The report that follows is the latest of the reports of ongoing research in schizophrenia produced by the Center for Studies of Schizophrenia of the National Institute of Mental Health. Before the Center’s formation, similar reports were prepared to meet largely internal administrative requirements. Then, as now, they served primarily as background material for the Director of NIMH’s annual budget presentation to Congress, giving him an organizing view of the loosely connected schizophrenia research projects that each year draw funds from the NIMH purse. In addition, the reports have long provided the Institute with a coherent summary of its overall effort in schizophrenia—a significant aid in determining priorities for coming years. Not until 1969, however, was the report made widely available to members of the mental health community outside the Institute. This year the report makes its second appearance in the Bulletin—an effort to give it the greatest exposure possible.

Preparing a compendium of ongoing research in schizophrenia is an arduous task. First, the Center asks grantees whose research deals with schizophrenia to provide brief reports of their most recent findings. Because of the wealth of up-to-date information collected in this way, the Center’s special report tends to concentrate on research carried out by NIMH grantees. An effort is made, however, also to include important research conducted by other investigators in the field, whose work may not presently be supported by NIMH. In addition, the report includes information collected by NIMH staff on site visits, summaries of research in progress in the NIMH Intramural Research Program, and biometric data collected by the NIMH Biometry Branch.

In selecting material for inclusion in the report, we try to focus on work we believe is “solid.” Nevertheless, we recognize that, by reporting preliminary findings before they have been subjected to long and careful scientific scrutiny, we may occasionally mislead our readers. Therefore, cautionary statements included in the report should be taken quite seriously. By the same token, it should be pointed out that the report itself has been reviewed by members of the Bulletin’s editorial advisory board. We enlist their help because we wish to make certain that the chance of systematic bias is minimized, that important new developments have not been overlooked, and that the summarization process has not distorted results. In an effort to get still further feedback, Center staff members present major portions of the report at professional association meetings, inviting their assembled colleagues to suggest significant research trends that should be highlighted in the current or upcoming editions of the report. We feel that this process of review and discussion supports our claim of offering a selective, highly summarized, but representative, overview of the efforts now being made to confront schizophrenia.—The Editors.
special report: schizophrenia, 1974

John G. Gunderson, Joseph H. Autry III, and Loren R. Mosher
with Sherry Buchsbaum

Continuing a favorable trend that has now been apparent for over a decade, recent data reveal a progressive decline in the number of resident schizophrenic patients in State and county mental hospitals. In 1970, there were 163,000 resident schizophrenic patients—17,000 fewer than the previous year. Significantly, there has been a continued acceleration in the rate of decline in the number of resident patients, which has gone from 3.4 percent in 1967 to 7.7 percent in 1969 to 9.4 percent in 1970 (see figure 1).

Not unexpectedly, the progressive decline in the number of resident psychiatric patients has been accompanied by an increase in the number of psychiatric patients discharged from State and county hospitals—a trend that has continued uninterrupted since the mid-1940's. Since 1955, the number of releases (discharges and escapes) has more than tripled, from 126,500 in 1955 to 419,000 in 1971 (see figure 2). Moreover, 1970 and 1971 are the first 2 years on record in which the number of releases has exceeded the number of admissions (Bethel and Redick 1972). The marked increase in State and county hospital discharges probably reflects a trend toward decreased use of long-term inpatient treatment facilities and increased reliance on such short-term facilities as community mental health centers and psychiatric wards in general hospitals. The percentage of patients diagnosed schizophrenic among the resident hospital population has remained remarkably stable at about 50 percent, since there has been an equal shift away from inpatient treatment for all diagnostic groups. In 1955, of the 1.7 million patient-care episodes recorded in all types of psychiatric treatment facilities, 77 percent were inpatient, but by 1969, inpatients accounted for only 45 percent of 3.7 million patient-care episodes. Yet, even though the number of schizophrenics given outpatient care has doubled since 1966, the majority (62 percent) of schizophrenics still receive inpatient treatment. In general, male schizophrenics tend to be admitted to inpatient care more often than females; under age 18, however, female schizophrenics are more likely than males to be hospitalized (Taube and Redick 1973).

