At present, schizophrenia is conceptualized as a clinical syndrome with apparent heterogeneity of etiologic and pathogenic factors. There is observed variability in age of onset, manifestation, pattern of progression, response to treatment and stress, associated biological and psychological features, and outcome of the illness. Most investigators assume that at least several disease entities will be defined within the schizophrenic syndrome, and that a more definitive nosology for schizophrenia and schizophrenia-like psychoses will emerge from further scientific study.

The most comprehensive, heuristic, and scientific approach to schizophrenia is provided by the biopsychosocial medical model, which incorporates biological, psychological and sociological factors. These factors give breadth to the scientific framework and are especially germane to research activities within the scope of this Panel. Opportunities for research on schizophrenia can be found in two associated areas of inquiry:

- **Treatment.** Treatment research addresses an array of approaches that can be categorized under two broad rubrics: pharmacologic and psychosocial.

  Pharmacotherapy refers to the antipsychotic drugs that induce biological changes, alter subjective experience and expression (symptoms), and thereby enhance social role performance. A proliferation of information in the neurosciences based on work with lower animals and nonhuman primates has widened our opportunities for developments in pharmacotherapy. We must expand our search beyond dopamine antagonist drugs to other neural systems that may play an important role in determining schizophrenic behavior.

  Psychosocial treatment allows the therapist and the researcher to investigate and attempt to ameliorate the ambient environmental factors that influence the vulnerable central nervous systems (CNS) of patients with schizophrenia. These factors exist at home, in the community, in the hospital and clinic, and in the workplace. The aforementioned growth of information also allows for new theories and sophisticated studies that address the mechanisms of socioenvironmental influences on behavior and central nervous system function. Innovative therapeutic and rehabilitative strategies can now be derived from such work.

  Research designed to assess the efficacy of various treatments not only strives to improve the quality of care received by schizophrenic patients but brings with it opportunities for the development of etiological hypotheses. There is an immediate and urgent need for well-developed assessment methodology.

- **Services.** If schizophrenic patients are to receive clinical, rehabilitative, and community support services efficaciously, it is vital to conduct well-thought-out research on the organization and financing of service delivery systems and the policies that affect them.

  As seen above, the number of disciplines and the range of clinical and scientific inquiry relevant to this Panel are many: research on treatment, environmental factors, rehabilitation, and services. These areas present varied and compelling research opportunities. In addition, the interplay with the content of the
other Panels is considerable.

The Panel's report reflects information gained through discussion among peers from the various relevant disciplines and fields of interest, testimony of experts, individual personal interviews, and written advice from a large number of highly respected experts from within and without the mental health community (see Appendix C).

It is written under the assumption that the reader will be concerned primarily with future opportunities in research and with procedures that facilitate the creative acquisition of new knowledge. Reviews of the current status of research in these areas and historical overviews are available (see Suggested Readings).

History clearly presents paradigms of success based on attention paid to compelling opportunities. An example is seen in the concurrent introduction of antipsychotic drugs and the focus on community-based care which together have reversed what was an ever-increasing need for psychiatric hospital beds. In 1955 that need exceeded 500,000 State and county beds. By 1984 that number had been reduced to 130,000. Patients now experience fewer relapses and reduced psychotic periods, reversing a trend that would have bankrupted the States' health care systems.

Treatment research itself offers new theories of disease mechanisms, such as the heuristic dopamine hypothesis. We now have evidence that the methodology used for clinical trials can be successfully applied to the study of interpersonal therapeutic and integrated drug/psychosocial strategies.

Theoretical and practical scientific methods and hypotheses are now in place, and opportunities based on recent and currently anticipated developments in a number of disciplines are available for investigation. Scientific manpower and research subjects (patients) must be identified, recruited, and developed to explore the many exciting scientific problems the field of schizophrenia research offers to clinical and basic science investigators.

Schizophrenia takes an enormous, worldwide toll in human suffering, lost potential, and financial commitment. The moral, clinical, financial, and scientific obligations to explore all avenues that might lead to understanding of its causes, treatments, and prevention should be parallel in magnitude. To date, this has not been the case, but from the vantage point of scientific opportunity, the moment is propitious and the payoff could be substantial.

