PART 1

Descriptive Aspects
Schizophrenia is one of the most important public health problems in the world. A survey by the World Health Organization ranks schizophrenia among the top ten illnesses that contribute to the global burden of disease (Murray, 1996). Because of its early age of onset and its subsequent tendency to persist chronically, often at significant levels of severity, it produces great suffering for patients and also for their family members. It is also a relatively common illness. Although estimates of rates in the general population vary, it appears to affect from 0.5% to 1% of people worldwide. Furthermore, it is an illness that affects the essence of a person’s identity—the brain and the most complex functions that the brain mediates. It affects the ability to think clearly, to experience and express emotions, to read social situations and to have normal interpersonal relationships, and to interpret past experiences and plan for the future. Some of its symptoms, such as delusions and hallucinations, produce great subjective psychological pain. Other facets of the illness produce great pain as well, such as the person’s recognition that they are literally “losing their mind” or being controlled or tormented by forces beyond personal control. Consequently, it can be fatal—a substantial number of its victims either attempt or complete suicide.

It is also an illness that is conceptually challenging, because its manifestations are so diverse. Over the past several centuries various attempts have been made to formulate a consensus about the definition and essence of schizophrenia. This introduction will review this conceptual history in order to provide a foundation for the later chapters in this book. Even at present, creating a consensus about how best to define the phenotype(s) of schizophrenia is a task that has not yet been successfully achieved. And yet the definition of the concept and its phenotype must provide a foundation for both the study of disease mechanisms and for the development of improved approaches to treatment and prevention.

The past: early concepts of psychosis

The term “schizophrenia” was only coined in the last century, and therefore it is sometimes assumed that it is a “new disease”, perhaps a consequence of the development of a complex highly-industrialized world and resultant stresses in lifestyle. Although the name for this illness is relatively new, the concept of psychosis is very old. Based on portrayals of similar psychotic states in early history and literature and on early medical descriptions, we know that schizophrenia-like psychoses have been recognized since at least the first millennium BC.

One of the earliest descriptions of a psychotic condition occurs in the book of Samuel in the Old Testament. After David successfully defends the Israelites against the Philistines by killing Goliath and then wins several subsequent battles, King Saul becomes increasingly paranoid about David’s military prowess, to the point of repeatedly making plans to murder David, and even attempting to do it himself:
... the evil spirit from God came upon Saul, and he prophesied in the midst of the house: and David played [music] with his hand, as at other times; and there was a javelin in Saul’s hand. And Saul cast the javelin; for he said, I will smite David even to the wall with it. And David avoided out of his presence twice. And Saul was afraid of David, because the Lord was with him, and was departed from Saul.

(1 Samuel 10–12)

In fact, Saul eventually begins to have hallucinatory-like experiences, seeking help from the witch of Endor, and also having visions of his former advisor, the deceased prophet Samuel.

If we move on to the classical era in Greece and Rome, there are many descriptions of paranoid schizophrenia-like psychotic states. Greek tragedy is filled with portrayals of individuals who are tormented by psychosis, and are often driven to committing horrendous acts while insane. In The Bacchae, Agave murders her son Pentheus with her own hands, driven by the delusional belief that he is a lion. In Medea, after Jason abandons his wife Medea, she falls into a psychotic rage that drives her to murder their two children with a sword, also murdering King Creon and his daughter by giving them a poisoned robe and chaplet that consumes them in a fiery painful death. In The Oresteia, Orestes is pursued by the Furies until he finally loses his reason and lapses into madness. And there are many more examples.

In the 16th and 17th centuries Elizabethan and Jacobean drama are similarly filled with portrayals of individuals who experience schizophrenia-like psychotic states. Some of the best known are in the plays of Shakespeare. Hamlet, Lear, Othello, and Lady Macbeth all experience psychosis. King Lear is a vivid and powerful example. Three main characters are all “mad”: Lear himself, Gloucester, and Edgar (pretending to be a “bedlam beggar”—an escapee from the Bethleham Hospital for the insane in London). As Gloucester says of Lear:

Thou say’st the King grows mad; I’ll tell thee, friend, I am almost mad myself. I had a son, Now outlaw’d from my blood; he sought my life. ... The grief hath craz’d my wits

(King Lear III.iv.169–174)

