Clinical Phenomenology

The ability to advance our knowledge about schizophrenia has been partially handicapped by our inability to define it precisely and consistently. There is no question that schizophrenia is a "real disorder" that produces severe and often persistent disabilities. For a variety of historical and conceptual reasons, however, there has been disagreement among clinicians and investigators as to the best ways to define this disorder. The principal and absolutely fundamental contribution that phenomenology and nosology can make is to identify some of the controversial issues so that their effect on research is recognized and to make a useful group of suggestions concerning these definitional issues. If we are to make any substantial progress in understanding the pathophysiology and etiology of schizophrenia or in developing improved treatments for it, knowing how to describe, define, and recognize it is a necessity.

One major controversy concerns the boundaries of the concept of schizophrenia. Should it be defined narrowly or broadly? In the late 1800's, Kraepelin chose a narrow definition, describing this illness as one with early onset and with progressive deterioration and cognitive impairment ("dementia praecox"). In 1911, Bleuler introduced the term "schizophrenia." He believed that the characteristic feature of schizophrenia was "splitting" or fragmenting of thinking processes in schizophrenia, a symptom that he referred to as "associative loosening." He believed that this abnormality was the distinguishing characteristic of schizophrenia and that certain other features such as affective blunting, ambivalence, and disordered attention were also of great significance. He did not believe that the illness necessarily led to deterioration, but he did think that schizophrenia was a heterogeneous group of disorders, referring to it as the "group of schizophrenias." Bleuler's concept was therefore quite broad. Although early work in schizophrenia tended to follow Kraepelin's definitions, the broad-based Bleulerian concept was widely adopted in research conducted in the 1950's and 1960's.

A further change in thinking came about in the early 1970's when Schneiderian concepts were popularized and some researchers adopted a narrower definition of schizophrenia. The main impetus for the implementation of narrower definitions was a desire to objectify the diagnostic process through the introduction of diagnostic criteria or computerized diagnostic systems. The Bleulerian concepts, while important, were difficult to operationalize and apply reliably. The movement toward narrower definitions culminated in the publication of DSM-III in the United States in 1980. The DSM-III definition is relatively narrow, requiring 6 months of symptoms before a diagnosis of schizophrenia can be made. This narrow definition was chosen to define a "core" group of schizophrenic patients for research and to prevent the overdiagnosis of schizophrenia in everyday clinical practice. The nosologists who developed the definition recognized it as a provisional compromise, a necessary step required until our understanding could be advanced sufficiently to identify causes.

As this historical survey indicates, any review of research in schizophrenia conducted during this century must take these changing...
on the schizophrenic patient, in which both schizotypal and schizoid traits are present. It is recognized that individuals with schizotypal or schizoid traits may show a wide range of behaviors that are similar to those of patients with schizophrenia. The schizotypal patient may exhibit odd or eccentric behaviors, unusual perceptual experiences, and a lack of social skills, but these traits are typically less severe than those found in patients with schizophrenia. In contrast, the schizoid patient may show a lack of social interest, aloofness, and a preference for solitude, but these traits are not accompanied by the same level of overt disorganization and disturbance as seen in schizophrenia.

Biological studies of the schizophrenia spectrum disorders are in their infancy. As noted previously, however, some biological correlates of schizophrenia have been observed in schizotypal patients. Such studies need to be extended.

Far more work needs to be done on the interaction between genetic factors and both organic and psychosocial environmental factors. When schizophrenic patients are compared to patients with schizotypal personality, for example, perinatal complications are more prominent in the patients with core schizophrenia. Other environmental insults have not yet been systematically examined in these two populations. In addition, psychosocial factors that might modify the genetic predisposition to schizophrenia-related disorders, either toward or away from the more severe chronic core schizophrenia, also need to be studied.

Molecular genetics is, of course, an especially promising area for future research. It is also an area where careful clinical evaluation and diagnosis may play a crucial role. Information about pedigrees collected for the purpose of seeking possible genetic markers will require a comprehensive database that lends itself to determining the effect of broad versus narrow definitions on identifying linkage. Since molecular genetic studies are especially likely to require cooperation between individuals working in a variety of centers, it is particularly important to develop evidence-based assessment techniques for such studies. These assessment techniques should not only meet the requirements of good reliability, but they should contain a detailed description of the broad range of clinical symptoms and other information such as age of onset and exposure to environmental risk factors.

Neurotransmitters, Neuroendocrine Systems, and the Selection of Informative Populations

Current Knowledge. The search for neurochemical abnormalities in schizophrenia has been substantially assisted by the development of the dopamine hypothesis and increasing knowledge concerning the mechanism of action of neuroleptic drugs. The dopamine hypothesis postulates that functional hyperactivity of the dopamine system at crucial anatomic locations in the brain is an important mechanism that produces at least some of the symptoms of schizophrenia. This hypothesis is supported by two major lines of evidence: (1) Antipsychotic drugs produce their behavioral effects through dopaminergic blockade; most of the antipsychotic medications currently in use have variable effects on serotonin, D₂ receptors, and D₄ receptors, but the bulk of existing evidence implicates the D₂ receptor in psychotic symptomatology. (2) Psychostimulant drugs with dopamine agonist effects can produce or exacerbate psychotic symptoms of schizophrenia.

The exploration of possible reasons for functional hyperactivity of the dopamine system are not reviewed in detail here, since it is covered more fully in other panel reports. Briefly, one line of research has focused on the study of dopamine metabolites, particularly homovanillic acid (HVA), which can serve as a measure of dopamine neural activity. Several studies have been completed, but they are difficult to interpret because of variability in patient samples, insufficient knowledge about the long-term effects of prior medication, and the scarcity of samples of drug-naïve patients or patients who have been off medications for very long periods of time. Nevertheless, the major thrust of these efforts appears to suggest that the neurochemical abnormality in schizophrenia is neither excessive dopamine production nor failure to metabolize it. The study of post-mortem brains has suggested instead that patients with schizophrenia may have an increase in D₂ receptors on postsynaptic neurons, thereby producing a functional hyperactivity. While this finding has been consistently reported by a number of investigators working in different centers throughout the world, the results of such studies must be interpreted cautiously, because of the possibility that long-term neuroleptic medication may induce postsynaptic receptor proliferation as a consequence of chronic blockade.

The development of in vivo imaging of neuroreceptor systems during the past several years has provided an important contribution to our understanding of the role of dopamine in schizophrenia. The development of techniques for the in vivo imaging of dopamine receptors has allowed researchers to better understand the changes in dopamine receptor density in response to different drugs and treatment regimens. This has been particularly useful in understanding the mechanisms of action of antipsychotic drugs, which typically lead to a decrease in dopamine receptor density. In addition, the development of techniques for the in vivo imaging of other neurotransmitter systems, such as serotonin and norepinephrine, has allowed researchers to better understand the role of these systems in schizophrenia.
understanding of the dopamine system in schizophrenia. Several different research groups have worked out highly sophisticated methods for quantifying numbers of receptors, and two studies concerning D₂ receptor density (Bₐdm) in schizophrenia have been reported during the past year. Unfortunately, the results of these two studies are in conflict. At present, it is not clear whether this conflict is a consequence of differences in patient selection or differences in methodology. The patient sample in which an increased number of D₂ receptors was found tends to be considerably older and more chronically ill than the patients with normal D₂ receptors. Both of these studies were conducted using schizophrenic patients who had never been medicated. These studies highlight both the importance of studying special rare but highly informative populations and the importance of careful phenomelogic description so that differences in findings can be interpreted intelligently.

The use of dopamine agonist probes has been an alternate strategy designed to identify special subpopulations of patients with schizophrenia and to attempt to identify patients particularly vulnerable to subsequent psychotic relapses. This strategy is based on the recognition that amphetamines may produce a psychosis resembling paranoid schizophrenia in a normal person. If this person is given neuroleptic medication, the psychosis abates. Further, dopamine agonist psychostimulants can provoke or exacerbate psychotic symptoms in schizophrenic patients at subpsychotogenic doses. The psychostimulants do not superimpose a drug psychosis on the schizophrenic

mone response is associated with chronicity and clinical deterioration, while exaggerated responses occur in younger patients with florid psychotic symptomatology. This line of thinking is consistent with the suggestion put forward by several investigators that hypodopaminergic activity actually characterizes late stages of the illness or is associated with prominent negative symptoms, while functional hyperactivity is more characteristic of acute forms and associated with positive symptoms.