**Underpinnings of Treatment and Intervention Research**

**Antipsychotic Drug Development.** New drug development and the evaluation of such compounds in treatment studies is of fundamental importance to advances in the treatment and understanding of schizophrenia. How that endeavor contributes to the understanding of the etiology and pathogenesis of the disorder will be discussed in another section. The focus of this section is research on the development of drugs that improve treatment response, prevent relapse, influence the course of the illness, and reduce side effects, especially tardive dyskinesia (TD).

A major effort to develop a variety of animal and tissue models that can serve as research tools for drug development relative to schizophrenia is warranted. For many years we have been restricted to animal models that depend on the capacity of a putative therapeutic drug to attach itself to postsynaptic dopamine receptors. Developments in psychopathology, tissue modeling, concepts of rodent behavior, and complex modeling in nonhuman primates create the opportunity for a radical change in the methodology of drug development. It is now possible to recognize highly specific domains of psychopathology as suitable targets for drug treatment development instead of attempting to model the entire clinical syndrome of schizophrenia. These domains, which include anhedonia, diminished social drive, reduced capacity for emotional arousal and modulation, limited capacity in sending and receiving social cues, and reduced cognitive abilities, can be identified or developed in animal models.

Our increased understanding of the physiology and biochemistry of behavior in rodents and the advances in basic neuroscience make it feasible to develop tissue models for drug screening that are relevant to the drug's ability to perturbate components of neural systems involved in behavior. It is increasingly evident that a wide range of neural systems are functionally involved in the establishment and maintenance of normal behavior, thought, and emotion. These systems are candidates for the study of etiology and pathogenesis, and for modification by pharmacological agents. It is now appreciated that multiple brain systems are involved in these behaviors, that each has many subcomponents of physiological significance, and that the interaction among systems is extensive and
complex. This complexity makes it unlikely that a single simple and direct pharmacologic intervention will be entirely curative or preventative. However, this same complexity highlights opportunities for therapeutic developments.

In the absence of a compelling, exclusive, and valid theory of the pathophysiology of schizophrenia, it is recommended that the field study the physiology, biochemistry, and pharmacoresponsivity of the neural systems underlying normal thought and emotion, and test them for relevance to the study and treatment of patients with schizophrenia. The relevant disciplines are well positioned to launch a major effort to evaluate the relevance and action of pharmacological agents on multiple neurotransmitter systems, such as the noradrenergic and serotonergic systems, and their effects at multiple points of entry—that is, how they modulate the receptor subsets and associated channels. In addition, the recent and exciting developments revealing the intimate evolutionary and physiological interaction between neural elements of the CNS and elements of the immune system promise important new concepts and theories of brain physiology and disease mechanisms. This will open the door for the development of entirely novel pharmacological agents for schizophrenia. The possibility of pharmacological manipulation of the immune system, which might alter vulnerability to schizophrenia or provide efficacious treatment for patients with schizophrenia, merits exploration.

The Panel believes that the opportunities in new drug development are broad, novel, and deserving of unequivocal and sustained research support. The development of animal and tissue models of pathological domains for drug screening purposes should receive increasing emphasis. Also, findings from studies aimed at etiological and pathogenic mechanisms will require translation into therapeutics and prevention. Issues of model development and drug screening in this regard should parallel those described above. Specific resource needs to foster these developments are addressed below.

**Psychosocial and Social Factors**

Research into the psychosocial factors involved in schizophrenic behavior should be seen as contributing to the treatment and prevention of relapse of the disorder as well as to the study of its etiology and pathogenesis.

Clinicians who attend patients observe them in interpersonal relationships. Their observations have often given rise to theories and testable hypotheses about the interaction of environmental stressors with the illness—for example, the diathesis-stress hypothesis, which provides a heuristic framework for the study of the pathophysiology of schizophrenia. In simplest terms, this formulation postulates that the likelihood that individuals vulnerable to schizophrenia, on the basis of genetic or other unspecified etiological grounds, will express that vulnerability as a disorder depends on the nature of the environmental experience each has.

Techniques drawn from psychophysiology, neuropsychology, cognitive sciences, clinical observation, psychopharmacology, neuroendocrinology, and imaging provide a basis for future multidisciplinary inquiries into the nature of stress and its effects on pathophysiology. As this work identifies individuals with different levels of vulnerability, it will also provide a basis for postulating etiological subgroups of schizophrenic patients and thus make a substantial contribution to etiological investigations. Increased understanding of the nature of the role of stressors in schizophrenia will lead to new theories. This will be a pivotal area for future research at the interface of practical therapeutic application and theory development regarding etiology and pathogenesis.

