What Is Schizophrenia?

One of the main questions related to schizophrenia is, naturally enough, what is it? Such a question may seem obvious, naive, impossible, or any combination of these. And certainly it is a bit demanding to expect that anyone could say what schizophrenia is in 1,000 words. On the other hand, we felt that it was worth the effort. We hope that presenting these brief discussions on "what is schizophrenia" by persons who have worked extensively in the field will allow the reader to note areas of overlap and disagreement as well as variations in emphasis. Although no one may yet be able to provide the definitive answer, at least this collection of informed opinions may help clarify the major questions. The group of essays by Solomon H. Snyder, Seymour S. Kety, and Michael J. Goldstein is the second in this series. Further collections of these statements will be presented in subsequent issues. Readers' responses and comments are cordially invited.—J.S.S., M.B.B., and S.J.K.

As a psychopharmacologist, I suppose my perspective on schizophrenia should be from the point of view of drugs. In fact, my first interest and involvement in schizophrenia research began when, as a freshman in medical school, I worked under the supervision of David Rosenthal at the National Institute of Mental Health conducting perceptual-motor studies of schizophrenics and reviewing the literature on psychological abnormalities (Snyder 1960; Snyder, Rosenthal, and Taylor 1961). What impressed me was how differently schizophrenics seemed to perceive the world as compared to normals, even in such a seemingly neutral task as Gestalt tests of perceptual closure, filling in gaps in perceived houses and stickmen. At a human level, I was struck by the suffering which had by no means been abolished despite the considerable number of neuroleptics to which the patients were exposed even then in 1959.

All of these impressions have remained with me now some 22 years later. Through the course of medical, psychiatric, and research training, I have not ceased to wonder at what extraordinarily unique alteration in the brain can account for human beings having their mental life sometimes consumed with visual or auditory hallucinations, delusions, and a fundamentally peculiar way of perceiving and thinking about the world.

What has biochemical research into drug action in schizophrenia taught us about the nature of the disorder? Of all the neurotransmitter systems explored in schizophrenia, the most compelling evidence for relevance to the disorder has to do with studies of dopamine. It is reasonably well accepted that a major antipsychotic action of the neuroleptics involves blockage of dopamine receptors. The relative potencies of neuroleptics in blocking one subtype of dopamine receptors, the D-2 receptors, correlate closely with clinical potencies of the drugs and their potencies in animal pharmacological tests which predict clinical antipsychotic effects (Creese Burt, and Snyder 1976; Seeman et al. 1976). These effects are by no means fortuitous, since the very considerable potencies of neuroleptics in blocking receptors for other neurotransmitters such as
histamine, $\alpha$-adrenergic, and serotonin receptors do not show any significant correlation with antipsychotic effects (Peroutka and Snyder 1980).

The other aspect of the dopaminergic story has to do with effects of stimulants. Amphetamine and related agents in large doses produce a psychosis which can be clinically indistinguishable from acute paranoid schizophrenia (Angrist and Sudilovsky 1978). The problem with amphetamine psychosis as a model of schizophrenia is that it mimics only one subtype of the disorder, and some investigators feel that it is not a perfect model. Thus, some researchers feel that patients with amphetamine psychosis do not display the classic schizophrenic abnormality in affect or thinking. On the other hand, the fact that amphetamine psychotics can fool very experienced psychiatrists into a diagnosis of schizophrenia in the absence of drug history argues in favor of some relationship. Perhaps more impressive than amphetamine psychosis is the finding that small doses of amphetamines can floridly exacerbate specifically schizophrenic symptoms without affecting in a marked way symptoms of patients with manic-depressive illness or neurosis (Janowsky and Davis 1976).

Amphetamines exert their actions by releasing catecholamines or blocking their reuptake inactivation. Some indirect evidence suggests that the amphetamine effects upon schizophrenic symptoms involve dopamine more than norepinephrine. Thus, methylphenidate is more effective than amphetamine itself in worsening schizophrenic symptoms and acts more upon dopamine than norepinephrine.