The shift from inpatient to outpatient treatment of schizophrenics, although generally welcome, has a sobering side. Inpatient stays for schizophrenics are growing increasingly shorter (the median length of stay in a 1970 survey of public mental hospitals was 60 days), but discharged schizophrenics tend to be readmitted to the hospital extremely frequently. The number of schizophrenic readmissions is more than twice that of schizophrenic first admissions and higher than readmissions for any other diagnostic group. It is estimated that one-third of schizophrenics require readmission 1 year after their initial discharge; by 2 years after discharge, the rehospitalization percentage rises to approximately 50 percent.

Statistics from Indiana suggest one reason for the disturbingly high readmission rate for schizophrenics. A retrospective survey of all schizophrenic patients who had enrolled for outpatient treatment at any of the State's public hospitals and whose subsequent treatment experience had ended in 1970 revealed that only 35 percent had actually received any treatment. Of the
remaining 65 percent, over half received nothing more than intake services or a diagnostic evaluation, and another 13 percent received only psychological testing. Of those who began outpatient treatment, about half abandoned it. Whether the failure of many schizophrenics to undertake or continue in outpatient treatment reflects the unavailability of such care, the systematic deselection of schizophrenic patients, the dissatisfaction of schizophrenic patients with the type of care provided, or a combination of these factors remains unanswered. Thus, it is possible that high readmission rates among schizophrenics may not reflect the absence of outpatient intervention facilities so much as the inability of such facilities to provide meaningful treatment experiences.

The growing impact of day-care programs, halfway houses, and community mental health centers has been responsible, at least in part, for the decreased number of patients treated in State and county mental hospitals. Nevertheless, only about 125 halfway houses for psychiatric patients existed in the United States in 1969. Most facilities of this type were concentrated in the East and were opened after 1965. The NIMH Office of Biometry estimates that, if halfway house facilities are appropriate for one-fourth of the patients discharged from State and county mental hospitals, at least five times as many halfway houses as were available in 1969 are needed today. As for day-care programs, despite a threefold increase in their number between 1962 and 1969, they accounted for only 2.6 percent of the schizophrenic admissions to treatment facilities in 1969. Their progress is linked, however, to the burgeoning role of the Community Mental Health Centers (CMHC's) because these facilities are more likely to include partial hospitalization programs than are either public or private mental hospitals. Between 1969 and 1970, the number of people admitted for services by the CMHC's increased by 39 percent. During the same time period, there was a 39-percent increase (to 51,000) in the number of schizophrenics treated in CMHC's. Among these schizo-
Figure 2. Patient movement data: State and county mental hospitals, 1950-1971.

These statistics demonstrate the shifting locus of treatment—out of the hospitals and into the community. Unfortunately, there is also evidence that existing aftercare or outpatient treatment programs are inadequate in number and, perhaps, in efficacy to manage the growing treatment burden imposed by the discharged schizophrenic. It must be recognized that the steady decline in the number of resident schizophrenic inpatients is not, in itself, evidence that the incidence and prevalence of schizophrenia is being appreciably altered. We must not allow statistics reflecting a decrease in resident patients to lull us into believing that schizophrenia is being more adequately dealt with than was formerly the case. For the most part, community facilities to which chronic schizophrenic patients are discharged offer few advantages over large institutional ones. In too many instances they are one-person “backwards,” affording little social contact and few opportunities for rehabilitation, meaningful work, or recreation. There is a pressing need for more careful evaluation of the life of the discharged schizophrenic both in terms of his impact on his family and the community and of the influence of familial, social-support-system, and treatment factors on his subsequent life course.

Diagnosis and Description

Until recently, research efforts to develop more precise diagnostic techniques have not commanded pronounced interest in the United States. But, today, American psychiatrists, somewhat belatedly following the lead of their European colleagues, are coming to

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1 Unpublished data from the Survey and Reports Section, Biometry Branch, OPPE, NIMH.
recognize the importance of diagnosis in accurately predicting outcome, in differentially assigning patients to particular treatment approaches, in making possible cross-comparisons of patients in different research projects, and so on.

Investigators attempting to develop more objective, reliable methods of classifying patients increasingly are using standardized structured interview schedules to arrive at clinical diagnoses. Grinker and Holzman (1973), for example, used the Schizophrenia State Inventory (SSI) to rate such characteristics of subjects as language problems, anxiety, pleasure, unintegrated self, and inconsistency-consistency axis of thinking, affect, and perception. The investigators, who report that these dimensions are essentially independent of one another, have identified five qualities that distinguish the young schizophrenic from the nonschizophrenic: the presence of a disorder of thinking; a diminished capacity to experience pleasure, particularly in interpersonal relationships; a strong tendency to be dependent on others; a noteworthy impairment in social competence; and an exquisitely vulnerable sense of self-regard. Anxiety, which Grinker had believed to be qualitatively different in schizophrenia, did not prove to be a differentiating characteristic of schizophrenic subjects.