The field also needs considerable development of its manpower, along with a strong determination to integrate its clinical and basic science investigators in an interdisciplinary effort.

The explosion of information about environmental impact on CNS development and functioning provides the broad paradigmatic framework for interest in potential environmental factors as contributors to the etiology and pathogenesis of schizophrenia. Other fields of medicine, as well, are now recognizing the potential for robust investigations targeting factors that interact with biological vulnerabilities to produce, exacerbate, or ameliorate disease. Such factors include environmental events, personality characteristics, subjective experience, and individual adaptive mechanisms and capabilities. For example, alterations in immune system functioning in reaction to psychosocial factors may substantially modify an individual’s vulnerability to infection, tumor development, and perhaps schizophrenia.
This Panel recommends that significant attention be given to the careful scientific study of psychosocial factors that may contribute to the etiology or to the modification of vulnerability to illness. This endeavor should emphasize the integration of information from the basic behavioral sciences into the conceptual framework of disease pathophysiology with the goal of developing psychosocial treatments that are based on that understanding.

Treatment Assessment

The treatment of schizophrenia remains one of the major challenges to research in modern-day medicine because of the prevalence, severity, and chronicity of the disorder. Adequate and appropriate treatment requires the integration of biological, psychological, and environmental approaches to address the needs of patients and their families. Furthermore, as we have discussed above, the disorder is clearly heterogeneous, and that fact complicates the treatment process. Its heterogeneity begs that the disorder be categorized into subgroups and requires different treatment requirements for individuals at different stages of their illness. In this section, we discuss three areas of treatment assessment research: pharmacological treatment, psychosocial treatment and rehabilitation, and integrated biological and psychosocial approaches. In each of these three areas we present a brief overview of current research and then highlight the most important and promising directions for future work. A later section of the Panel Report deals with resource needs for this work. In this section, however, we identify research opportunities that require either major conceptual innovation or innovative modes of support.

Pharmacologic Treatment. Antipsychotic drug treatment, which is usually chronic and may be required for a lifetime, is central to the therapeutic management of schizophrenic patients. Neuroleptic drugs represent the first effective treatment for schizophrenia. They function both to control acute psychoses and prevent subsequent relapse, thereby facilitating rehabilitation and psychosocial treatment of patients. Nevertheless, existing agents have significant liabilities. First, they do not cure schizophrenia (and do not always affect aspects of the deficit state significantly). Second, they have troublesome and serious side effects for many patients, especially TD. Earlier we focused our attention on the development of new animal models to aid in the early screening of drugs. New models need to address behaviors that characterize specific aspects of schizophrenia, such as attention and anhedonia. We stressed attention to biological models of the disorder as fruitful sources of hypotheses for creation of not only new, but novel, chemical entities, and the importance of expanding these efforts to neurotransmitter systems beyond dopamine. Further, the development of drugs based on the differentiation of the dopamine system into its D_1 and D_2 receptor subtypes needs to be exploited.

Drug development costs in the pharmaceutical industry may exceed $100 million per successfully marketed product. Such astronomical costs reflect, in part, stricter drug regulations in the United States and other countries in recent years which apply both to animal and human research. At the same time, changes in drug patent laws (the Waxman-Hatch Act) have shortened the effective patent exclusivity time in which drug sponsors expect to recover their development costs, so that adequate return on investment may not warrant underwriting extremely expensive development.

Antipsychotic drug development is particularly expensive, thus placing this therapeutic domain at a disadvantage compared to others. Currently, clinical trials must be conducted largely in inpatient settings in facilities where "bed costs" are partially or totally subsidized, e.g., Veterans Administration (VA) and State hospitals. Thus, early drug evaluations are conducted largely in chronic and treatment-resistant populations, in facilities that often lack the staffing and support services essential to high-quality clinical research. Such testing also limits the generalizability of results to a specifically defined schizophrenic population. Later we address research needs that are specific to this patient population, but in this section, we emphasize the difficulty of using a potentially treatment-resistant population, which may also represent particular subgroups of the larger population in relatively early drug screening. The situation may well reduce the likelihood of identifying "breakthrough" drugs because the testing population may be unresponsive to them or not include the subtypes of schizophrenia potentially responsive to the drug.