If blocking actions of dopamine alleviates schizophrenic symptoms while enhancing dopamine effects worsens them, we have a "dopamine hypothesis" of drug actions in schizophrenia. It should be emphasized that this by no means establishes that dopamine systems are specifically abnormal in schizophrenia. The fundamental abnormality might be in some other system which is somehow linked to dopamine neurons. Only a direct demonstration of abnormalities in schizophrenic brain could answer this question. Measurements of dopamine itself have shown some possible abnormalities, but results are inconclusive (Bird, Spokes, and Iversen 1979). If schizophrenics are hypersensitive to dopamine, perhaps they have too many dopamine receptors. There have been reports of increased numbers of dopamine receptors in schizophrenia (Lee et al. 1978; Owen et al. 1978), but in recent studies controlling for drug dosage we have obtained evidence that these effects are in fact secondary to the well-known capacity of chronic neuroleptic administration to augment numbers of dopamine receptors (Burt, Creese, and Snyder 1977; Mackay et al. 1980).

Of course, those who would search for a specific biochemical abnormality in schizophrenia must bear in mind the considerable likelihood that schizophrenia is heterogeneous. If there are 10 or more distinct diseases which all share the symptoms of schizophrenia, then the likelihood of finding the specific abnormality in any one of these forms is lessened considerably. Nonetheless, it is possible that patients with classical clinical symptoms of schizophrenia and a strong family history all suffer from a single disease entity. At a minimum biochemical investigations should pay close attention to clinical distinctions of subgroups based on symptoms, family history, course, or age of onset (Bird, Spokes, and Iversen 1979).

In any event, though we cannot assert any causal relationships, dopamine does seem to play a role in mediating drug actions in schizophrenia and is somehow linked to systems that are abnormal in schizophrenia. I continue to be impressed with the fact that the relief of schizophrenic symptoms by neuroleptics is rarely total. How might we go about finding out the fundamental abnormality? Sifting through schizophrenic urine, blood, and spinal fluid is probably more difficult than looking for a needle in a haystack. Understanding how drugs act in schizophrenia has been more heuristic. Accordingly, since neuroleptics are far from a panacea, I would advocate major efforts toward developing antischizophrenic drugs acting by novel mechanisms. This represents a challenge to the drug industry, since presently used animal tests merely select for dopamine receptor blocking activity. Nonetheless, a variety of biochemical and pharmacological strategies can be employed. Once new and effective drugs are available, we would hope to find out how they act, an endeavor which in turn might provide clues to what is fundamentally wrong in the schizophrenic brain.

References
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Progress in all of the branches of medicine has depended upon accurate and perceptive observations with the tools at hand and an intellectual process similar to that which developed in other branches of science for the recognition of common features or unifying concepts and the formulation and evaluation of hypotheses. Before gross, microscopic, or chemical pathology was able to differentiate morbid processes, and microbiology, biological chemistry, toxicology, or epidemiology had advanced sufficiently far to identify etiology and pathogenesis, a groundwork had been laid by phenomenological syndromes defined simply on the basis of common course and symptoms and the presumption which this suggested of common features in the underlying pathology, if not etiology. Many of the descriptions of these syndromes are among the classics in medicine and made further progress possible as new methods of observation were developed.

In psychiatry, the syndrome of schizophrenia is the most venerable and one of the most useful of these phenomenological clusters. It had its inception in the closing years of the last century when Emil Kraepelin observed that syndromes previously described as hebephrenia, paranoia, and catalepsia had enough important features in common to permit their conceptualization as parts of a single and broader syndrome which he called dementia praecox. Recognizing that "... there is in the domain of psychic disorders no single morbid symptom which is thoroughly characteristic of a definite malady," he emphasized that "... the composition of the entire picture made up of its various individual features, and especially also the changes which it undergoes in the course of the disease..." was necessary for its differential diagnosis and ultimate understanding (Kraepelin 1913, p. 257). In conscientious detail he described the major features and more than 50 individual symptoms which together characterized the syndrome.
Eugen Bleuler (1911), a contemporary of Kraepelin who maintained cordial relations with him, was quick to recognize the importance of Kraepelin's contribution, elaborating upon it and giving it a new name—schizophrenia. He was careful to point out that the whole idea originated with Kraepelin and that almost exclusively to his work was to be attributed the grouping and description of the separate symptoms. He could not, however, "...shirk the uncomfortable duty of coinage a new name for this disease...the present one seems to be awkward." In their separate textbooks and monographs, they described the "fundamental" and "accessory" features, that is, the characteristic and the nonspecific manifestations which several generations of psychiatrists throughout the world found useful in recognizing the syndrome and differentiating it from others, particularly manic-depressive illness. The differentiations, it is true, were imperfect, but not notably more so than those among many medical syndromes when they had to depend only on clinical observation. Neither of the originators thought they were describing a single disease but a syndrome of heterogeneous etiology (Bleuler called it "the group of schizophrenias") with common "morbid processes" which probably accounted for the symptomatic features they had in common.