The desire for greater objectivity in classifying patients has led to the development of computer programs for psychiatric diagnosis. Two pioneers in this field are Spitzer and Endicott (MH 08534), who recently developed a new system of computer-derived diagnoses, DIAGNO III. Designed to assist the clinician in making differential diagnoses, DIAGNO III differs from its predecessor, DIAGNO II, in that it uses input from the Mental Status Examination Record and the Psychiatric Anamnestic Record, two standard psychiatric interview forms, while DIAGNO II used a research interview. The output lists one or more "most likely" diagnoses as well as diagnoses that "should also be considered," and outlines the rationale for the diagnosis chosen. In a study of 162 psychiatric inpatients, the agreement between the admission clinical diagnosis and the computer diagnosis was kappa .60 (kappa is a measurement of agreement corrected for chance agreement).

In still another approach, Astrachan et al. (1972) have devised a symptom checklist and scoring system, the New Haven Schizophrenia Index (NHSI), for the diagnosis of schizophrenia. Using the NHSI, they correctly identified 87.6 percent of patients clinically diagnosed as schizophrenic while misidentifying as schizophrenic 15.6 percent of acutely disturbed nonschizophrenic patients. The diagnosis of schizophrenia using the NHSI is heavily weighted by symptoms of thought disorder and delusions.

Each of the three symptom-based approaches described above shares a format that reflects usual clinical practice, but adds the systematization necessary for research.

Prognosis

Part of the effort to refine diagnostic categories has revolved around the prediction of outcome in different subgroups of patients. Interest in defining prognostic indicators in schizophrenia has focused principally on two major categories of variables as outcome predictors—symptom patterns and social factors (past or present). Carpenter and Strauss' (1973) study of the relationship of prognosis to the presence of Schneiderian first-rank symptoms in their sample of patients is an excellent example of the symptom-pattern approach. (Carpenter and Strauss' findings are discussed below, in the section on "Cross-Cultural Studies."

Klein, Person, and Itil (1972) used the second approach to prognosis (i.e., social factors) in their study of the social environments and families of 136 chronic patients. They concluded that the present status of the patient's life provided the most valid prognostic clues. For example, they found that family agreement with and participation in treatment was significantly related to improvement. In contrast, most of the patients' remote family and social experience—for example, childhood behavior that differed from peers', power position in family, patterns of coping with family authority, play behavior, precipitating events to illness, and exposure to social trauma—failed to show any significant influence on the outcome of illness. Such sociobiological variables as number of relatives with schizophrenia, incidence of complications in mothers' pregnancies, complications around birth, and incidence of physical health problems also were unrelated to improvement. This is in contrast to the findings of McCabe et al. (1971) (see the "Genetics" section) who reported that a poorer prognosis was correlated with an increased number of relatives with a diagnosis of schizophrenia. It is possible that the differences in results stem from the different...
ways in which the two patient samples were derived—Klein et al.'s from the back wards of State hospitals (a relatively homogeneous group) and McCabe's from a heterogeneous series of schizophrenics consecutively admitted to hospitals. Thus, the Klein group's sample is selected for severity and prolonged hospitalization as compared with McCabe et al.'s more representative selection. Because the families in Klein et al.'s study showed wide variation in the level of continued involvement with their chronically hospitalized offspring, it is not surprising that this factor was more closely related to outcome than familial presence of schizophrenia (for which there is only a narrow range possible) in this homogeneous patient sample.

As part of a large collaborative drug study, Schooler, Boothe, and Goldberg (1971) examined the relationship of 97 social background variables to symptom severity at admission in 480 newly hospitalized schizophrenic patients. Symptom severity was positively correlated with having foreign-born parents, a foreign language being spoken in the home, having a unique position in the sibship, being male, having a poorly functioning mother, and parents having had a history of mental illness. The investigators also found that circumstances surrounding the process of hospitalization related to levels of illness; for example, patients who were involuntary admissions, who were strongly opposed to hospitalization, and who were admitted because of active psychotic behavior demonstrated more severe symptomatology. The amount of improvement seen after 5 weeks of drug treatment was related to sociobiological variables, remote family and social experiences, and level of preillness psychosocial functioning. It is noteworthy that Schooler, Boothe, and Goldberg's results tend to confirm McCabe et al.'s conclusion that outcome is related to presence of schizophrenia in the family and level of preillness competence. Because these two samples were similarly selected, they lend further credence to our suspicion that the different results obtained by the Klein and McCabe groups reflect different sampling procedures.