Classic clinical trials methodology serves the biomedical community well, and has become a standard of excellence for the evaluation of efficacy and toxicity of treatments.
The field of clinical psychopharmacology can take justifiable pride in the central and early role it played in employing these experimental models before the legislative mandate. However, current requirements for short-term, placebo-controlled trials as the sole (or primary) criterion for drug approval in the United States need urgent reassessment. Other known experimental designs need to be considered, and perhaps more important, a search for new methods needs to be mounted. For example, long-term trials involving discontinuation designs or comparisons of varying dosages may provide design alternatives to the short-term placebo-controlled trial. Beyond these alternative clinical trial models, the identification of clear physiological markers of drug response could provide an alternative to experimental controls. Such activity may involve mental health agencies, primarily the National Institute of Mental Health (NIMH), academia, the pharmaceutical industry, and the Food and Drug Administration (FDA).

A further way to accelerate the human studies and clinical trial phases of drug development for schizophrenia is to provide independent support to investigators to assess new compounds. Such support would allow investigation of compounds in areas where a pharmaceutical sponsor was not seeking to develop a New Drug Application. Independent investigators or groups of investigators may also be able to proceed more rapidly to assess compounds if they have resources available and do not have to assemble a clinical research team anew for each project. An NIMH program that provided ongoing support to investigators to carry out clinical trials and even open studies of new compounds could accelerate drug development. The Institute had such a program earlier in its history, the Early Clinical Drug Evaluation Unit (ECDEU) program, which provided grant support for clinical research units that had the capacity to initiate trials rapidly. A modernized version of that program focused on schizophrenia would provide a valuable adjunct to the drug development activities of the industry and the regulatory process of the FDA. In addition to the capacity to initiate trials rapidly, such a program would also allow for long-term trials that are not readily supported now and, because the units would be ongoing, would have significant cost advantages as well.

The effectiveness of clozapine in the treatment-refractory population is encouraging because it provides evidence that some patients who have had a consistently poor response to typical neuroleptics may be capable of drug responsiveness. It also raises an important issue in drug development—one that has relevance both for improvement of treatment and for the understanding of schizophrenic disorders. In general, the search for new drugs has followed the assumption that all schizophrenic illnesses are treatable in the same fashion and that little attention need therefore be paid to the development and testing of medications which may have advantages to particular subgroups of patients. Given this pervasive thinking, drugs that are tested in broad and heterogeneous populations may not be identified as superior for a particular subgroup. Thus, the identification and characterization of schizophrenic subgroups relevant to particular treatment approaches needs to be carried out in research facilities where subgrouping as a strategy is appreciated. In addition to the potential benefits of developing new drugs, results of treatment studies represent a valuable tool in the differentiation and clarification of subgroups in schizophrenia.

Beyond the development of new chemical entities with which to treat schizophrenia, the Panel recognizes the urgent need to address the treatment challenge presented by individuals suffering from schizophrenia now. Gains in the safe and effective use of currently available treatments or treatment combinations will have a major impact on the lives of these patients and their families. Answers to the following questions must be found within our growing knowledge of the variability in patient treatment response:

- How long do neuroleptic drugs need to be continued in patients who have not relapsed?
- Does drug responsiveness change over time after repeated episodes and courses of administration? Does response vary depending on stage or severity of illness? Does prior neuroleptic drug exposure alter subsequent therapeutic response or course? Is there drug-induced withdrawal or tardive psychosis?
- What are the treatment requirements of both very early onset (preadolescent) and late onset (after age 45) forms of schizophrenia?
- What are the gender-related differences in schizophrenia that are relevant for treatment response? What can we learn about pathophysiology from gender differences?
- Why does the average dose of neuroleptic medication used to treat...
schizophrenia vary in different parts of the world?
• What is the incidence of TD in patients who receive neuroleptic drugs for the first time? Can novel compounds and innovative treatment strategies reduce the incidence?
• What can we learn about schizophrenia from the apparently lower risk to schizophrenic patients, as compared to those with affective disorder, of developing neuroleptic-induced dyskinesias?
• Are there pathophysiological markers for TD risk? Can drugs be developed that do not place patients at risk for TD?
• How can we treat TD?

If we turn our attention, research resources, and personnel to these questions, we can expect answers within the next decade.