It would be well to review the "schizophrenic symptoms" which Kraepelin and Bleuler described because of a recent tendency to reject them. The syndrome was described as "a specific type of alteration of thinking, feeling and relation to the external world which appears nowhere else in this particular fashion." Among the characteristic symptoms were "weakening of judgment, of mental activity and of creative ability, the dulling of emotional interest and the loss of energy...loosening of the inner unity of intellect, emotion and volition in themselves and among one another..." In their further characterization they described disorders of association, incoherence or blocking of thought and speech, impoverishment of affect, inappropriate affect, inability to establish affective relationships with others, a tendency to divorce oneself from reality, bizarre and tangential thinking, stereotypies, and mannerisms and tics of various sorts. An insidious onset in adolescents and young adults with various premorbid difficulties was noted in a large majority of cases, as was a prolonged course and dementia, or at least a failure to return to earlier levels of intellectual integration. Particular types of auditory hallucinations and delusions were described and their frequency pointed out, although both Bleuler (p. 204) and Kraepelin (p. 248) emphasized that hallucinations and delusions were present in many psychoses and were not of special importance in diagnosing the presence of schizophrenia. Recent studies (Carpenter, Strauss, and Bartko 1973; Pfohl and Winokur, in press) which took into account manifestations of schizophrenia as described by Kraepelin and Bleuler found them to be consistent and effective in differentiating that syndrome from manic-depressive illness and other types of psychosis.

Over the past 50 years two trends have developed around or within the original concept of schizophrenia. On the one hand, syndromes were found which resembled the classical syndrome only in certain characteristics, and these were appropriately designated by terms which expressed both their similarity to and separation from the classical syndrome. These have included "schizophriniform psychosis," "schizoaffective disorder," and "schizoid personality." Sometimes terms were adopted which assumed a relationship to schizophrenia which was not conclusively established, such as "latent," "borderline," "atypical," "pseudo neurotic," "acute," or "good prognosis" schizophrenia. A serious epistemological infraction, however, came from Schneider (1959) who completely altered the concept of schizophrenia but retained its original name. Features regarded by both Kraepelin and Bleuler as fundamental and specific (impoverishment of affect, disturbances in personal contact and rapport, ambivalence, lack of volition, depersonalization, and stereotypies) he specifically rejected and arbitrarily established one of the first "operational" diagnoses of schizophrenia, restricted to particular types of hallucinations and delusions which Bleuler and Kraepelin had regarded as accessory and nonspecific. No attempt was made originally to demonstrate that Schneider's "first rank symptoms" successfully and more economically described the original syndrome, and where that crucial assumption has been tested more recently in several studies, the first rank symptoms have not been shown to be either characteristic or discriminating. The resultant disillusionment has led some to disparage the value of "schizo-
psychotic symptoms" in diagnosis, but the evidence which has been adduced to defend that position has rested almost entirely on Schneider's criteria rather than the detailed descriptions of Kraepelin and Bleuler, who alone had the right and the responsibility to define the syndrome they had delineated or named.