**Future Needs.** For such neurochemical investigations, the study of special informative groups is especially important. Of highest priority is the study of drug-naïve patients. The long-term effects of neuroleptic drugs on the dopamine system are not known at present, but it is definitely possible that effects could remain for months or even years. Most of the work completed to date has involved patients who have been withdrawn from medications for only a few weeks and who had previously been under treatment for variable amounts of time. Much more careful attention needs to be given to the differential effects of duration of treatment and duration of the withdrawal period in such studies. Unti such information is carefully collected, however, the study of drug-naïve patients in as many centers as possible is crucial. This strategy is important in many types of investigation, but it is particularly imperative in the study of neurochemical systems, since the drugs used to treat schizophrenia act directly on these systems.

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neurochemistry of specific priorities in the brains. The ictal system are still it is effects could reach years. Laid to date, the have medications for which had treatment for. Much needed is the effects of duration and duration in such a manner is never, the in many but it is part of the study of patients. of recent results, results are to interpret because samples often mix patients with acute and chronic duration and with prominent positive or negative symptomatology. Future studies should focus on discrete "purified" subgroups of patients such as first-episode acute patients versus chronic end-stage patients, or groups with clearly defined positive symptoms versus clearly defined negative symptoms. In neurochemical studies conducted to date, clinical description of patients has often lagged behind the laboratory technology.

As techniques for studying neurotransmitter systems with positron emission tomography (PET) continue to evolve, it will also become increasingly important to attempt to understand abnormalities in the dopamine system not only in relation to clinical phenomena but also in relation to specific brain subregions. For example, several reports during the last year have indicated that hyperactivity (either as measured by glucose use or by blood flow using oxygen 15) occurs in subcortical brain regions. These findings provide an interesting complement to earlier reports of hyperfrontality in schizophrenia seen with both glucose use as measured by PET and regional blood flow as measured by the xenon inhalation technique. These findings suggest that a possible imbalance may occur in different functional components of the dopamine system (i.e., frontal projections vs. nigrostriatal or limbic projections), which could produce marked differences in clinical symptoms and in the course of the illness. As this anatomical dissection of the neural circuitry involved in schizophrenia continues, it will become increasingly important to provide detailed cross-sectional and longitudinal descriptions of patients. Ultimately, it will be important to map possible shifts in chemical and metabolic balances in patients over time in relation to changes in clinical phenomenology.

These neurochemical studies require special clinical settings. Since such studies must be done either on drug-naive patients or patients who have been withdrawn from medication for long periods of time, they must be conducted in settings where such patients can be managed with careful clinical supervision and sensitive and compassionate support. The patients themselves and third-party payers cannot be expected to support research endeavors that involve the absence of treatment. In order to support such neurochemical research, the development of special clinical research settings will be required.

Neuropathology and Structural Approaches

Current Knowledge. Since Kraepelin's original description of the disorder, investigators have hypothesized that many schizophrenic symptoms could be explained by some type of brain abnormality. Early work in this area, such as that conducted by members of Kraepelin's own colleagues (including Alzheimer, Nissl, and Brodmann), failed to yield conclusive results, although they diligently sought neuropathological abnormalities in both the frontal and the temporal lobes. More recently, however, there has been a resurgence of interest in neuropathology which has suggested a variety of different types of abnormalities. For example, in a series of post-mortem studies of the basal ganglia and limbic system, a 20 percent decrease in the size of the internal pallidum was noted, as well as a 20-40 percent decrease in the limbic portions of the temporal lobe, including the dentate gyrus, subiculum of the hippocampus, parahippocampal gyrus, and amygdala. The temporolimbic abnormalities have been most consistently reported, with at least four different groups of investigators noticing some type of abnormality in the hippocampus or parahippocampal gyrus. In addition, cytarchitectonic studies have demonstrated reduced numbers of neurons in layers 2, 3, and 4 of the prefrontal cortex, as well as abnormalities in the cingulate gyrus, which are consistent with a developmental abnormality rather than neuronal loss later in life.

These neuropathological findings are important because they point to specific brain regions that could be involved in producing the symptoms of schizophrenia. Limbic substructures, such as the hippocampus, play an important role in encoding and storing memory. Other limbic structures have functional importance for regulating affect and emotional responsiveness, as does the cingulate gyrus and the prefrontal cortex. One persistent problem in post-mortem studies conducted to date has been the difficulty in relating site of abnormality to clinical features of the illness before death. This limitation has unfortunately partially diminished the resolving power of such post-mortem neuropathological studies and highlights the importance of collecting prospectively, if possible, detailed clinical information about those whose brains are donated to post-mortem tissue banks.
In vivo brain-imaging techniques have also been applied to the study of brain structure in schizophrenia. Computer tomography (CT scanning) was the earliest technique to be used, and during the past 10 years many CT studies have been conducted. Abnormalities described included an increased ventricular-brain ratio (VBR), cortical atrophy as measured by enlarged sulci, cerebellar atrophy, and reversed cerebral asymmetry.

By far the most consistent finding has been ventricular enlargement as measured by an increased VBR. This finding has been consistently replicated in a large number of studies conducted throughout the world. Important issues in interpreting these studies include the effects of medication, chronicity, and institutionalization; the selection of control samples; and the prognostic and pathophysiologic significance of ventricular enlargement. Some partial answers to these questions have been provided. Studies examining ventricular size in young first-episode patients have indicated that they show a high rate of ventricular enlargement, suggesting that the finding is probably not a consequence of chronicity, treatment, or institutionalization. Investigators have applied a variety of statistical methods to more chronic patients studied with CT scanning to determine whether confounding factors associated with chronic illness could explain an increase in ventricular size; quite consistently, the analyses have shown little or no relationship between type of treatment, duration of treatment, or effects of institutionalization. When ventricular size is plotted over time in a cohort of schizophrenic patients of varying ages and a group of normal subjects of varying ages, the lines of both groups have parallel slopes; ventricular size increases steadily with age in both samples, but the schizophrenic patients have a larger ventricular size at onset.

Attempts have also been made to correlate ventricular size with clinical picture and response to treatment. There is some suggestion that ventricular enlargement is associated with poor premorbid adjustment, negative symptoms, cognitive impairment, and a poor response to neuroleptic drugs. Much more work needs to be done in this area, however, particularly research using improved clinical definitions.

Future Needs. The thrust of this research has been to suggest that morphological changes occur in a subgroup of schizophrenic patients. Many important questions remain about the significance of these findings.

While structural abnormalities have often been found, either through neuropathological techniques or through in vivo imaging techniques such as CT, they have only been consistently found in a subgroup of patients. For example, the frequency of ventricular enlargement ranges from as low as 5 percent in some studies to as high as 40-50 percent in others. It is never found in all patients. Much more work needs to be done to determine the meaning of this finding and its relationship to genetic and/or environmental risk factors. The twin and high-risk studies described earlier, which applied CT scanning to informative populations such as monozygotic twins discordant for schizophrenia or the children of schizophrenic mothers for whom birth records were available, illustrate especially powerful applications of such imaging techniques to the evaluation of mechanisms. Other examples include longitudinal prospective studies of first-episode patients and evaluation of ill and well members of multiply affected families.

In the present and future, it seems likely that in such structural studies CT scanning will be largely supplanted by the use of magnetic resonance imaging (MRI). MRI has a number of advantages over CT scanning. It does not involve the use of ionizing radiation, provides superb gray/white resolution, and is able to image in multiple planes, including sagittal and coronal in addition to transaxial planes. Thus, it permits the evaluation of a number of important brain regions which cannot be seen readily with CT scanning, such as the hippocampus and amygdala, basal ganglia nuclei, and areas of the prefrontal cortex. Investigators are currently attempting to develop software that will provide semiautomated volumetric assessments. These methodological developments should significantly advance the sensitivity and accuracy of in vivo structural imaging to characterize the neuropathology of schizophrenia.