Another study addressing the impact of preillness level of competence on prognosis was conducted by King and Pittman (1971). Relating historical data to prognosis, they found that the longer the duration of symptoms prior to first admission, the worse was the prognosis for remission of symptoms. King and Pittman also confirmed Vaillant's (1964) earlier finding that affective symptoms or a family history of affective symptoms tend to predict remission. Accordingly, they conclude that diagnoses of acute schizophrenic episode and schizoaffective schizophrenia appear to be diagnoses of remitting illnesses.

**Cross-Cultural Studies**

A major focus of current studies in this area is the cross-national evaluation of the validity of diagnosis and the prognostic capabilities of various diagnostic systems. For example, the International Pilot Study of Schizophrenia (IPSS), an ambitious transcultural investigation in nine countries undertaken by the World Health Organization, has as a principal aim the development of research instruments that can be reliably applied in many cultures (Sartorius MH 09239). Among the instruments that have resulted from this effort are a present state examination schedule (originally developed by Wing and his collaborators and specially adapted for cross-cultural use in the IPSS), a psychiatric history schedule, and a social description schedule. These instruments have been translated into eight languages and have proven reliable in the nine participating countries (Colombia, Czechoslovakia, Denmark, India, Nigeria, the Republic of China, the Union of Soviet Socialist Republics, the United Kingdom, and the United States of America). The IPSS has further demonstrated that similar groups of schizophrenic patients can be identified in the nine countries. In all field centers, a high proportion of schizophrenic patients exhibited lack of insight, predelusional signs, flatness of affect, experiences of external control, and auditory hallucinations. There was also a similarity across centers in the proportion of schizophrenic patients having delusions, derealization, and disturbance of mood. The number of schizophrenics demonstrating psychomotor disorder (negativism, compliance, mannerisms, and similar abnormal behavior), pseudohallucinations, and affective changes (other than incongruous affect) was relatively low. Using three separate methods of classification—clinical diagnosis, computer diagnosis, and cluster analysis—a “concordant” group of schizophrenic patients has been identified in each of the research centers. Patients included in this homogeneous group will be the subject of particular attention in the 2-year followup now being conducted. Further studies of this group may help to lay the groundwork for a transculturally applicable definition of schizophrenia. Overall, the IPSS findings suggest significant differences among the clinical pictures of schizophrenia and other psychoses in the various centers; interestingly, greater clinical similarities were found across the nine field
centers for affective psychoses than for schizophrenia. Analysis of followup data will allow comparison of symptom change and outcome and prognostic factors within and across diagnostic groups and centers.

Investigators in some centers have used the data collected for the IPSS to examine questions of particular interest to themselves. For example, Carpenter and Strauss (1973) of the U.S. field center studied the implications of their IPSS data for Schneider's classification of schizophrenia. Schneider's system, which is highly regarded and widely used throughout Europe, is based on the presumption that there is a group of easily and reliably observed symptoms that are found only in schizophrenia. These symptoms are grouped into 1) first-rank symptoms (FRS's), which are considered pathognomonic of schizophrenia in the absence of an organic brain syndrome (see table 1); 2) second-rank symptoms, which may be used as evidence for the presence of schizophrenia but are less diagnostic than FRS's; and 3) symptoms that may be present but are not diagnostic. Carpenter and Strauss examined the FRS's in an attempt to determine 1) whether FRS's are pathognomonic of schizophrenia, 2) the frequency distribution of FRS's in recently admitted schizophrenics, 3) whether FRS's are related to prior duration of illness, and 4) whether FRS's are of prognostic significance. One hundred and forty-one patients, including 34 with affective psychoses, were studied. Because of the nature of the present state examination, inadequate data were obtained on FRS's numbered 2 and 3, and these were dropped from the data analysis. Approximately 64 percent of patients in this sample who had been diagnosed schizophrenic had one or more FRS's. Patients diagnosed as paranoid schizophrenic had a significantly higher frequency of FRS's than non-paranoid patients. Of the FRS's, delusional percepts, which were found in 49 percent of schizophrenic patients, were the most common, followed by thoughts broadcast, which were evident in 33 percent of schizophrenics. The remaining FRS's were found in 12 to 20 percent of the schizophrenic sample. Because one or more FRS's were found in 31 percent of patients with a diagnosis of affective psychosis and in 9 percent of patients with a diagnosis of neurotic or personality disorder, Carpenter and Strauss concluded that FRS's were not pathognomonic for schizophrenia. Followup data obtained at 2 years did not reveal any significant relationship between FRS's and outcome (based on patients' functioning during the 12-month period preceding followup assessments). Although use of Schneider's diagnostic concepts increased diagnostic reliability, Carpenter and Strauss concluded that they have neither high discriminating diagnostic value nor predictive ability. This study does not support the common European view that schizophrenia is a qualitatively distinct diagnostic entity with pathognomonic signs and symptoms and predictable course.