Because of the accretions to the original syndrome, parochial differences in emphasis or interpretation of the symptoms as originally described, and a willingness on the part of some to accept entirely different criteria for diagnosis, there has emerged a need to establish some minimal standardized description of the syndrome and putative subtypes. In doing so, it has been relatively easy to measure reliability or agreement between raters, and by specifying very concrete and obvious symptoms to enhance that reliability. Establishing the validity of these more parsimonious descriptions, however, is much more difficult. The most appropriate procedure in the case of a syndrome established entirely by clinical phenomenology would be to test the reliability of diagnoses made by the suggested criteria against diagnoses which would have been made by Kraepelin and Bleuler or, in the absence of that ultimate validation, by careful attention to tenets they established in their writings. That has rarely been done and the usual practice is to make use of a consensus of psychiatric opinion. Since that varies over time and from one school of psychiatry to another, the standardized operational concepts of schizophrenia have also varied, sometimes in contradiction of emphatic caveats by the original founders of the syndrome. Bleuler anticipated that problem 70 years ago: "Naturally nothing is gained thereby except another symptomatological picture which is then called a disease and which moreover is misleadingly defined by the same terms as the qualitatively and quantitatively quite different Kraepelinian concept" (p. 278). Strauss and Gift (1977) recently applied a number of operational definitions of schizophrenia to the same group of 272 patients with sobering results. The number of those patients selected as "schizophrenic" varied from 4 to 68! The value of standardized operational diagnostic strategies lies mainly in the economy that they offer in description and communication. The description of the syndrome which each provides is necessarily arbitrary and incomplete and offers little reason for assuming that any one of them defines "true" schizophrenia.

The DSM-II (American Psychiatric Association 1968) definition of schizophrenia encompassed the descriptions of Kraepelin and Bleuler but deviated in including "acute schizophrenia," which is characterized mainly by hallucinations and delusions, despite Bleuler's admonition that these are "partial phenomena of the most varied diseases whose presence is often helpful in making the diagnosis of a psychosis, but not in diagnosing the presence of schizophrenia." Our study of schizophrenic adoptees and their biological and adoptive relatives used global diagnoses based on DSM-II and Bleuler's descriptions. Although milder but chronic schizophrenia-like disorders (latent and uncertain schizophrenia) were found to be concentrated in the biological relatives of chronic schizophrenic adoptees, this was not the case for acute schizophrenia. These results would have been anticipated by Bleuler (Kety 1980).

DSM-III (American Psychiatric Association 1980) recognizes the fundamental schizophrenic symptoms of Kraepelin and Bleuler and attaches considerable importance to them in its narrative description of the characteristic features of schizophrenia, while giving them less weight in the minimal required criteria than a number of accessory symptoms. By removing "acute schizophrenia" and recognizing a chronic course and deterioration from a previous level of functioning, it has come closer than DSM-II to Kraepelin's original concept, but has also removed "simple schizophrenia," which both Kraepelin and Bleuler had recognized as a form of schizophrenia, including it with "latent schizophrenia" under the rubric of "schizotypal personality disorder."

The DSM-III criteria and the earlier Research Diagnostic Criteria have recently been subjected to the crucial test of validity by applying them to patients described and diagnosed by Kraepelin (James and May 1981) and have stood up reasonably well, especially in the case of the more typical chronic schizophrenics or manic-depressives. Where characteristic features of both illnesses are present, DSM-III would make a diagnosis of schizophrenia if the schizophrenic manifestations preceded those of affective disorder or were of longer duration. Bleuler would have gone even further in rejecting the significance of affective symptoms: "All of the phenomena of manic-depressive psychosis may also appear in our
disease; the only decisive factor is the presence or absence of schizophrenic symptoms" (Bleuler, p. 304).

If, as appears likely, both schizophrenia and major affective disorder are syndromes of heterogeneous etiology and pathology, the occurrence of some cases which have characteristics of both is not surprising, and assigning them to one or the other syndrome on the basis of clinical symptoms alone will necessarily be arbitrary. The existence of pure forms of the two syndromes, however, suggests that there are different malfunctioning systems or processes in the brain which are involved in each, resulting from different or even the same etiological factors. In the case of numerous medical and neurological disorders, a particular etiological process may affect different organs, systems, or processes resulting in different symptomatic syndromes, pure or mixed, depending on the degree and complexity of involvement. Where we add to this the recognition that different etiological factors may affect the same symptom producing a similar picture, the distance between describing the syndromes and elucidating the underlying processes, may bring us closer to that goal. In fact, some progress based on each of these disciplines is now apparent.

References


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I find it easiest to conceptualize schizophrenia from a life span developmental perspective. A person who develops a schizophrenic reaction in late adolescent or early adult years typically faces a major developmental task involving a transition from one life role to another. Thus, psychotic breaks most frequently occur in the last year of high school or shortly after graduation, during the freshman year of college, or shortly before or immediately after college graduation. For those who do not pursue higher education, similar transition points such as entry into the job market or armed services are correlated with a psychotic break-down.