It is also quite important to supplement the structural techniques with functional or dynamic techniques, including the measurement of regional cerebral blood flow with either cortical probes or single photon emission computed tomography (SPECT), as well as PET. Another area that needs particular attention is the development of in vivo nuclear magnetic resonance (NMR) spectroscopy which can provide a wealth of metabolic information that is not available with any other technique. At least these dynamism used in unimagined never-real confoundings cerebral bloo.

The potential of these techniques is not fully realized, however, since many centers have not acquired adequate imaging equipment and do not have the expertise to interpret their results. The development of standardized protocols for the use of imaging in schizophrenia research is an important step toward improving the quality and comparability of data from different centers.

Medication Issues

Current knowledge of the role of medication in the treatment of schizophrenia is limited, and more research is needed to understand the effects of different antipsychotic medications on brain structure and function.

In conclusion, the use of brain-imaging techniques in the study of schizophrenia has provided valuable insights into the pathophysiology of the disorder. However, many important questions remain unanswered, and further research is needed to fully understand the significance of these findings.
Medication Versus Disorder Issues

Current Knowledge. Treatment with neuroleptic drugs has a confounding effect on the pathophysiology of schizophrenia. This effect may vary depending on the type of variable under investigation. It is not likely that neuroleptics will affect genomic DNA or gross anatomic brain structure. On the other hand, antipsychotic medications can contaminate most physiological, behavioral, and biochemical measures. For example, abnormalities in dopamine transmission (as reflected by dopamine receptor density and affinity) can be obscured or even caused by treatment with neuroleptics. Studies in animals have demonstrated that the administration of antipsychotic medications increases the number of brain dopamine receptors. Medications also influence brain electrical activity and can potentially influence a variety of neurophysiological measures. They affect the extrapyramidal system in particular, producing a Parkinsonian syndrome, thereby affecting the clinical assessment of phenomenology, especially negative symptoms. Of course, antipsychotic drugs are highly effective for diminishing positive symptoms. Thus, studies that attempt to evaluate intercorrelations between clinical and biological variables will be subjected to many confounders when patients are studied on medication.

Investigators have tried to grapple with this problem in a variety of ways. Statistical corrections have often been applied to data to covary effects of treatment. The use of extended washout periods so that patients can be studied while free of medication has been more valuable. These studies are logistically difficult to accomplish and therefore frequently involve relatively small samples. As has already been mentioned, the study of never-medicated patients represents the ideal situation, but such patients are particularly rare. Therefore, samples must necessarily be quite small, and never-medicated patients may be an atypical sample of schizophrenic subjects.

Future Needs. To interpret the effects of neuroleptic medication on these various parameters, we need a series of well-designed drug withdrawal studies that will provide information concerning the relationship between medication, clinical symptoms, blood levels of the drug, and ideally some measure of chemical activity in the brain. Such studies would give us a relatively definitive answer to the following important questions: How long is long enough for drug withdrawal? On which variables do drugs have the greatest effect? What is the relationship between blood level, receptor occupancy, and clinical symptoms? How do these measures correlate with other variables such as brain electrical activity, cerebral perfusion, and other commonly used biological correlates? The selection of the appropriate type of sample for such studies remains a persistent problem. For expensive complex studies that necessarily involve small samples (such as the study of drug-naive patients), two different strategies are possible. One is to use a very narrow definition of schizophrenia that will help purify the sample. Narrow definitions typically rely on specifying chronicity (duration of 6 months or longer). This approach has the advantage of ensuring that the diagnosis is relatively certain, but the disadvantage that informative patients who only recently became ill may be excluded. An alternative strategy, which may be preferable in some instances (e.g., the study of drug-naive patients), is to collect a series of phenomenologically typical schizophrenic patients who do not necessarily have established chronicity and follow them longitudinally to identify those with sufficient chro-
nicty to meet relatively narrow definitions.

In general, a longitudinal approach to studying selected patient groups is highly desirable. Groups that can be particularly informative in determining the effect of medication include young schizophrenic patients (less than 5 years' duration of illness), never-medicated and first-episode patients and adolescent high-risk individuals (e.g., offspring of schizophrenic patients and, perhaps, psychostimulant and hallucinogenic drug abusers). This approach permits investigators to identify patients either before they receive medication or relatively early in the course of treatment. It permits diagnosis to be validated prospectively over time instead of cross-sectionally in a narrow timeframe. It also allows correlations to be made between baseline phenomenological and biological variables, as well as a variety of outcome variables such as treatment response and course of illness.

Since such prospective longitudinal studies can be costly and labor-intensive, they are best performed in patient groups that have the maximum likelihood to yield significant results. Young nonchronic patients have the advantage of having had relatively less treatment exposure and may still be on the linear portion of their evolution of illness curve as compared to more chronic patients who have had longer treatment and whose illness may have "levelled off" and clinically ceased to change.

Gaps in Present Knowledge

A substantial number of gaps in our present knowledge of schizophrenia have already been enumerated under the heading Future Needs in each of the previous sections. In addition, there are a number of other areas that require further exploration.

There are many promising areas of investigation in which abnormalities in schizophrenia have been demonstrated, but which have not been related to clinical heterogeneity in schizophrenia. Examples include SCPM, abnormalities in vestibular functioning, and neurological soft signs. These kinds of abnormalities need to be related to clinical variation both within patients themselves and within their family members (preferably using designs that will permit the identification of spectrum disorders or subclinical phenomena in family members). Using this approach, investigators can generate hypotheses to help "slice up" the schizophrenias into more clinically and biologically homogeneous groups, making pathophysiological and etiological research more fruitful.

Much more work needs to be done on the personality disorders that may be within the schizophrenia spectrum. For example, it is not clear whether both paranoid personality and schizotypal personality bear the same relationship to core schizophrenia. Further, observation of relatives of schizophrenic patients has indicated that these relatives may have numerous peculiarities that are not actually diagnosable as either type of personality disorder, although they do have some important sub syndromal features such as odd ideation or asociality.

As this example indicates, research in schizophrenia must work at multiple levels. Too frequently, conceptualization has been only at the diagnostic level or perhaps at the syndromal level. In fact, investigators must both think and code their data at multiple levels, including diagnoses, syndromes, symptoms, and signs. This is important because our current diagnostic systems are only provisional. We have not yet identified "true" diagnoses which, by definition, represent disorders for which we know the mechanism or cause.

The evaluation of subsyndromal degrees of schizophrenia-like pathology is particularly challenging. Our ability to measure delusions exceeds our grasp of mildly aberrant personal beliefs (e.g., superstitions, beliefs about clairvoyance, peculiar ideas about bodily health). Our assessment of affective blunting and inappropriateness is also much cruder than needed for assessing subclinical deficits. Promising beginnings in this area include the analysis of vocal inflections from recorded voice samples and work on the ability of schizophrenic patients to interpret facial expressions as denoting emotional states. A multifaceted approach using structured interviews and rating scales, self-report questionnaires, special test situations such as facial recognition assessment, and mechanical methods such as voice analysis may be required to cover the full range of relevant phenomena.

Analyses in future studies need to stay closer to original data. The internal coherence of a symptom or assessment picture may afford valuable clues for isolating new syndromes, thereby assisting in evaluating the heterogeneity of schizophrenia. But such dissection is possible only under the following conditions: A wide array of measurements is needed. These must include not only clinical phenomena such and phen relat cogn ess be a dare shoul Al read awa tags are t data prov inex later eses and oth crosh lish addi asse view part Ida sess chiv livin prof chiv mor with case usef ferent whe be d popi vide usef stud resu pati Di hist
such as hallucinations, delusions, and abnormal affective and motor phenomena, but also measures related to cerebral status such as IQ, cognitive performance, and handedness. Social pathology such as anhedonia and asociality should also be assessed, and thorough and standardized neurological examinations should be conducted for all subjects.

All these measures need to be readily retrievable and not done away with at some intermediate stage of data coding. Uncoded data are unanalyzable data. Ideally, such data should be collected so that they provide a long-term repository for information that can be available for later investigations as new hypotheses arise 4-5 years into a project, and that will also be available to other investigators who wish to cross-check hypotheses and establish continuing standardization. In addition to standard techniques of assessment such as structured interviews, several other approaches are particularly useful and promising. Ideally, one should videotape assessment sessions of patients to archive clinical phenomena in a visible living library. Later studies can then profitably reanalyze existing archives, rediagnosing patients in more subtle ways than are possible with structured interviews or even case histories. Such archives are also useful in comparing results in different centers and determining whether differences in results may be due to differences in patient populations. For example, such videotape libraries would be very useful to compare the patients in studies that produce conflicting results in different schizophrenic patient samples.