Psychosocial Treatment and Rehabilitation. In a previous section, we identified the need to develop novel psychosocial treatments based upon the growing understanding of the nature of schizophrenic deficits in such functions as attention, learning styles, and vulnerability to stress. In this section, we identify opportunities for the assessment of psychosocial treatments and for the application of existing treatments to unstudied subgroups.

The following developments in the design and assessment of psychosocial treatments for schizophrenia have contributed to the recent gains in this area: (1) Treatments have been developed based on our empirical understanding of schizophrenia. (2) Treatment interventions have been well specified and defined. (3) The methodology of clinical trials has been used to assess psychosocial treatment efficacy. Because of these developments, we now have data showing that psychosocial treatments, both those that address the patient directly, such as social skills training, and those that intervene at an environmental level, such as family interventions, have demonstrable effects in influencing the course of schizophrenic illness.

These trends in psychosocial treatment research must be strengthened and expanded in the next generation of studies to address the following considerations:

• The characteristics of the illness may be partially defined by special treatment requirements at various stages of the illness. There may also be treatment-relevant subgroups within the disorder (e.g., patients with negative symptoms, inappropriate affect, hallucinations, or social skills deficits). It is of the utmost importance to design studies to identify these potential subgroups and then to develop treatment strategies that address them. Furthermore, such strategies must be seen in the light of longitudinal treatment administration and followup observation.

• How well a patient responds to treatment and the subsequent course and outcome of the illness are factors that have been linked to the environment. The environment, for all persons, is highly individual and is seen in such things as major life events, important interpersonal relationships, praise or lack of praise, reasonable or unreasonable demands, requirements for adaptive change, and expectations for improvement. Clinical observation, cross-cultural studies, and analyses of ward and home environments support this conclusion. Further, interventions that have focused on altering specific aspects of the environment have proved beneficial. Thus, life’s common events open avenues of research. The Panel recommends research directed toward the characterization and design of environments based on an understanding of the specific environmental needs of schizophrenic patients. Such studies must extend beyond the inpatient hospital and home environments that have been studied to date and include day hospitals, community residential facilities, work settings, and intermediate care settings. A new emphasis on protective environmental factors is of particular importance.

• We need to develop and assess psychosocial strategies that will enhance patient compliance with medication and will motivate them to participate in other treatments. Substantial gains in therapeutics can be achieved by research directed at strategies designed to increase the percentage of patients who successfully negotiate the bridge between inpatient and outpatient treatment.

• Recent advances in neuropsychology suggest that subtle deficits persist after active periods of psychotic illness. These cognitive and attentional deficits may interfere with the patients’ capacity to benefit from psychosocial treatments such as social skills training or vocational rehabilitation. The assessment of such specific deficits and the design of focused interventions to remediate them provide an opportunity to enhance the success of a wide range of available treatment interventions.

Integrated Psychosocial and Medication Treatment. Although we have addressed biological and psy-
chosocial treatments for schizophrenia separately in this report, the Panel clearly recognizes that drug treatment always involves psychosocial elements which are consistently present regardless of treatment regimen and significantly affect the course and outcome of the illness. Further, psychosocial interventions involve pharmacological or biological elements. Thus, the optimal treatment research design requires attention to both modalities. Despite the importance of such research, most psychopharmacological studies ignore concurrent psychosocial or treatment intervention factors; most studies of environmental events or psychosocial treatments ignore pharmacological treatment factors. In the decade between 1976 and 1986, only two studies formally examined the added and interactive effects of medication and psychosocial treatment.

The Panel strongly recommends that psychosocial treatment intervention research approaches be rapidly integrated into novel drug strategies as they are developed. The basic hypothesis that requires exploration is whether greater gains with novel drugs may be achieved when psychosocial treatments are introduced concurrently. Specifically, clozapine, recently shown to bring some relief to otherwise treatment-resistant patients, carries with it fewer debilitating side effects than other neuroleptics and, consequently, should be studied in that population along with psychosocial treatments such as social skills training, cognitive rehabilitation, and environmental support. Similar strategies should be applied with other novel compounds as their basic utility becomes clearer.

Opportunities for research on integrated psychosocial and pharmacological treatment generally require long-term studies; short-term therapies recently developed in other mental disorders do not have a realistic parallel in schizophrenia. The need for long-term studies in this area is addressed by Panel recommendations for research facilities that allow for such work.