In addition to these historical and literary portrayals, which document that schizophrenia-like illnesses have been present for at least three millennia, the “medical” literature of these early times provides parallel evidence that psychotic disorders similar to schizophrenia were recognized as important medical illnesses. They are described in the writings of our early medical forefathers, such as Hippocrates, Galen, or Soranus of Ephesus. The disorders described by these forefathers do not map perfectly on to modern classification systems, but they have surprising similarities. Mental illnesses were clearly seen as “physical” in origin, deriving either from an imbalance of humors (yellow bile, black bile, phlegm, and blood) or to an imbalance in the brain. In general, five groups of illnesses were described: melancholia, phrenitis, mania, hysteria, and epilepsy. Mania was essentially equivalent to our concept of psychosis. Psychotic disorders were not, however, further subdivided until the late 19th century.

The past: further delineation of psychoses and early definitions of schizophrenia

Kraepelin (1919) gave us the conceptual framework that created the modern concept of schizophrenia. One of Kraepelin’s many great contributions was to take the general concept of psychosis and to subdivide it into two major groups, based on his observation of differences in course and outcome. One group of patients who were psychotic had an episodic course, typically with a full remission of symptoms. A second group of psychotic patients had a chronic course and typically progressed to a deteriorated state. He named these two groups “manic-depression” and “dementia praecox”. Although this distinction is so familiar today that we scarcely think about it, it was a major intellectual achievement at the time, and it has influenced psychiatric classification and the concept of schizophrenia for more than a century.

Kraepelin did not, however, consider psychotic symptoms to be the most important features of dementia praecox. When he spoke of symptoms, those that he considered to be most fundamental were what we today would call negative symptoms. Negative symptoms include abnormalities in cognition and emotion: alogia, avolition, anhedonia, affective blunting, and (in some conceptualizations) attentional impairment. Kraepelin said:

There are apparently two principal groups of disorders that characterize the malady. On the one hand we observe a weakening of those emotional activities which permanently form the mainsprings of volition. ... Mental activity and instinct for occupation become mute. The result of this highly morbid process is emotional dullness, failure of mental activities, loss of mastery over volition, of endeavor, and ability for independent action. ... The second group of disorders consists in the loss of the inner unity of activities of intellect, emotion, and volition in themselves and among one another. ... The near connection between thinking and feeling, between deliberation and emotional activity on the one hand, and practical work on the other is more or less lost. Emotions do not correspond to ideas. The patient laughs and weeps without recognisable cause, without any relation to their circumstances and their experiences, smile as they narrate a tale of their attempted suicide.

(Kraepelin, 1919, pp. 74–75)
Such passages in Kraepelin’s textbook indicate that he perceived negative symptoms to be the most important symptoms of schizophrenia. Nevertheless, his comprehensive description of schizophrenia covered a broad range of symptoms, including delusions and hallucinations.

Bleuler (1950), on the other hand, tried to clarify the group of schizophrenias by very explicitly attempting to identify what he considered to be the underlying fundamental abnormality. Consequently, he divided the symptoms of schizophrenia into two broad categories: fundamental and accessory symptoms. Bleuler believed that the fundamental symptoms were present in all patients, tended to occur only in schizophrenia, and therefore were pathognomonic. The accessory symptoms, on the other hand, could occur in a variety of different disorders. Depending how one interprets and summarizes his writings, one can argue that Bleuler identified four, five, or six fundamental symptoms of schizophrenia. These included the loss of the continuity of associations, loss of affective responsiveness, loss of attention, loss of volition, ambivalence, and autism. These symptoms correspond relatively closely to those we currently refer to as negative symptoms. They reflect abnormalities in basic cognitive and emotional processes, which (in Bleuler’s thinking) provided the basis for other types of symptoms observed in the illness. Accessory symptoms, on the other hand, include phenomena such as delusions and auditory hallucinations. Bleuler wrote:

Certain symptoms of schizophrenia are present in every case and in every period of the illness even though, as with every other disease symptom, they must have attained a certain degree of intensity before they can be recognized with any certainty. ... Besides the specific permanent or fundamental symptoms, we can find a host of other, more accessory manifestations such as delusions, hallucinations, or catatonic symptoms. ... As far as we know, the fundamental symptoms are characteristic of schizophrenia, while the accessory symptoms may also appear in other types of illness.