Detailed records summarizing case histories should also be maintained, however, in addition to videotape libraries and structured interviews. They provide a compact and easily conveyed method for describing patients in greater detail than is obtained through checking and listing symptom criteria.

The intercenter (and not merely intracenter) reliability of measurements needs to be continually assessed. If this is not done, a confusion of tongues results and nonreplications are given greater weight than they deserve, producing unwarranted pessimism. The ready availability of videotape equipment makes such intercenter reliability studies much easier to do.

Specific Recommendations

In addition to the recommendations contained in the body of the Panel Report, the group reached an overall consensus about several major needs that are described below:

- There is a need for improvement in standardization and definition of clinical samples. This need covers a broad range of issues and includes a number of specific recommendations.

1. There is a continuing need for improved clinical assessment techniques. These may vary, depending on the goal of the study, but areas of need include comprehensive evaluation of patients at index admission or assessment, sensitive techniques to assess change in treatment studies, and methods to map the longitudinal course of the illness. At the moment, acceptable instruments are available for cross-sectional evaluation and possibly for past history, but acceptable instruments are not available to map longitudinal course at regular intervals over time.

The instruments currently used to assess change in treatment studies should be updated and more specifically targeted to schizophrenia.

2. There is a need for a consensus as to the "bare minimum" which should appear in the published description of any patient sample and in any clinical data base that is used to study schizophrenic patients in research settings. We do not make specific recommendations as to this "bare minimum," but it might be appropriate to convene a consensus conference to undertake this task. It is quite clear that the bare minimum should not be too bare. Studies that invest heavily in the collection of biological or outcome measures are penny wise and pound foolish if they scrimp on the phenomenological description of patients. This is particularly important because we do not know the definition or boundaries of schizophrenia. The process of understanding the definition and boundaries must resonate back and forth between good phenomenology and good biological measures.

3. There is a need to collect archival resources and to have multiple groups study the same patients. Whenever possible, the same patient populations should be studied by more than one research group. This will optimize the use of limited patient resources and also address issues of replication in a timely fashion. More objective measures (such as audio and video recording with frequency analysis) need to be developed for the recording and archiving of clinical data which can then be analyzed by more than one research group.

4. There is a need to identify and designate research facilities that are well equipped to train other investi-
gators in clinical assessment and phenomenology. Such training centers could be used to raise the general level of sophistication concerning the difficult issues involved in phenomenology and nosology, as well as to create improved consistency in definition and assessment across a variety of research sites in the United States. This is essential if we are to be able to compare results from various centers and to understand why replications do or do not occur.

- Studies of schizophrenia should include both cross-sectional and longitudinal components as far as this is possible. They also should include both clinical (including medication data) and biological measures. Schizophrenic patients will need to be compared to both normal controls and patients with other non-schizophrenic neuropsychiatric disorders with and without similar medication usage. The assessment of both clinical and biological parameters in combined cross-sectional and longitudinal studies should increase the scientific power of the studies and make the studies more economical in long term.

- The various definitional and boundary issues described in this report have not yet been resolved. The best way to resolve them is through careful research. Therefore, there should be no premature closure on definitional or boundary issues. Some studies may require broad definitions (e.g., epidemiological studies and possibly family studies) while other studies may require relatively narrow definitions (e.g., expensive biological studies on samples that are difficult to collect).

- Increasingly, studies should tailor their study of populations and their definitions of schizophrenia to specific hypotheses and questions. There is no “best” definition of schizophrenia, but there may be a “best” sample to address a particular question. For example, drug-naïve patients are the ideal population to study abnormalities in neurotransmitter systems. Multiplex families and extended pedigrees are the best population to explore issues in molecular genetics. Other unique populations are also valuable—e.g., twins and high-risk samples.

- There is a need for continuing basic research in both phenomenology and nosology. Research in phenomenology at a descriptive level is useful, but it is also important to try to tie phenomenology to objective measures. Additionally, research instruments need to be developed that empirically and accurately assess some of the abnormal clinical features of schizophrenia such as abnormal thought processes, affect, and social interactions.

- It is also very important to understand phenomenology better by investing in research in normal individuals and animals. Since the study of the phenomenology of mental illness looks at abnormal behavior, cognition, and emotional response, we need careful definitions of the normal if we are to identify and understand the abnormal. For example, greater knowledge about auditory perceptual systems may improve our understanding of the mechanisms that produce abnormal perceptions such as auditory hallucinations. Improved understandings of normal brain structure and function will permit us to recognize and define neural abnormalities in schizophrenia. Mapping normal patterns of neural circuitry or neurochemical systems will assist us in identifying neurochemical aberrations in schizophrenia.

- Ultimately, research in nosology and phenomenology must integrate neurobiology. There is little point in studying phenomenology alone, despite the need for good basic research in phenomenology. The ultimate goal of clinical definition is to understand mechanisms and causes. In the case of schizophrenia, a major portion of the etiology is clearly neural. As this report has indicated, many areas are promising. These include research to explore relationships between clinical symptoms and brain structure and function (neuroimaging and in vivo neurochemical studies), work using molecular genetics and other emerging approaches and technologies, and growth of special resource facilities such as brain banks. In such studies, the very best phenomenology must be joined to the very best neurobiology.

- To permit these efforts to unite phenomenology and neurobiology, investment in research infrastructure in psychiatry is necessary. Clinical research facilities that will permit the study of drug-naïve and never-medicated patients are needed. Post-mortem tissue banks must be assembled to study the neuropathology of schizophrenia. DNA banks are needed for molecular genetic studies. In some instances, expensive technological equipment must be purchased. The various in vivo brain-imaging techniques are an important example. At present, many investigators have difficulty in obtaining access to MRI, NMR spectroscopy, SPECT, or PET equipment. Since these imaging techniques have great resolving power for interrelating phenomenology and neurobiology, as well as for dissecing clinical searching for chemical mechanisms improving a treatment, supposing centers either on psychiatric or those suffering.

- To achieve clinical research increased application between b and pharmacological. One of these disciplines is about the need for another so that it in neuroscience during the 198 implemented i psychiatry. Th Mental Health vening power opportunities and it should be important through the d science clinic to the st Ultimately, th goal should be on so strong clinical phenom ed in single ir study of schiz by a sophictic "clinical neurals who com and commit with a strong neuroscience.

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secting clinical heterogeneity, searching for metabolic and neurochemical mechanisms, and developing improved approaches to treatment, support is needed for imaging centers emphasizing research on psychiatric patients, particularly those suffering from schizophrenia.

- To achieve the kind of integrative clinical research that is needed, increased opportunities for interaction between basic neurobiologists and phenomenologists must be encouraged. Over the short term, each of these disciplines must learn more about the needs and goals of the other so that the rich developments in neuroscience that are emerging during the 1980’s and 1990’s can be implemented in clinical research in psychiatry. The National Institute of Mental Health should use its convening power to facilitate such opportunities whenever possible, and it should continue to emphasize the importance of this interaction through the development of neuroscience clinical research centers targeted to the study of schizophrenia. Ultimately, the Institute’s long-term goal should be to make the interaction so strong that neurobiology and clinical phenomenology are integrated in single individuals and the study of schizophrenia is pursued by a sophisticated new generation of “clinical neurobiologists”—individuals who combine clinical excellence and commitment to patient care with a strong grounding in basic neuroscience.

**Suggested Readings**


A Comment on Andreasen and Grove

While preparing our own research in the field of thought disorder in schizophrenic patients, we scrutinized the article "Thought, Language, and Communication in Schizophrenia: Diagnosis and Prognosis" by Nancy C. Andreasen and William M. Grove, which was published in the Schizophrenia Bulletin (12:348-359, 1986). A verification of the statistics revealed some relevant inconsistencies which we find worthwhile to report.