Despite the recognition that, in general, long-term treatment and research are at the core of integrated treatment for schizophrenia, research is also needed to identify integrated strategies that maximize treatment efficacy during increasingly brief hospital stays and during the period immediately following discharge.

In this area, as in the discussion of assessment of pharmacological treatments, the Panel recognizes the importance of developing novel research designs and experimental methods that will enhance our ability to detect treatment effects on the multiple levels of patient functioning. Integrated treatment strategies that focus on the individual patient and attempt to develop social support systems need to be developed and assessed. The integration of treatment elements into larger scale service systems is discussed in a subsequent section.

Services and Services Research

Services research seeks to extend the understanding of the treatment of schizophrenia into the actual delivery environment, in the recognition that one-fourth of hospital beds in the United States are used for patients with this diagnosis. Further, hospital bed utilization is only a reflection of a larger community-based population, about half of which is not receiving services at all, much less optimal services.

Services research begins, in effect, where treatment research ends. It is concerned with the translation of efficacious treatments to the larger noncontrolled delivery environment, the characterization of service systems, and the design of large-scale research that will subsequently affect both clinical practice and public policy in the design of delivery systems. Thus, services research is conducted on multiple levels, ranging from the clinical examination of treatment practices through the facilities level to the systems or organizational level. The Panel stressed the importance of basing design and implementation of service delivery systems on research knowledge. The cost of such evaluation is modest in comparison to the cost of implementation. Early evaluation might avoid the proliferation of untested and unproven strategies.

There is an enormous cost associated with schizophrenia, both to the individual and to the Nation, which mandates that cost-benefit and cost-effectiveness research be extended rapidly at the community level. Strict attention must be paid to both methodology and study designs that assess the cost-benefit of specific services and system level interventions.

Many crucial elements of the systems of care have not been studied empirically and require such examination. For example, case management has become one of the models through which services are provided to schizophrenic patients. The term encompasses a wide range of actual practices. For example, in some settings case managers function as
primary therapists; in others, they are ombudsmen who negotiate with service providers on behalf of clients. Experimental trials of various forms of case management are needed to determine the sources of their relative effectiveness and efficiency.

A second example involves examination of a variety of strategies to ensure continuity of care. Residential care for schizophrenic patients currently includes long-term institutional settings, designated community placements, general nursing homes, single-room occupancy in welfare supported hotels, and patients' family homes. The advantages and disadvantages of these settings need to be related to costs and benefits to the community, the patients, and their families.

Research on how policy decisions affect schizophrenic patients, their families, and the community is needed. Although the study of a wide range of policy-driven outcomes is important, perhaps the most important and easily addressed is mental health financing. Financial decisions made by States can provide naturally occurring experiments which should be examined to determine the impact of varying State service systems and payment mechanisms on treatment delivery and ultimately on course and outcome. Experimental capitated programs that provide a mixture of psychiatric, rehabilitative, housing, and social services are judged by the Panel to be worthy of attention. These should be compared to more traditional methods of delivery to gauge their efficacy.

Systems research provides an opportunity to link services research and the more molecular treatment research that we discussed earlier. The development and maintenance of population-based data sets on patients and their usual treatment and outcome, coupled with the conduct of carefully controlled treatment trials in patients drawn from these populations, will provide contextual information about the controlled clinical trials that can hasten the application of results to wider populations. In essence, such data bases would determine the generalizability of controlled trials to an epidemiological base.

Special Resource Issues

Issues addressed here concern fundamental resources necessary for an ambitious pursuit of the best research opportunities anticipated during the next decade. We address areas where the basic ingredients either do not presently exist or are so dramatically underdeveloped as to place special demands on existing resources.

Patient Populations. We are particularly concerned with patient/research subject populations. There are a number of factors that have helped to create a crisis in developing several of these cohorts of importance.

Shifts in health care financing in academic centers make it virtually impossible to conduct studies with design demands that deviate from "standard" community practices and guidelines for length of stay, third party payment, etc.

As a result of deinstitutionalization, only a highly skewed, usually treatment-resistant and chronically ill population of schizophrenic patients, is readily available for patient research. These patients are found in State facilities and VA hospitals where, despite the presence of large numbers of patients, research is difficult; there are some examples, however, that can provide a model.