(Bleuler, 1950, p. 13)

When Kraepelin called the disorder “dementia praecox”, he intended to highlight the fact that it had an early (“praecox”) onset and therefore differed from another type of dementia described by his friend and colleague, Alois Alzheimer. However, in choosing the term “dementia”, he wished to highlight the fact that the illness had a chronic and deteriorating course. His contemporary Swiss colleague, Eugen Bleuler, admired many of Kraepelin’s ideas, but he took exception to the fact that chronicity and deterioration were inevitable. Therefore, he chose to rename the illness in order to highlight his own view that a fragmenting of thinking, sometimes referred to as “thought disorder”, was the most important feature, and also to eliminate the concept that deterioration was inevitable. He chose the name “schizophrenia” (schiz = fragmenting, splitting; phren = mind, Gk). Bleuler’s name eventually prevailed over Kraepelin’s. Today many feel that either is an unfortunate choice, because each leads to misunderstanding about the nature of the illness by the general public. Too often people assume that the name refers to a “split personality”. However, to date no good substitute has been identified.

Since Bleuler’s fundamental symptoms involve cognition and emotion, since negative symptoms (a related but also slightly different concept) also involve cognition and emotion, and since “cognitive dysfunction” in schizophrenia is currently a topic of considerable interest, some clinicians and investigators find the interface between cognition and negative symptoms confusing. The word “cognition” has multiple meanings in cognitive psychology and clinical usage (Andreasen, 1997). Sometimes it refers to all activities of “mind”, including emotion and language. Sometimes it refers to “rational” as opposed to “emotional” processes. Sometimes it is used very narrowly to refer to performance on objective neuropsychological tests or experimental cognitive psychology tests. Heuristically, the term “cognition” is probably most useful in the context of schizophrenia when it is used to refer to the broadest meaning (activities of mind). Since negative symptoms are closely tied to defects in basic cognitive processes (e.g., volition, ability to think abstractly, initiation of thoughts and language, attributing affects to experiences), assessing them at the clinical level may provide a relatively direct “window” into cognitive impairments in schizophrenia. While Kraepelin and Bleuler did not refer to their clusters of fundamental symptoms by calling them “negative”, this appears to be the point that they were making. In a sense, therefore, negative symptoms may be the most fundamental and clinically important symptoms of schizophrenia.

Neither Kraepelin nor Bleuler actually used the terms “positive symptoms” or “negative symptoms”. While various sources for these terms can be cited (Berrios, 1985), one of the earliest and most prominent was Hughlings-Jackson (1931). Although Hughlings-Jackson’s work was not published until much later, in the late 19th century Jackson speculated about the mechanisms that might underlie psychotic symptoms:

Disease is said to “cause” the symptoms of insanity. I submit that disease only produces negative mental symptoms, answering to the dissolution, and that all elaborate positive mental symptoms (illusions, hallucinations, delusions, and extravagant conduct) are the outcome of activity of nervous elements untouched by any pathological process; that they arise during activity on the lower level of evolution remaining.

(Hughlings-Jackson, 1931)

Thus Hughlings-Jackson believed that some symptoms represented a relatively pure loss of function (negative
symptoms answer to the dissolution), while positive symptoms such as delusions and hallucinations represented an exaggeration of normal function and might represent release phenomena. Hughlings-Jackson presented these ideas at a time when Darwinian evolutionary theories were achieving ascendance, and his concepts concerning the mechanisms that produced the various symptoms were clearly shaped by a Darwinian view that the brain is organized in hierarchical evolutionary layers. Positive symptoms represent aberrations in a primitive (perhaps limbic) substrate that is for some reason no longer monitored by higher cortical functions. Thus Hughlings-Jackson’s concept of negative and positive symptoms rather closely resembles those which are currently discussed. Although most investigators do not necessarily embrace the specific mechanism that he proposed, they accept his view that they must be understood in terms of brain mechanisms, as well as his basic descriptive psychopathology.