As we understand it, the research undertaken by Andreasen and Grove tried to demonstrate the usefulness of the Scale for the Assessment of Thought, Language, and Communication (TLC) (Andreasen 1978) in differentiating between hebephrenic, manic, schizoaffective, and paranoid patients. The claim is that the TLC establishes a consistent and specific pattern of formal thought disorder in each of those clinical diagnostic groups. These profiles are claimed to be specific enough to predict group identification reliably.

In table 2 (p. 351), frequencies of thought, language, and communication abnormalities are compared among groups. It is stated explicitly in a footnote on the same page that frequencies are compared between patient groups only, with normals being excluded. This makes sense, for the normals show, as can be readily expected, a relative paucity of thought disorder when compared to the patient groups. The results of the $\chi^2$ calculation are presented, and the authors conclude:

The patient groups differ significantly from one another on nearly all types of language abnormality that occur with any frequency. [p. 351]

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definitions into account. Unfortunately, several decades ago, investigators did not realize how important it was to specify how they identified a particular cohort of patients as schizophrastic. Consequently, interpreting and generalizing research findings of the past has been difficult.

In this report, we attempt to review our collective experience in research and to make concrete recommendations and suggestions about the way that research in schizophrenia can advance in the future. In this context, it is important to keep the basic purposes of the study of phenomenology and nosology in mind. The ultimate goal of any system for diagnosis or clinical description is to provide insights into the etiology and pathophysiology of a given disorder. With a clear understanding of etiology and pathophysiology, effective therapy and ultimately prevention can take place. However, before meaningful insights can be acquired, well-defined homogenous populations of the disorder need to be identified for study. This is a particular problem for the study of schizophrenia because the diagnosis is made on the basis of clinical findings that are not unique to schizophrenia. Taking the course of the illness into consideration can increase the diagnostic accuracy, but difficulties still remain. Considering biological as well as clinical measures in combined cross-sectional and longitudinal studies should enhance diagnostic accuracy even further.

Schizophrenia appears to encompass a spectrum of neuropsychiatric disorders with a spectrum of clinical phenotypes. Within the clinical spectrum are clusters of phenotypes that can be identified for more focused study. The causes of schizophrenia are presumably due to a number of differing etiologies: some purely genetic, some purely acquired or "environmental," with most cases of schizophrenia probably due to a combination of genetic and acquired etiologies. These different etiologies presumably operate through a number of neuro-chemical and psychobiological mechanisms to provide the resulting clinical spectrum of the disorder (figure 1).

Figure 1. Pathogenesis and spectrum of schizophrenia

![Diagram showing genetic background, environmental stressors, neuro-biological, and psychobiological mechanisms leading to the clinical spectrum of schizophrenia.](image)
The Authors Reply

We would like to thank Drs. Szor and Melijson and Ms. Melijson for pointing out an inconsistency between the footnote on Table 2 and the statistics reported therein (Andreasen and Grove 1986). The authors are indeed correct that the $\chi^2$ values given in the table pertain to comparisons with the group of normals included, rather than excluded as the footnote indicates. (For what it is worth, this represents a copy editing error and not a computational one. This mistake eluded both authors and an extraordinarily meticulous secretary!)

Where the authors of the letter go astray is in their assumption about the goals of the study. The goals of the study were numerous, but they did not include the one attributed to us. We did not intend to use the Scale for the Assessment of Thought, Language, and Communication (TLC) to classify patients as finely as the commentators indicate. We planned to compare the schizoaffective, paranoid, hebephrenic, and manic patients on TLC ratings and on other measures as well, including psycholinguistic tasks involving sentence comprehension (syntax and semantics) and discourse cohesion. These results have been reported elsewhere. In the Bulletin article, we simply intended to demonstrate a replication of previous findings about the diagnostic specificity of TLC abnormalities at the level of major diagnostic groupings: mania versus schizophrenia. This is the sort of analysis that was presented in the original Archives of General Psychiatry articles (Andreasen 1979a, 1979b) reporting on the TLC, and we wish to document that the discriminant function we used in that study was very similar to the optimal discriminant function estimated in this study for distinguishing manic patients from schizophrenic patients. The reader can easily satisfy himself that the Bulletin article does not contain any reference to classifying patients as to, for example, hebephrenic versus paranoid on the basis of TLC ratings. Since we did not intend to use the TLC in this way, we were neither particularly surprised nor chagrined to discover that it could not be so used with high confidence. In contrast, patients can be sorted into mania versus schizophrenia based on their TLC ratings with reasonable accuracy. Table 2 demonstrates two different points. It shows that the various patient groups do differ on high-frequency TLC abnormalities. The table also replicates the original TLC study finding that such abnormalities as derailments, which have been hitherto supposed to be specific to schizophrenia, are seen as commonly in mania.

We do not think that our copy editing error, while most unfortunate, seriously challenges the validity of the conclusions we, in fact, drew from the study, namely that previous work using the TLC to classify patients into manic versus schizophrenic groups using discriminant analysis was rather closely replicated in this second study.

References


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Unfortunately, this statement is not correct (see Table 1). It is true only when normals are included (in contradiction to the above statement).

Andreasen and Grove's (1986) $\chi^2$ values are precisely the ones corresponding to a $5 \times 2$ contingency table with the two attributes being type of individual (normal, hebephrenic, manic, schizoaffective, paranoid) and score (up to 1, above 1).

When the normals are excluded (as Andreasen and Grove reported doing), and a $4 \times 2$ contingency table is built to test for differences in score value between the four patient groups, significance is drastically reduced (see our calculation in Table 1).

There are very few TLC abnormalities on which the four patient groups show significant differences, and the global rating differences are not significant. In our view, this mistake puts in doubt the conclusions of the article.
independent sample. We hope that this response clarifies the relationship of table 2 to our conclusion.

References


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Audio Tapes on Schizophrenia Available

Guilford Publications announces DSM-III Personality Disorders: Diagnosis and Treatment, a diagnostic and treatment guideline by BMA Audio Cassettes. The guide was developed to help practitioners improve their skills with the diagnosis and treatment of personality disorders.

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includes a current section that describes cross-sectional phenomenology, as well as a section that records a broad range of symptoms that occurred in the past. It is organized to permit diagnoses to be made using the RDC. The SADS is a highly reliable, widely used standardized instrument that has proved very valuable in the study of schizophrenia; its major limitation is that its coverage of some symptoms of schizophrenia is relatively incomplete, particularly negative symptoms. With the development of DSM-III, investigators felt there was a need to have a structured interview with broader symptomatic coverage that would permit investigators to inquire about all the symptoms that are included in the DSM-III criteria. Several additional interviews have been developed to meet this need. One is the Structured Clinical Interview for DSM-III (SCID) and a second is the Comprehensive Assessment of Symptoms and History (CASH). The former is somewhat briefer and has less extensive symptom coverage, while the latter is more time-consuming but also provides a broader informational data base.

Although the available structured interviews vary in their psychometric properties, all four instruments certainly meet the minimum criterion of good interrater reliability. Several have been extensively studied to evaluate the effects of collecting information from multiple sources and multiple informants, the validity of retrospective recall, and other important aspects of interviewing that can affect validity in addition to reliability. Consequently, at present investigators who wish to conduct research in schizophrenia have a strong range of choices available to them when they proceed to select instrumentation for clinical description and diagnosis.

The third major step during the past several decades has been the development of rating scales to assess symptoms more briefly and to measure changes over time. Instrument design for clinical description must meet a broad range of needs. These include the need to make a diagnosis, the need to describe current and past symptoms comprehensively, and the need to make brief daily or weekly assessments in a repeated measures design. The latter need is particularly important for studies designed to assess response to treatment. The Brief Psychiatric Rating Scale (BPRS) was the earliest scale to enjoy wide use in such research, and it remains an important clinical standard. It has been supplemented by a number of additional instruments that increase coverage and provide more detailed description, such as the Scale for the Assessment of Thought, Language, and Communication; the Scale for the Assessment of Negative Symptoms (SANS) and its complementary scale, the Scale for the Assessment of Positive Symptoms (SAPS); the Abnormal Involuntary Movements Scale (AIMS); and the Global Assessment Scale (GAS). The psychometric stability of all these scales has also been well documented.