If hospital statistics are to be believed, affective disorders are much more common in London than in New York, while schizophrenia is relatively more common in the latter city. Zubin (MH 09191) and his colleagues, a group of investigators based at Biometrics Research in the New York State Department of Mental Hygiene and in London, have for several years been attempting to understand the sources of this interesting cross-national difference in the incidences of schizophrenia and affective disorders. From the first, they hypothesized that the different incidences might reflect systematic differences in diagnostic practices in the two countries. This hypothesis was supported by the results of an analysis of diagnostic ratings made by American and British psychiatrists who observed identical videotapes of patient interviews. Patients tended to be diagnosed schizophrenic by American psychiatrists if they showed some disorganization of thought, even if associated with marked mood disturbance; British psychiatrists, on the other hand, were inclined to diagnose the same patients as suffering from an affective disorder (Cooper et al. 1972). Interestingly, differences in the incidence of schizophrenia and affective disorders in New York and London hospitals did not become apparent until the 1940's. One explanation offered for

Table 1. Schneider's first-rank symptoms.

1. Hears voices speaking his thoughts aloud.
2. Experiences himself as the subject of hallucinatory voices, arguments or discussions.
3. Hears hallucinatory voices describing his activity as it takes place.
4. Experiences delusional percepts.
5. Experiences somatic passivity.
6. Experiences thought insertion.
7. Experiences thought withdrawal.
8. Experiences thought broadcast.
9. Experiences externally controlled or imposed affect
10. Experiences externally controlled or imposed impulses.
11. Experiences externally controlled or imposed motor activity.
the disparities observed in the diagnostic habits of American and British psychiatrists is the influence, in the New York City area, of prominent professors who espoused and taught a very broad concept of schizophrenia (Kuriansky, Deming, and Gurland 1974).

One of the problems with standard psychiatric diagnostic systems is that they are set up to assign a diagnosis to a patient. This system is exemplified in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders of 1968 (DSM-II). Gurland et al. (in press), in the U.S.-U.K. Cross-National Studies, found that neither a single recorded diagnosis nor even the multiple diagnoses presently allowed in DSM-II are adequate in classifying patients. In an attempt to test the value of alternative diagnoses, Gurland et al. studied consecutive admissions to a State psychiatric hospital in New York and an area mental hospital in London. Each patient was examined by a team of six project psychiatrists who assigned him or her a main diagnosis and, if the main diagnosis was uncertain, an alternative diagnosis. The investigators report interesting differences in symptoms and outcome among three groups of patients. The first group had a main diagnosis of affective disorder and no alternative diagnosis (the classic A group); the second group had a main diagnosis of schizophrenia and no alternative diagnosis other than a subtype of schizophrenia (the classic S group); and the third group had a main diagnosis of affective disorder and an alternative diagnosis of schizophrenia (the mixed A-S group). Not surprisingly, the classic A group had the most favorable outcomes and the least severe symptomatology, while the classic S group had the most unfavorable outcomes and the most severe symptomatology. The mixed A-S group was intermediate to the classic A and S groups in outcome and symptom severity. There was also greater disagreement between project and hospital staff diagnoses for the mixed A-S group than for the two other groups. Gurland et al. conclude that alternative diagnoses can be illuminating qualifiers of the main diagnosis, providing an analysis of the uncertainty of diagnostic categories and alerting psychiatrists to which diagnoses require further refinement. Without an alternative diagnosis, the mixed A-S group would have been classified as classic A. Yet the two groups have different symptom patterns and prognoses—and that in itself is good cause for separate classification.