The writings of Kraepelin, Bleuler, and Hughlings-Jackson laid down a descriptive and conceptual foundation for contemporary thinking about the symptoms and definition of schizophrenia. Both Kraepelin and Hughlings-Jackson attempted to understand symptoms in terms of their underlying neural mechanisms. While Hughlings-Jackson stressed the importance of the interplay between brain regions that were hierarchically organized, Kraepelin discussed the possible localization of the various symptoms in the prefrontal, motor, and temporal cortex. Kraepelin and Bleuler both stressed the importance of a loss of cognitive, affective, volitional, and attentional function in schizophrenia. Kraepelin clearly believed that these could be the most debilitating and central symptoms of the disorder, while Bleuler stated that they were pathognomonic. Throughout most of the 20th century, Bleuler’s perspective predominated. Clinicians all over the world were taught to define and diagnose schizophrenia based on the symptoms Bleuler saw as fundamental, such as associative loosening and affective blunting.

**The present: Schneiderian symptoms, psychosis, and the dominance of diagnostic criteria**

For a variety of historical reasons, this emphasis shifted in the 1960s and 1970s. This change in emphasis arose primarily from an interest in improving diagnostic precision and reliability. Because they are essentially “all or none” phenomena, which are relatively easy to recognize and define, florid psychotic symptoms such as delusions and hallucinations were steadily given greater prominence and indeed even placed at the forefront of the definition of schizophrenia.

The emphasis on florid psychotic symptoms arose because of the influence of Kurt Schneider and the interpretation of his thinking by influential British psychiatrists. Schneider was greatly influenced by the work of Karl Jaspers, who explored phenomenology and created a bridge between psychiatry and philosophy. Jaspers believed that the essence of psychosis was the experience of phenomena that were “non-understandable”, i.e., symptoms that a “normal” person could not readily imagine experiencing. Schneider, like Bleuler, wished to identify symptoms that were fundamental. He concluded that one critical component was an inability to find the boundaries between self and not-self and a loss of the sense of personal autonomy. This led him to discuss various “first-rank” symptoms that were characterized by this loss of autonomy, such as thought insertion or delusions of being controlled by outside forces (Schneider, 1959; Fish, 1962; Mellor, 1970).

Schneiderian ideas were introduced to the English-speaking world by British investigators and began to exert a powerful influence on the concept of schizophrenia. An emphasis on Schneiderian first-rank symptoms satisfied the fundamental need to find an anchor in the perplexing flux of the phenomenology of schizophrenia. Schneiderian symptoms were incorporated into the first major structured interview developed for use in the International Pilot Study of Schizophrenia (IPSS), the Present State Examination (PSE) (Wing et al., 1974). From this major base, they were thereafter introduced into other standard diagnostic instruments such as the Schedule for Affective Disorders and Schizophrenia (SADS) (Endicott & Spitzer, 1978), Research Diagnostic Criteria (RDC) (Spitzer et al., 1978), and the Diagnostic and Statistical Manual (DSM-III) (American Psychiatric Association, 1980).

The emphasis on positive symptoms, and especially Schneiderian symptoms, derived from several concerns. The first was that Bleulerian symptoms were difficult to define and rate reliably. They are often continuous with normality, while positive symptoms are clearly abnormal. In addition to concerns about reliability, work with the IPSS and the US/UK Study also indicated that in the US the concept of schizophrenia had broadened to an excessive degree, particularly in the North-eastern parts of the US (Kendell et al., 1971; Wing et al., 1974). Thus, in the US there was clearly a need to narrow the concept of schizophrenia. Stressing florid psychotic symptoms, particularly Schneiderian symptoms, was a useful way to achieve this end, since it appeared that schizophrenia was often being diagnosed on the basis of mild Bleulerian negative symptoms. When diagnostic criteria such as the RDC and later DSM-III were written, these placed a substantial emphasis on positive symptoms and essentially ignored negative symptoms.

While there have been many good consequences of this progression and of the interest in Schneider’s work, there have also been problems.
From a Schneiderian perspective, Schneider’s work and point of view have been oversimplified and even misunderstood. As a Jasperian phenomenologist, Schneider was in fact deeply interested in the subjective experience of schizophrenia—in understanding the internal psychological processes that troubled his patients. For him, the fundamental core of the illness was not the specific first-rank symptoms themselves, but rather the internal cognitive and emotional state that they reflected. It is somewhat ironic that he has become the symbol of objective quantification and reductionism. He himself was a complex thinker who was concerned about individual patients.