A fourth important step has been the development of scales to assess mild or "spectrum" forms of schizophrenia. Interest in such scales has grown particularly during the past 5-10 years as investigators have become increasingly concerned that a highly restrictive or narrow definition may not be the most powerful one to use in some forms of research (e.g., genetic and family studies).

Some of the more recent structured interviews, such as the SCID or the CASH, contain sections that assess the spectrum disorders in detail. In addition, several free-standing interviews, such as the Schedule for Interviewing Borderlines (SIB), have been developed. An interview has also been developed to assess a broad range of personality disorders, including paranoid, schizoid, and schizotypal: the Structured Interview for DSM-III Personality Disorders (SIDP).

Future Needs. The development of these various instruments and scales represents a substantial body of work in the area of phenomenology and diagnosis during the past several decades. It has provided the psychiatric community with a very sound base on which to build further research. Nevertheless, a number of important future needs remain. As subsequent sections of this report indicate in more detail, future work in schizophrenia will move into new areas that will require additional clinical instrumentation.

One clear future need is more careful longitudinal and prospective studies, particularly of informative patient populations such as first-episode patients, patients early in the illness, or patients who have never been medicated. As yet, no long-term prospective study that employs the type of standardized instrumentation described above to identify index cases has been completed. We need to know a great deal more about the course and outcome of schizophrenia to plan treatment, to advise families about prognosis, and to make long-term public policy plans. We need rigorous scientific studies that will
it structured SCID or the way that assess in detail. In the World Mental Health Study (WMHS), have reviewed the assessments of psychiatric diagnosis, schizophrenia, and personality disorders. The development of its and scales body of knowledge suggests severe problems in many cases, a need for more comprehensive assessment, and a need for longitudinal follow-up. Specific instruments must be developed for the collection of information at regular standardized intervals (e.g., 6-month intervals). Some preliminary work has been done in this area, but considerably more needs to be done. In particular, the reliability and validity of such longitudinal information must be carefully assessed.

We also need to determine the accuracy of symptomatic and diagnostic information that is collected cross-sectionally but attempts to evaluate clinical history retrospectively. This type of clinical evaluation has formed the basis for most epidemiological research, which depends on a single contact with an individual who describes his past psychiatric history to an interviewer who is “blind” (i.e., makes the diagnosis without any prior information to bias his judgment). Patients with schizophrenia may have difficulty in recalling their past symptoms and course. It seems likely that the best way to make a definitive diagnosis of schizophrenia and schizophrenia spectrum disorders is to obtain as much information as possible from a wide variety of sources, although this is much more difficult and time consuming. The relative value of these different strategies must be assessed, as well as the ability of patients to recall past symptoms. This methodological work will become increasingly important as more and more effort is put into collecting large pedigrees that contain many members likely to be either mildly ill or well, such as occurs when extended pedigrees are collected for molecular genetic studies. For these studies, we need strong lifetime diagnostic instruments, as well as instruments targeted to collecting screening information through the family history method. The Family History Research Diagnostic Criteria (FHRDC) have good reliability and high sensitivity and specificity for core schizophrenia but are considered weaker for the evaluation of milder spectrum disorders. Another instrument that is not as widely known was developed at the New York State Psychiatric Institute. This family informant schedule generates DSM-III diagnoses with questions to be asked for each diagnosis and specific criteria for “probable” and “certain” within each diagnostic category.

As such studies of samples that may contain some mild “subclinical cases” continue, there will be an increasing need for subtle measures of psychopathology. This will require exploration in several directions. One approach has been the development of subjective rating scales. Examples of this type of scale that have already proved useful include the Scale for Physical Anhedonia, the Scale for Perceptual Aberrations and Psychotic-like Phenomena, and the Scale for Social Anhedonia. To date, these have been used to detect mild symptomatology in populations of college students, and they are currently being applied in several family and genetic studies. While the predictive validity of these scales still needs considerable work, they may potentially be useful as sensitive measures of clinical phenomena that might otherwise be ignored in clinical interviews or direct observation.

Yet another area of future need is for laboratory-based microanalyses of behavior that may prove useful in solving some of the problems inherent in studying milder forms of illness. Some work in this area has already been completed. One example involves the use of automated assessment of the acoustic properties of speech to develop an objective measure of affective blunting. It has been shown that patients who are rated clinically as having affective blunting tend to show a decrease in the frequency and amplitude of their intonational patterns. Patterns of hesitation in the patient’s speech or possible associations between subvocal speech and electromyographic recordings of patients with auditory hallucinations are other possible avenues of investigation. The development of such objective empirical measures is relatively labor-intensive, but it is also potentially quite useful in providing an objective physiological validator of clinically observed phenomenology. It may ultimately lead to increased understanding between clinical phenomena and basic biological processes.

A final area into which research is likely to advance is the development of post-mortem tissue banks. Work with post-mortem samples in the past has been seriously handicapped by a lack of appropriate clinical information. As prospective efforts are organized to collect post-mortem brains, it will be very important to develop an agreed-upon clinical descriptive base for such tissue banks. Since this data base will collate information from living relatives, hospital records, and other
sources, it provides a major instrumentational challenge.

Specific Symptoms Versus Characteristic Symptoms

Current Knowledge. When Kraepelin originally described the syndrome of dementia praecox, he characterized it by a broad range of symptoms. Bleuler, who gave us the term "schizophrenia," modified the comprehensive clinical description provided by Kraepelin and suggested that some symptoms were specific to schizophrenia and pathognomonic of it. Bleuler's influence on the concept of schizophrenia was pervasive for many years, leading investigators to believe that characteristic symptoms of schizophrenia could be identified that would occur in this disease alone.

Bleuler suggested that the pathognomonic symptom of schizophrenia was thought disorder, which he described as "associative loosening." Many years of research have been devoted to attempting to develop highly specific methods for assessing thought disorder, but when these attempts were pursued carefully, they usually led to the conclusion that thought disorder (defined either as disorganized speech or as difficulty in organizing concepts) might also occur in other disorders such as mania, depression, or dementia. A type of thinking disturbance highly specific to schizophrenia has not been identified.

Other indicators of schizophrenia include psychotic symptoms such as hallucinations and delusions. However, patients with other disorders such as mania or depression may also manifest these symptoms during an acute phase of illness, although psychotic symptoms do tend to resolve as the mood disorder episode itself resolves. Schneider's first-rank symptoms, specific types of delusions and hallucinations thought for a time to be specific to schizophrenia, have also been found to occur in other disorders. Likewise, negative symptoms such as blunted affect or poverty of speech are quite common in other disorders such as depression. It seems clear at present that symptoms unique to schizophrenia have not been identified. No single symptom can be considered pathognomonic of this disorder. Rather, it is characterized by a polythetic cluster of symptoms, usually expressed in a particular course or pattern.

Since schizophrenia is a perplexing disease characterized by multiple symptoms of very different types, the best clinical descriptions of schizophrenia and the best research data bases must be comprehensive. They must give major weight to the very broad range of symptoms that are carefully and reliably defined. This is the best strategy as long as we must resolve major issues such as the boundaries of the concept, delimitation from other disorders, and the evaluation of a variety of possible mechanisms and etiologies.

Many of the diagnostic criteria and structured interviews currently available give a strong emphasis to psychotic symptoms such as delusions or hallucinations, also sometimes referred to as positive symptoms. An emphasis on the importance of positive symptoms was a natural and logical strategy at a time when psychiatrists were struggling to achieve objective and reliable descriptions that could be widely used in clinical and research settings. Positive symptoms such as delusions and hallucinations are striking and usually clearly present or absent.

Unfortunately, however, for a time a strong emphasis on positive symptoms led to a de-emphasis on the importance of negative or deficit symptoms. The reemergence of an interest in negative symptoms has been an important step forward during the past few years. While positive symptoms represent an exaggeration or distortion of normal function (i.e., hearing voices when they are not there), negative symptoms represent a diminution or loss of normal function. Negative symptoms include affective blunting (loss of the ability to express emotions fluently), alogia (impoverished nonfluent speech), avolition (loss of drive), anhedonia (loss of the ability to feel emotional attachment or experience pleasure), and attentional impairment. These negative symptoms account for a great deal of the emotional and social morbidity of schizophrenia, since they lead to social isolation and withdrawal, difficulty in holding a job or remaining in school, and impaired ability to relate to others.