Fleiss et al. (in press), in another study conducted under the auspices of the U.S.-U.K. Cross-National Project, have found that, in New York, patients diagnosed as having an affective disorder differ only slightly in amount of psychopathology (as measured by a standard interview) from patients labeled schizophrenic. In London, by contrast, there are marked differences in psychopathology between age groups. In both London and New York, patients with affective disorder tend to be older than patients diagnosed schizophrenic. Fleiss et al. believe the age differences are more a result of diagnostic habit than of differences in psychopathology between the two patient groups. In London, but not in New York, samples of patients diagnosed as suffering from affective disorder contain more females than samples of patients diagnosed schizophrenic. Again, the authors believe the difference in sex composition reflects— as do the age differences—diagnostic prejudices. If criteria were applied uniformly to males and females, Fleiss et al. maintain, more male affectives and more female schizophrenics would be found in London hospitals than is now the case. The results of this study are consistent with other findings of the U.S.-U.K. Project, in that phenomenological descriptions (i.e., based on standard interview items) seem to characterize patients more accurately than does a diagnostic label.

The difficulties with psychiatric diagnosis are well illustrated by the U.S.-U.K. results cited above. Diagnosis, to be meaningful, must serve a function. Too often its function becomes subservient to the process of choosing a label. Thus, although the intent of diagnosis may be the communication of information in a summary form, it may actually convey misinformation if insufficient attention is paid to the complexities and variability of human behavior during the diagnostic process.

Diagnosis is seen by some as having been written in stone, by others as a sacred cow that should be discarded. Perhaps the dispute could be mediated more effectively if diagnosis were viewed from a functional perspective. This approach would allow researchers to use different diagnostic processes tailored to suit their needs (e.g., reliability and replicability) as compared with those of clinical practice (e.g., as a guide to drug usage or prognostication). Thus, the question is not who is right and who is wrong but, rather, how to serve a variety of needs with an appropriate variety of practices.

Psychological Functioning

Despite many attempts to characterize the psychological functioning of schizophrenic patients, there is little agreement about the nature of the basic psychological processes associated with this disorder. Among the research questions that commonly have been posed in this area are: Is there a difference in what the schizophrenic perceives? Is there a difference in the way the schizophrenic processes what he perceives? What can these differences (if they exist) say about the personality
structure and defenses of the schizophrenic? Although few would quarrel with the pertinence of these questions, much controversy has surrounded the research methods used to answer them and the interpretation of the data generated.

Correlations between perceptual behavior and personality structure, for example, have been notoriously difficult to replicate. An aspect of perceptual style that has generated interest and controversy in the field is stimulus intensity control. As defined by Schooler and Silverman (1969), the term

... refers to the intensity with which perceptions are experienced. In sensory response studies conducted with low or ordinary ranges of stimulation, hypersensitive individuals experience stimuli intensely. Under conditions of high-intensity stimulation... their responses are attenuated. Such individuals are labeled reducers. Apparently because of their automatic tendency to attenuate high-intensity sensory input they are relatively tolerant of painful stimulation. On kinesthetic figural after-effect procedures... reducers underestimate the size of a "test bar" after having rubbed an interpolated stimulation bar for a period of time. Those on the other end of this dimension, who are termed augmenters, show a notable intolerance for pain but a relative tolerance for reduced sensory input. They respond on the kinesthetic figural aftereffect procedure by overestimating the test bar after having rubbed the interpolated stimulation bar [p. 459].

Striving to explain inconsistencies in the perceptual style of augmentation/reduction, Schooler and Silverman (1971) studied personality correlates of this dimension in acute as well as chronic schizophrenics. Using stimulus augmentation factor scores (stimulus augmentation being the tendency to overestimate the size of the test bar after having rubbed the interpolated stimulation bar), they found receptiveness to emotional stimuli and intellectual ability associated with high scores in acute schizophrenics and low scores in chronic patients. Using the Petrie task, another kinesthetic figural aftereffect (KFA) procedure in which blocks rather than bars are used, they found that overestimation of a block larger than the original comparison block correlated with passivity among chronic and acute patients. In contrast, overestimation of a block smaller than the original comparison block was related to psychological and intellectual intactness in both acute and chronic patients and to behavioral and conceptual expansiveness only among chronic. It should be noted that the validity and reliability of both Silverman's and Petrie's procedures have been questioned. Platt, Holzman, and Larson (1971) and M. Buchsbaum (unpublished data) have found only low test-retest reliability for these procedures. And both Schooler and Silverman (1971) and M. Buchsbaum (unpublished data) have found low or negligible correlations between Petrie's and Silverman's KFA tasks.