Other facilities in the public sector such as general hospitals, partial care settings, and outpatient clinics serve large populations of patients. Although these settings frequently have problems similar to those of long-term inpatient facilities, there are few integrated models for the study of schizophrenic patients in the full range of treatment settings.

In academic settings, investigators can readily develop the multidisciplinary teams now seen as necessary to schizophrenia research. These are not the settings that readily develop adequate patient populations, though, because the patients found there are generally treatment-responsive and discharged early, or bed costs are such that chronically ill patients are financially unable to stay at such sites.

The field has recently come to appreciate that "samples of convenience" and those drawn from highly skewed populations, such as those mentioned above, may contribute to the production of results that are not generalizable to other patient populations of interest and may not be replicable. In addition, it is now clear that large numbers of patients are needed for certain study designs to meet requirements for adequate statistical power to test hypotheses which may require multisite collaborative studies.

Listed below are the specific patient/research populations that the Panel sees as crucial to progress in the field:

First episode patient. It is extremely important to develop far greater ca-
pacity to identify and study schizophrenic patients beginning with their initial episode. This will require study of a broad range of patients with psychotic disorders, because the firm diagnosis of schizophrenia is not always possible upon first episode.

The ability to scrutinize the relationship of various biological, psychological, and imaging parameters and treatment response is crucial, as is the capacity to study phase-specific treatment response in this population. There is considerable evidence that deterioration in most forms of schizophrenia plateaus within 5 to 10 years of onset. Thus, longitudinal treatment studies aimed at decreasing long-term deficits and TD will be severely compromised if they are not implemented early in the illness.

The drug-naive patient. As research on the etiology of schizophrenia is being focused on abnormalities of brain function and structure, dysfunctions of the immune system, and other biological hypotheses (e.g., viral illness), it is almost impossible to draw etiological conclusions because of the confounding effects of course of illness and treatment. Much of the modern literature on brain function in schizophrenia is based on patients who have had extensive drug treatment; most studies have been cross-sectional rather than longitudinal. On the basis of both empirical studies and logic, it is becoming increasingly clear that many biological characteristics may be profoundly altered by antipsychotic drug treatment. For example, it is hypothesized that neuroleptic drugs alter the number of dopamine receptors. Thus, studies of patients who have been repeatedly exposed to neuroleptics may not provide an appropriate population in which to test the hypothesis of dopaminergic activity in schizophrenia. This hypothesis and others can be clearly tested, however, in prospective, longitudinal studies of first-break, drug-naive psychotic patients. Unfortunately, drug-naive patient populations are very difficult to acquire, largely because we lack the ability to identify first-break patients and because the special therapeutic environments necessary to facilitate both treatment and study are lacking. Cross-cultural collaborative studies with centers that have drug-naive patient populations are indicated.

The antipsychotic drug-refractory patient. A major therapeutic dilemma involves innovative treatments for patients who show incomplete or minimal response to antipsychotic neuroleptic medication. Some alternative treatments are ready for evaluation, and exciting new opportunities should emerge from the drug development initiatives described above. The ability to study new drugs and psychosocial treatments in this population is crucial to the advancement of therapeutics and theories of illness mechanisms.

The chronic deinstitutionalized patient. An ever-increasing proportion of the schizophrenic population is found in the community in supported environments, in their families' homes, and most tragically, on the streets. It is difficult to bring this patient population into the framework of treatment research, and we run the risk of judging an effective treatment for them to be ineffective because it has been studied only in the selected and skewed population that comes to accessible research facilities.

Childhood schizophrenia. There is virtually no scientific study of childhood schizophrenia relevant to psychosocial factors, biologic and psychosocial therapeutics, or services. This population is dramatically underserved by the research community. The patient population and the research expertise necessary to study these populations require urgent development.

Late-onset schizophrenia. There have been few American studies of this population. As America "grays," the problem will become increasingly evident, and well-designed, long-term prospective studies will be warranted.

Dual diagnosis: drugs and alcohol. Although data increasingly indicate that patients with schizophrenia frequently abuse both alcohol and illegal substances, there has been almost no research attention to their treatment needs. Perhaps the most frequent attention has been to exclude them from study. Thus, the question of whether response to treatment of schizophrenia is altered by the presence of drug or alcohol abuse needs to be answered. The design and evaluation of treatments for substance abuse specifically targeted for individuals with schizophrenia is also required.