The development of diagnostic criteria has also had both advantages and disadvantages. When DSM-III was originally developed, it was intended only as a “provisional consensus agreement” based on clinical judgment. The criteria were created by a small group of individuals who reached a decision about what to include based on a mixture of clinical experience and research data available up to that point. The criteria were chosen to serve as a gatekeeper that would include or exclude individual cases, and they were not intended to be a full description of the illness. Unfortunately, they are now sometimes treated as a textbook of psychiatry. Further, the criteria have become reified and given a power that they originally were never intended to have.

Diagnostic criteria have substantial and undeniable advantages: they improve reliability, provide a basis for cross-center standardization both nationally and internationally, improve clinical communication, and facilitate research. However, they may also have potential disadvantages and even abuses: they provide an oversimplified and incomplete view of the clinical picture, discourage clinical sensitivity to individual patients and comprehensive history-taking, lead students and even clinicians to believe that “knowing the criteria is enough”, reify an agreement that was only intended to be provisional, and discourage creative or innovative thinking about the psychological and neural mechanisms of schizophrenia.

**The future: beyond diagnostic criteria and the search for fundamental mechanisms**

As the present moves toward the future, corrective readjustments are already beginning to occur. Paradoxically, these often occur by returning to the past and coming back full circle to the work of Kraepelin, Bleuler, Jackson, and Schneider.

Clinically, the emphasis on negative as well as psychotic symptoms is leading to increased interest in the full range of symptoms of schizophrenia and in developing methods for treating that full range. The development of atypical antipsychotics, which may affect a broader range of symptoms than the older “typicals”, has been helpful in effecting this change (Green et al., 1997; Tollefson & Sanger, 1997).

The interest in negative symptoms has been complemented by a return to an interest in cognitive aspects of schizophrenia. Many negative symptoms are cognitive in nature—alogia (poverty of thought and speech), avolition (inability to formulate plans and pursue them), and attentional impairment. While their assessment may emphasize objective aspects of behavior in order to achieve reliability, their underlying essence is in the domains of thought and emotion. Increasingly, therefore, investigators are returning to the original insights of Kraepelin and Bleuler that the core symptoms of schizophrenia represent a fundamental deficit in cognition and emotion. This in turn has led to recent initiatives to incorporate assessments of cognitive function into clinical drug trials (Green & Neuchterlein, 2004).

Several prominent investigators have turned from a focus on explaining and “localizing” the specific symptoms of schizophrenia to a search for more fundamental underlying cognitive mechanisms (Andreasen, 1997). Examples include Frith’s (1992) hypotheses concerning an inability to think in “metarepresentations”, Goldman-Rakic’s (1994) studies of working memory, our descriptions of cognitive dysmetria (Andreasen et al., 1996), or the work of Holzman et al. (1976), Braff (1993), Swerdlow and Geyer (1993), and Freedman et al. (1991) on information processing and attention. These cognitive models provide a general theory of the disease that is consistent with its diversity of symptoms, permit testing in human beings with a variety of convergent techniques (e.g., imaging, neurophysiology), and even permit modeling in animals. This efficient and parsimonious approach offers considerable hope for the future because it facilitates the search both for improved treatments and for molecular mechanisms.

Finally, the growing maturation of the field of complex genetics offers many potential opportunities for understanding the mechanisms of schizophrenia at the molecular level and hope for improved pre-emption, prevention, and personalization of care. The most pressing need facing those engaged in this work is to identify more meaningful ways to define the phenotype of schizophrenia. The success of the Human Genome Project has conceptually revolutionized our thinking about the ways in which the search for phenotypes must be guided. It has created a new discipline that is sometimes referred to as “phenomics” (Freimer & Sabatti, 2003). The primary task of this new discipline is to delineate the various phenotypic components that comprise the phenome—in this case the phenotype of a disease, schizophrenia. Phenomics takes a broad approach to defining the concept of the phenotype. That is, the phenotype includes not just clinical symptoms and other “behavioral” measures, but also morphological, biochemical, and physiological characteristics. What will eventually emerge from
a phenome approach is a more valid and etiologically-based definition of disease phenotypes that may be quite different from those created by using the clinical level alone, as has been the tradition in psychiatry and the rest of medicine for the past century. These improved phenotypes will advance the field in several ways. One is to assist in the identification of individualized treatment strategies that are more rationally based and data-driven. A second is to improve our knowledge of disease mechanisms at the neural and genomic levels so that more targeted treatment strategies can be developed.

**References**


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