Because of the above-mentioned difficulties, as well as to minimize motivational and performance variables, Buchsbaum and Silverman (1968) developed a neuro-physiological analog of the Petrie procedure. In this procedure, augmenters are those whose average evoked response (AER) amplitudes increase with increasing stimulus intensity, and reducers are those whose AER amplitudes decrease with increasing stimulus intensity. It has been hypothesized that augmentation/reduction reflects the functioning of a central nervous system mechanism that modulates the perceived intensity of stimulation. The AER procedure is not reliably correlated with the Silverman and Petrie KFA tasks but, in contrast to these KFA measures, is itself reliable (Buchsbaum and Pfefferbaum 1971 and Soskis and Shagass 1974). Recently, Landau et al. (in preparation) used the AER procedure to study a group of unmedicated acute schizophrenics. As originally predicted by Silverman, the acute schizophrenics were AER reducers, and differed significantly from age- and sex-matched normal controls as well as from patients with affective disorders.

Difficulties with short-term memory have been hypothesized to account for the disorders of attention and thought found in many schizophrenics. Koh (MH 18991), pursuing this short-term memory hypothesis, tested immediate recall of word lists in young schizophrenic patients who were free from sustained psychotic disturbance. Compared to normals and nonschizophrenic patients, the schizophrenics were inefficient in taking advantage of the associative, affective, syntactic, and semantic cues experimentally provided for mnemonic organization of the word lists. On the other hand, schizophrenics given a recognition task demonstrated intact organization and search processes and intact storage organization of permanent memory. Koh interprets these results as suggesting that the thought disorder or associative dyscontrol noted in schizophrenic patients might be a secondary manifestation of a deficit in early stages of information processing, especially at the short-term memory phase. Koh is now attempting to define this deficit more precisely.

In a recent study, Tokar (MH 18042) used the Psycholinguistic Word Map Matrix to examine language patterns and conceptual organization in schizophrenic patients and normal subjects. In this task, subjects were
found by Harrow et al. is quite commonly reported
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groups (i.e., the test's nonspecificity for schizophrenia)
neural processes. The overlap between diagnostic
categories of objects. The overlap between diagnostic
classification. The first three characteristics were found

Schizophrenic controls (depressive and personality
disorders), but were also found in many acute non-

Tokar believes that this relatively simple test may
provide a useful objective measure of language patterns
and conceptual disorganization reflective of underlying
schizophrenic personality structure. A particularly
important aspect of this measure is its sensitivity to the
role of emotion in determining responses; for example,
anger affects the schizophrenics' performance. Indeed,
from one point of view, their performance on this
measure can be seen as reflecting sensitivity to affective
issues.

Numerous measures have been used in attempts to
identify, characterize, and quantify the thought disorder
commonly found in schizophrenic patients. One such
measure is the Object Sorting Test (OST), in which the
subject is asked to sort everyday objects (e.g., utensils,
pen, eraser) into groups based on a common charac-
teristic. Since its development by Goldstein and Scheerer
more than three decades ago, the OST has been modified
and scored in a variety of ways. Recently, for example,
Harrow et al. (1972) scored the test for behavioral
overinclusion, idiosyncratic thinking, and rich asso-
ciation. The first three characteristics were found
more frequently in schizophrenics than in non-

schizophrenic controls (depressive and personality
disorders), but were also found in many acute non-
schizophrenic patients. Judgments of behavioral over-
inclusion were based on observation of overt behaviors—
for example, the total number of objects sorted;
conceptual overinclusion was defined as using unusually
broad concepts in grouping objects; and idiosyncratic
thinking involved peculiar or odd, rather than too broad,
groupings of objects. The overlap between diagnostic
groups (i.e., the test's nonspecificity for schizophrenia)
found by Harrow et al. is quite commonly reported
when schizophrenics are compared with other psychi-