The distinction between positive and negative symptoms has been useful both as a way of organizing and simplifying clinical thinking, and as a way of beginning to explore the underlying mechanisms behind symptoms. One widely discussed hypothesis during recent years has been the "two-syndrome hypothesis" of schizophrenia. This hypothesis suggested that there are two main subtypes of schizophrenia. Type 1 or positive schizophrenia was characterized by good premorbid adjustment, acute onset, prominent positive symptoms, a good response to and hyperdexamethasone. Type 2 was premorbid with prominent cognitive and brain abnormal neurochemical manifested and a ment. It thus not dichotomy, hypothetisson-simplificaticn generate su negative symptoms type of species. Can positively hyperdexamethasone brain structures suggest an evolution to a poorer one. These all are still in unresolved issues.

Future Need is the correct character. The number of definitive negative symptoms should continue to be used in understanding their relationship to symptoms, such as delusions and hallucinations, and the way in which beginning to explore the underlying mechanisms behind symptoms. One widely discussed hypothesis during recent years has been the "two-syndrome hypothesis" of schizophrenia. This hypothesis suggested that there are two main subtypes of schizophrenia. Type 1 or positive schizophrenia was characterized by good premorbid adjustment, acute onset, prominent positive symptoms, a good response to and hyperdexamethasone. Type 2 was premorbid with prominent cognitive and brain abnormal neurochemical manifested and a ment. It thus not dichotomy, hypothetisson-simplificaticn generate su negative symptoms type of species. Can positively hyperdexamethasone brain structures suggest an evolution to a poorer one. These all are still in unresolved issues.
response to neuroleptic treatment, and hyperdopaminergic transmission. Type 2, or the negative syndrome, was characterized by poor premorbid adjustment, insidious onset, prominent negative symptoms, cognitive impairment, structural brain abnormalities (as opposed to neurochemical abnormalities) as manifested by ventricular enlargement, and a poor response to treatment. It now seems clear that this dichotomy, while heuristic and hypothesis-generating, was an oversimplification. Its value has been to generate such questions as: Are negative symptoms due to some type of specific neural mechanism? Can positive symptoms be related to hyperdopaminergic activity in specific brain regions such as limbic structures? Do negative symptoms suggest a more irreversible course or a poorer response to treatment? These all represent questions that are still in need of an answer.

**Future Needs.** Future research on the characteristic symptoms of schizophrenia should focus on a number of different areas. One area is the definition and significance of negative symptoms. These efforts should continue to focus on the best way to identify them, to determine their relationship to positive symptoms, and to identify their longitudinal course. Confounding variables, such as the tendency of neuroleptic medication to produce akinesia or the effects of institutionalization or psychotic symptoms themselves, must be disentangled in the study of negative symptoms so that we can determine important issues such as prognostic significance, response to treatment, and underlying mechanisms. The relationship between negative symptoms and the deficit syndrome (an enduring form of negative symptoms) must be explored to isolate primary from secondary negative symptoms and to clarify the many physiological processes that can lead to the final common pathway of negative symptoms.

Isolating a relatively pure subgroup of patients with primary negative symptoms, which may perhaps be done at this point by identifying patients with persistent negative symptoms and the absence of positive symptoms, is probably the best strategy at present. Once such a set of patients has been identified, the underlying neural mechanisms should be explored, particularly with techniques that permit direct examination of the central nervous system such as in vivo brain imaging.

Another clinical issue in need of further exploration is the response of negative symptoms to treatment. It is sometimes assumed that negative symptoms, whenever present, will not improve with treatment. This belief is potentially dangerous since it could lead to therapeutic nihilism. To address this issue, a series of well-designed treatment studies using careful definitions and standard neuroleptic therapy should be undertaken. In addition, a search for alternate treatments that may be more powerful or more specific should be initiated, whether they be new classes of neuroleptic drugs or tactics involving social rehabilitation.

In addition to controlled treatment studies, naturalistic prospective studies of patients identified relatively early in the illness are also needed to document the course of both positive and negative symptoms over time.

Finally, investigators must also continue to pursue the search for the mechanisms that are responsible for the various symptoms of mental illness. For this work, the study of both normal individuals and animal models is important and fundamental. For example, we need to understand the mechanisms that govern normal auditory perception and encoding of auditory information in long-term memory stores to develop neural models that might explain the production of auditory hallucinations. As is discussed in more detail below, the development of techniques such as brain imaging is particularly useful in this pursuit, since they permit in vivo evaluation of brain function in normal individuals through the use of cognitive challenges and permit investigators to determine if these functions are abnormal in patients suffering from schizophrenia. Other strategies involve the use of physiological measures such as electroencephalographic (EEG) techniques or smooth pursuit eye movements.

**Biological Subtyping of Schizophrenia**

**Current Knowledge.** The study of phenomenology and nosology is not an end in itself. The primary goal of nosology is to identify a method for classifying illnesses that subdivides them on the basis of pathophysiological mechanisms and ultimately etiology. This means that we ultimately seek a nosology of schizophrenia that will be based on neurochemical, neuropathological, genetic, and environmental mechanisms.

Current nosologies are based primarily on phenomenology—that is, the cross-sectional clinical picture
of the illness and its evolution over time. Our nosologies tend to subdivide schizophrenia into acute and chronic, disorganized and paranoid, and more recently positive and negative subtypes. Phenomenology is a reasonable place to begin, particularly when powerful biological measures are not available. It will always remain an important foundation for nosology, even a biologically based nosology, since a clinical discipline such as medicine usually seeks to understand biological subtypes in terms of clinical correlates.

The most likely working hypothesis concerning schizophrenia is that it is not a single illness produced by a single pathophysiological or etiological mechanism, or even by a single clear clustering of mechanisms, but rather a heterogeneous group of disorders that share some clinical characteristics in common but are etiologically diverse. One model that we can borrow in clarifying the problem of identifying etiological subtypes is the example of mental retardation. Mental retardation is a syndrome characterized by impaired intellectual functioning beginning relatively early in life. We now know that some types of mental retardation, such as phenylketonuria (PKU), are due to an abnormal gene that produces an inborn error of metabolism. Yet some disorders that are “genetically” caused, such as trisomy-21, are not explicable on the basis of classic Mendelian patterns of transmission (but are instead influenced by environmental risk factors such as increased maternal age). Some forms of mental retardation, such as lead encephalopathies or cerebral palsy accompanied by mental retardation, are due to a very prominent environmental component. Further, the mechanisms producing the symptoms of mental retardation range from neurochemical and metabolic to structural, and they can be either irreversible or reversible if diagnosis is achieved at an early stage.

Parkinson's disease provides a similar model that perhaps brings us even closer to an illness like schizophrenia. Patients with Parkinson's disease have a very similar phenomenology, with variable amounts of tremor, rigidity, akinesia, affective blunting, and cognitive impairment. This syndrome is produced by a single mechanism, neuronal loss of the cell bodies of dopamine-producing neurons in the substantia nigra, and we therefore know that the mechanism producing the Parkinsonian syndrome is a functional hypofunction in the dopamine system. Substantial clinical improvement of symptoms is produced if this dysfunctional system receives exogenous supplements of dopamine in the form of l-dopa. Thus, Parkinson's disease represents a clear clinical syndrome with a single recognized pathophysiological mechanism. Yet we know that the etiology of Parkinson's disease is heterogeneous. Some people have developed this syndrome as a consequence of having encephalitis during major epidemics of influenza. Others, as in the case of Parkinsonian complex of Guam, have been exposed to a relatively isolated environmental agent. Yet others develop Parkinson's disease on a familial and hereditary basis. As we grow to understand more about the various biological mechanisms that produce the variable symptoms of schizophrenia, we may discover that a variety of different etiological agents are producing this syndrome by acting on crucial brain regions such as the frontal lobes or limbic system.

Other models are, of course, possible. Many medical illnesses, particularly those affecting the central nervous system (CNS), have a variable clinical picture from time to time, depending primarily on the brain region involved. Multiple sclerosis (MS) and syphilis are both examples. In these cases, although the symptoms and course are variable, the illness is single rather than heterogeneous. The phenomenology suggests multiple illnesses, when this is in fact not the case. The variable symptoms in schizophrenia could, as is the case with MS, reflect CNS lesions that wax and wane over time.