The search for specific, acute life events which trigger the psychotic break has not always been successful as the developmental transition points associated with a schizophrenic reaction are frequently normative stressors for all young people rather than extraordinary in nature. When extraordinary life events precede a psychotic break, these have important prognostic implications.
Since most schizophrenic reactions are associated with demands for separation from one's nuclear family, independent vocational functioning, or heterosexual acceptance and adequacy, how can we account for the preschizophrenic individual's particular vulnerability to these life demands? The vulnerability model of Zubin and Spring (1977) provides me with the best scheme for answering this question. My own clinical and research experience suggests that persons at risk for subsequent schizophrenia vary widely in their biological risk for the disorder based upon evidence from family history data or obvious trauma to the brain at birth. Consider a case with notable biological vulnerability: Jimmy was born after 50 hours of difficult labor with obvious signs of anoxia resulting from prematurity. With a poor Apgar score, he was obvious to all. In other instances, a biological vulnerability may exist, but because we lack any clear-cut vulnerability markers, we cannot evaluate its presence in any specific case. A biological vulnerability interacts sequentially and synergistically with the significant life events that transcend the developmental periods from infancy to late adolescence. Of all life events, those occurring within the matrix of the primary family group seem most significant. Congruent with the observations of Lidz, Fleck, and Cornelison (1965), we have found that the family relationships of preschizophrenics are notable for their disturbed patterns of communication, negative emotional climate, and deviant role structures. These aversive family relationships are incompatible with the growth of social competence and self-esteem in an already vulnerable person.

Once a schizophrenic reaction has occurred, the person undergoes a series of altered states which are often very uniform in character across persons. As suggested by Malcolm Bowers (1974), the phases of a psychotic breakdown follow a rough sequential order, terminating in the classic symptoms of schizophrenia as described in DSM-III (American Psychiatric Association 1980). This suggests that the underlying biological mechanisms are highly patterned and reflect a stereotyped functional disorganization of brain neurophysiology and biochemistry activated during a psychotic reaction. The major contribution of biological psychiatry to our understanding of schizophrenia has been to provide us with remarkable insights into the dysfunctional neurochemical patterns associated with the active phase of schizophrenia.

When remission from the active psychotic state occurs, and it mostly does to some degree nowadays, due largely to neuroleptic treatment, the patient is still highly vulnerable to a multiplicity of environmental events. This is particularly true at the present time as the periods of inpatient stay are extremely brief and the subsequent remissions highly tenuous. Because the released schizophrenic person frequently looks reasonably well put together at the time of release to the community, there is a strong tendency to underestimate vulnerability to relapse and to encourage premature reintegration into social and vocational life. The vulnerability of the postpsychotic state is similar to that of the prepsychotic state, only exaggerated by a factor of 100. To use a crude analogy, if the prepsychotic individual had an unusual sensitivity to sounds at the level of ordinary speech, then in the postpsychotic state even a whisper is exac ruthingly disturbing. Maintenance pharmacotherapy can do much to reduce this vulnerability to environmental stimuli but is not sufficient to forestall relapse in over half of the cases. Once again, there appears to be a special sensitivity to attributes of the intrafamilial environment during this highly vulnerable period. Criticism, emotional overinvolvement, or premature pressures from significant others to resume normal role functions seem to enhance the likelihood of relapse with an active psychotic state. Just how these family attitudes and behaviors increase the vulnerability to the return of the psychotic state is not well understood, but it is increasingly clear that when family intervention programs support and encourage less pressure and a more benign emotional climate, re-
lapse rate can be lowered significantly. Whether multimodal aftercare programs which combine pharmacotherapies and family therapies affect the longer term adaptation of the previously schizophrenic person is not known.

References


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Free single copies of Special Report: Schizophrenia 1980 and Special Report: Schizophrenia 1976 are available to requesters. Both reports summarize recent results of schizophrenia-related research. Topics covered include diagnosis, genetics, biology, psychophysiology, perception and cognition, family studies, and treatment. Although the 1976 edition contains less recent material than the 1980 report, it is more compact and easier to read.

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