Gender considerations. Gender differences may cut across all the specific patient populations we have already discussed. We already know that there are gender differences in treatment response, age of onset, and course of the illness. The impact on the parenting capabilities of persons with schizophrenia and the impact on children being reared by a parent with schizophrenia also merit study, and may lead to hypotheses about etiology, treatment, and prevention. Researchers have deve-
developed samples that will permit direct assessment of gender-related disease effects.

**Mechanisms.** Enhanced resource mechanisms are necessary at all levels of research; several are of special interest to schizophrenia treatment research. Mechanisms are needed to recruit, train, and sustain the research work force, especially young developing investigators.

Substantial financial support and incentive mechanisms are required to identify, develop, and tap patient populations. The Panel specifically recommends the following mechanisms:

- Coordinate research among centers where substantial patient populations exist (e.g., State, VA, private mental hospitals, and outpatient community facilities).
- Support clinical investigators whose role is to establish and sustain the high-quality clinical services that are required to conduct long-term studies. Such resources could be used by multiple investigators in collaborative ventures.
- Juxtapose clinical research centers with epidemiological cohort development so that studies of treatment and pathogenic factors can be developed within a sampling frame.
- Develop facilities and funding for clinical studies of new drugs that are independent of pharmaceutical industry support but that allow cooperative development involving both industry and academic interests. An example of such a mechanism was discussed in the section on pharmacologic treatment.
- Establish population-based data sets which can serve as sampling frames for services research and treatment studies. Development of ethical methods to enable investigators to identify individuals within these systems is crucial.
- Develop centers of integrated research activities that will allow ready interplay between the preclinical and clinical sciences, and between therapeutics and etiological theories. These centers require expensive patient resources.
- Enhance the contributions of the pharmaceutical industry to treatment research by bringing representatives of industry and regulatory agencies, research program administrators, and clinical and preclinical investigators together. Aims would include (1) clarification of the opportunities and obligations for industry, (2) identification of regulatory procedures that can facilitate drug development, and (3) creation of scientific interplay between leading disease specialists, neuroscientists, and drug development experts. It is desirable for NIMH to become a participating institute in The Forum on Drug Development and Regulation sponsored by the Institute of Medicine to ensure a focus on schizophrenia.

**Conclusions**

Research to provide better, more effective treatments for individuals suffering from schizophrenia is vital and will have significant consequences in improving the lives of patients and their families. Further, treatment research has been and will be a major source of theory about etiology and pathogenesis. A great deal of what we know about CNS physiology has grown directly from the study of pharmacological and psychosocial influences on brain physiology and structure. The most durable biochemical hypotheses in the field of schizophrenia research have been drawn from observations of the effects on behavior of drug therapy and from the putative understanding of those effects on relevant neural systems. For example, the noradrenergic hypothesis of anhedonia, the dopamine hypothesis, and the transmethylation hypothesis of psychoses have all emerged from the clinical observation of drug effects. Deriving etiological and pathophysiological hypotheses of disease from the observation of such effects will continue to be of therapeutic benefit in the psychotic or otherwise symptomatic patient.

The Panel recommends that in the future the deployment of research resources explicitly recognize that treatment research is of profound significance to the study of etiology. Mechanisms are needed to bring etiologically oriented theorists together with clinical scientists who draw observations from clinical trials. This is important for heuristic theory development and development of testable hypotheses. Hypothesis testing is likely to require interdisciplinary approaches, including the interplay between animal and tissue models on the one hand, and clinical scientists on the other. Clinical research settings are needed in which rigorous treatment research can be carried out to evaluate the pathogenic determinants of schizophrenia.

**Suggested Readings**


Donaldson, S.R.; Gelenberg, A.J.; and Baldessarini, R.J. The phar-


Hargreaves, W.A., and Shumway, M. Effectiveness of services for the severely mentally ill. Health Services Research, in press.


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Announcement

The World Psychiatric Association Regional Symposium will be held in Granada, Spain, March 29 through April 1, 1989. The theme of the Symposium will be "Mental Health Community Services."

For further information, please contact:

Secretaria
Simposio Regional
Avda. del Sur, 13
18071 Granada, Spain
Telephone: 58-206102

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Announcement

The New York State Psychiatric Association is sponsoring a symposium entitled "Optimizing Outcome In Schizophrenia" scheduled for Saturday, November 5, 1988, at the Roosevelt Hotel, New York, NY.

For further information contact:

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