This review of various possible models for biological subtyping, which indicates that there are many areas of uncertainty and ambiguity, should not be taken to indicate that we have failed to make substantial progress in our understanding of schizophrenia during recent decades. As subsequent sections of this panel report indicate, and as other panel reports also demonstrate, major achievements have already occurred and improved our understanding of the interplay of neurobiological, environmental, and genetic factors in schizophrenia.

Genetic studies, such as those of twins or adopted offspring, have indicated that genetic factors clearly operate in producing some cases of schizophrenia. Research combining the study of twins with the use of brain-imaging techniques has suggested that environmental factors, such as perinatal complications, may interact with an underlying genetic substrate to produce the schizophrenia syndrome in vulnerable indiv

Future directions nosology must prepare itself for descriptions that are more specific and are no longer to be considered as "schizophrenia.

Since we are only just beginning to comprehend the variety of factors involved, the importance of nosology cannot be underestimated. The appropriate approach to the problem is:
individuals, while those who are spared these environmental insults are also spared from having the illness. The examination of ventricular enlargement, as assessed by computed tomography in high-risk individuals who have also been evaluated prospectively for early environmental insults such as birth injury, has led to similar conclusions. Careful exploration of the dopamine hypothesis has made it clear that abnormalities in this neurotransmitter system may explain certain symptoms of schizophrenia. Imaging and neuropathological studies have focused increasingly on specific brain regions such as the hippocampus or the prefrontal cortex and attempted to examine the interaction between affected brain regions and clinical picture. All of this work provides a firm foundation for future initiatives that attempt to identify biological subtypes of schizophrenia.

**Future Needs.** Future efforts should continue to explore the various nosological and mechanistic models described above, attempting to combine careful phenomenological description of samples with intelligently selected biological correlates. Since we are not certain which of the various nosological models actually applies to schizophrenia, we must maintain an open mind and be prepared to explore a variety of hypotheses. In a practical sense, this means that while the possibility that schizophrenia is a single illness must be entertained, biological heterogeneity is more likely, and we should attempt to address this problem in future research.

Two strategies for dealing with this complex task are probably appropriate. On the one hand, relatively small, well-designed, hypothesis-driven studies of single biological mechanisms are highly appropriate. Examples include molecular genetic studies of single large multigeneration pedigrees densely affected with schizophrenia and related psychoses which might assist us in identifying a form of schizophrenia analogous to PKU. Another example would be in vivo neurotransmitter studies to examine dopaminergic abnormalities in young never-medicated patients with classic dementia praecox phenomenology who are then followed at regular intervals for a period of years. Small, elegantly designed, hypothesis-driven studies concerning specific subtypes must be complemented, however, with relatively large sample studies that combine comprehensive clinical description with multifaceted biological descriptions. "Biological subtyping" in which a single biological correlate is examined in relationship to a minimally described phenomenological base is not likely to be very useful. Of course, multifaceted large sample studies must also be informed by multiple hypotheses, or they are likely to produce large data sets that are uninterpretable due to problems of statistical analysis.

**Conceptual Boundaries and Genetic Approaches**

**Current Knowledge.** The boundaries of the schizophrenia spectrum have been another fundamental problem in schizophrenia research. Not only must we determine whether this disorder is in fact a heterogeneous group of subtypes, but we must determine how broad this range of subtypes actually is. Some definitions of schizophrenia have been relatively narrow, including only patients with severe longstanding incapacity. Since Fleuler introduced the concept of the “group of schizophrenias,” however, most investigators have worked from a broader concept and included patients who combine psychotic features with affective features, as well
as patients with mild nonpsychotic disorders characterized predominantly by eccentric behavior and a variety of negative symptoms.

Genetic and family studies have provided one useful tool for determining the breadth of the schizophrenia spectrum. Although the results of such studies are not conclusive, they tend to suggest that the concept of schizophrenia should be relatively broad and should include a spectrum of disorders.

Family studies were among the earliest investigations of genetic factors in schizophrenia. These studies have consistently indicated that the relatives of schizophrenic patients have a higher risk for schizophrenia than the approximately 1 percent observed in the general population. In addition to documenting that schizophrenia has a genetic component, family studies have also been used to explore the boundaries of the schizophrenia spectrum. These studies have shown that the relatives of schizophrenic patients also have a relatively increased rate of both schizoaffective disorder and schizotypal personality, suggesting that these disorders may have some relationship to narrowly defined schizophrenia.

In one of the largest family studies of schizophrenic probands, the relatives of schizophrenic patients not only had an increased morbid risk for chronic schizophrenia itself and for schizophrenia-related personality disorders, but also for other psychotic disorders including schizoaffective disorder, atypical psychosis, schizophreniaiform psychosis, and psychotic affective disorder. Therefore, it appears that there may be genetic factors shared between schizophrenia and many other psychotic disorders.

Twin studies have also been used to explore both the genetic component in schizophrenia and the boundaries of the schizophrenia spectrum. Concordance rates in monozygotic twins range from a low of 36 percent to a high of 72 percent for schizophrenia or probable schizophrenia. If other related disorders, such as schizoid personality, are also included, then the concordance rates are higher. Thus, the schizophrenic phenotype appears to be both variable and broad, even when genetic factors appear to be identical. The Genain quadruplets provide a particularly informative insight in this context. They showed no single phenomelogic or biologic profile characteristic of all schizophrenic patients, but instead ranged from mild to severe.

Study of the adopted children of schizophrenic mothers is yet a third strategy that has been used to evaluate genetic components in schizophrenia. This strategy is a particularly powerful one, since it isolates relatively pure genetic factors and excludes role modeling in the development of schizophrenia. Adoption studies have supported a major genetic component in schizophrenia. The adoption studies conducted in Denmark have also indicated that schizotypal personality appears to be genetically related to core schizophrenia.

Much less work has been done on the relationship between schizophrenia and relatively pure paranoid disorders. The available data suggest that these disorders may be less closely related to core schizophrenia, but considerably more work needs to be done in this area.

Other methods apart from genetic techniques have also been used to examine the relationship between the various disorders on the schizophrenia spectrum. For example, in some studies, patients with both schizophrenia and schizotypal personality share an impairment in smooth pursuit eye movements (SPEM) and poor performance on a backward masking task, suggesting biological commonalities between at least a subgroup of schizotypal patients and chronic schizophrenic patients. Investigators have also used response to treatment as a method of exploring the schizophrenia spectrum; they have shown that some patients with schizotypal features or borderline personality respond to antipsychotic medication.

Future Needs. It is clear that in the future the boundaries of the schizophrenia spectrum should be explored further using the above methods and other techniques as well. This exploration should be done with an appreciation that genetic factors implicated in schizophrenia may be expressed variably and with the recognition that more than one set of genetic determinants may be involved in the pathogenesis of schizophrenia. In addition to nuclear, core, or chronic schizophrenia, other related disorders should also be evaluated, including schizotypal personality disorder, paranoid disorders, psychotic affective disorders (noting features such as mood-congruent vs. incongruent symptoms), atypical psychoses, and schizophreniaform, schizophrenial, schizoid, and borderline personality disorders.

Most family studies conducted to date have begun by ascertaining patients suffering from schizophrenia. Only rarely have such studies indexed the milder or spectrum forms to determine if given the rel banana collaborators on schizophrenia.

Given the relative schizophrenia chronology, this possibility disorder of the spectrum had been in the terrible disorder compared to the schizotypal case in the literature on schizophrenia.

Definitive studies, e.g., patients with the schizophrenia spectrum in the schizophrenic group in the future, are still in progress.

Biological studies of schizophrenia are in their infancy. Although, however, some studies have been performed in schizophrenia.

Far more work is needed on the interactive factors and biopsychosocial environment. When schizophrenia compared to other personal perinatal complications, prominent in schizophrenia, biological symptoms have not been clearly examined. In addition, factors which interact with predisposing related disorders in the core schizophrenia studied.

Molecular genetics are especially important in schizophrenia research, where careful diagnosis may make a difference also for the purposes.