than negative symptoms to conventional neuroleptics, so too some negative symptoms may be more sensitive to treatment than others. Not only will the detailed mapping of the ways phenomenology may change in response to treatment be of assistance to the clinician, but it may also help ultimately in developing new and more useful methods for subtyping schizophrenia. Drugs that differentially affect serotonin or GABA (γ-aminobutyric acid) systems as opposed to dopamine systems (or even D_1 vs. D_2 receptors within the dopamine system) may ultimately permit a pharmacological dissection of the schizophrenic subtypes that will have a more meaningful pathophysiological basis.

Importance of Longitudinal Studies. Studies that emphasize the importance of predictive validity by treating outcome as an independent variable will inevitably rely heavily on detailed longitudinal studies. Just as there has been a dearth of treatment studies, so too there has been a serious lack of longitudinal studies in schizophrenia, particularly longitudinal studies that have been done prospectively.

Longitudinal studies initiated in the 1980's should not only be prospective, but should also include a representative sample of first-episode patients. These patients should be described with a thorough data base that incorporates a detailed description of phenomenology in combination with measures of previous educational, occupational, and social functioning and a maximal amount of information about risk factors (e.g., season of birth, perinatal complications, childhood illnesses, and family environment). Intake into such a study should probably use a relatively broad definition of schizophrenia to facilitate the determination of the boundaries of the concept and search for subtypes. These patients should then be followed prospectively at 6-month intervals for a long period (ideally at least 10 years). In a study of this type, treatment can obviously not be controlled, since any sample of patients in whom treatment can be controlled for a long period of time will not be representative of the schizophrenic population. In view of that fact, treatment must instead be carefully described and documented. Because we do not yet know the extent to which the course of schizophrenia may vary, depending on social and environmental factors, ideally we need prospective studies conducted in several different regions of the United States that represent variable demographic and ethnic mixes (e.g., rural vs. urban or Northern European vs. Southern European).

Prospective studies of this type will give us relatively definitive information about the natural history of schizophrenia and its long-term outcome. They should permit us to resolve the recurrent question as to whether schizophrenia is best defined as a chronic deteriorating illness, a single illness that can be variable in outcome, or a heterogeneous group of illnesses that are variable in outcome.

Integration of the Biotype and Phenomenotype. Studies of predictive validity and longitudinal studies may be substantially strengthened through the inclusion of biological measures that may be informative about the underlying mechanisms of illness. Unless some miraculous breakthrough occurs, neither phenomenology alone nor biology alone is likely to solve the riddle of schizophrenia. Study of the phenomenotype becomes a purely descriptive exercise leading to increasing refinements in distinctions and definitions, but lacking a rootedness in curiosity about underlying biological mechanisms. Biological studies in isolation lend themselves to endless collection of laboratory measures, all too many of them peripheral in origin, that only too often are collected "because they are there" (i.e., they are things that can be measured). All too frequently, this has led biologists to conclude that they can get no help from phenomenology, since it fails to identify groups that differ on biological measures.

Increasingly, however, clinical investigators who are astute in phenomenology are astute in biology, and vice versa. There is a growing recognition that one must move freely and flexibly between thinking about the clinical picture of schizophrenia and thinking about how this clinical picture might be biologically caused. Astute investigators are now often using a full data base encompassing many aspects of the phenomenotype in conjunction with the study of two or three related biological aspects, such as brain imaging and platelet monoamine oxidase in twin studies (Reveley et al. 1982).

Mapping of Clinical Symptoms Through Brain Imaging. As noted above, one can attempt to understand the symptoms of schizo-

phrenia through what we know about brain functioning in normal individuals. For example, the negative symptoms of schizophrenia represent a loss or diminution in those functions usually mediated through the frontal lobes, leading some investigators to postulate that they may represent a frontal lobe deficit (Andreasen et al. 1986).

Brain-imaging techniques, particularly single-photon emission tomography and positron emission tomography, lend themselves eminently well to the examination and localization of clinical signs and symptoms. For the first time, it has become possible actually to observe the brain as it works, or as it fails to work. Several studies have documented "hypofrontality" in patients suffering from schizophrenia (Ingvar and Franzen 1974; Buchsbaum et al. 1984; Morihisa, Duffy, and Wyatt 1985; Andreasen et al. 1986; Berman, Zec, and Weinberger 1986; Weinberger, Berman, and Zec 1986). To date, little effort has been made to relate this potential frontal deficit to clinical features of the illness. As brain-imaging techniques become more widely available and less expensive, thereby lending themselves to the study of relatively large samples with a broad range of symptoms, it may be possible to determine whether the differences in clinical phenomenology of some patients suffering from schizophrenia reflect underlying differences in cerebral functioning. This will permit powerful unification of the biotype and the phenomenotype.

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