Genetics

In the early 1960's, David Rosenthal, Seymour Kety,
and Paul Wender began to plan a series of studies that,
they hoped, would at last establish—one way or the
other—whether heredity did or did not play some role in
causing schizophrenia. Without such evidence, they
They took advantage of naturally occurring adoptions to study the genetic predisposition to schizophrenia. According to Gunderson, and Buchsbaum (1973), it appears that being biologically related to a schizophrenic increases the risk for schizophrenia among offspring of schizophrenics and in monozygotic as compared with dizygotic twins. But such studies never offered incontrovertible evidence of a genetic predisposition to schizophrenia. So long as the offspring of schizophrenics were reared in disturbed families or in an environment disrupted by a parent's psychosis in the rearing parent is not a strongly pathogenic factor in the development of schizophrenia. Why did Rosenthal, Kety, and Wender succeed where so many past investigations had failed, or at least proved inconclusive? Earlier genetic studies had been relatively consistent in finding 1) heightened rates of schizophrenia among offspring of schizophrenics and 2) increased concordance rates for schizophrenia in monozygotic as compared with dizygotic twins. But such studies never offered incontrovertible evidence of a genetic predisposition to schizophrenia. So long as the offspring of schizophrenics were reared in disturbed families or in an environment disrupted by a parent's frequent hospitalizations, and so long as twins concordant for schizophrenia both grew up in the same, possibly pathogenic, atmosphere, the hypothesis that only environmental factors were critical in the etiology of schizophrenia remained viable.

What was needed to settle this controversy was a research design that separated the two major disputed variables—familial genes and familial rearing. And this design is what Rosenthal, Kety, and Wender provided. They took advantage of naturally occurring adoptions to separate the effects of heredity and environment. In an exhaustive investigation conducted in Denmark, Rosenthal, et al. (1968 and 1971) compared the mental health of the adopted-away offspring of one or more schizophrenic parents with that of controladoptees whose biological parents had no history of mental illness. Using a related strategy Kety et al. (1968 and 1971) compared the prevalence of mental disorder in the schizophrenia spectrum or other psychiatric diagnoses.

The prevalence of psychiatric disorder both within and outside the schizophrenia spectrum in the relatives was about triple that found from the records of psychiatric hospitals.

Whereas psychiatric diagnoses outside the schizophrenia spectrum were not higher in the biological relatives of the adopted schizophrenics than in the controls, the schizophrenia spectrum disorders (especially borderline or latent schizophrenia) were significantly concentrated in the biological relatives.

The diagnosis of schizoid or inadequate personality was made equally among the biological relatives of the schizophrenic and control adoptees.

The adoptive relatives of the schizophrenic probands did not differ significantly from the adoptive relatives of controls with respect to any of the diagnoses in the schizophrenia spectrum or other psychiatric diagnoses.

Seventeen of 33 biological families of the adopted schizophrenics showed one or more cases of definite or uncertain schizophrenia, as compared with 5 of 34 biological control families.

**Parental Influence**

Attempting to assess the impact of rearing by a psychotic parent, Fischer (1971) compared the incidence of psychopathology in the offspring of monozygotic (MZ) twins discordant for schizophrenia. Fischer found no significant difference in the frequency of psychopathology in the offspring of index schizophrenic twins as compared to the offspring of their nonschizophrenic co-twins. This finding, Fischer contends, "could probably best be explained if a genetic factor equally present in the schizophrenic and normal MZ twins was wholly or partly responsible for the syndromes we call schizophrenia." Although conceding that other factors, "such as the equal personality traits in the twins," could have influenced the result, Fischer concludes that overt psychosis in the rearing parent is not a strongly pathogenic factor in the development of schizophrenia.
Fischer's conclusion is consonant with Bleuler's (1974) finding of no significant differences in the incidence of psychosis in the offspring of schizophrenics, who often were reared by a psychotic parent, and the siblings of schizophrenics, who generally did not have a psychotic parent.

Based upon the findings reviewed above, rearing by a psychotic parent does not appear to be a strongly pathogenic factor. Many theorists have maintained, however, that schizophrenia is transmitted by parental behavior that, although not overtly psychotic, is characterized by certain specific communicational deviances. Two prominent exponents of this view, Wynne and Singer (1972), have now completed a study of adoptive parents of normals. Although it is unclear whether the observed communication deviance among biological parents of schizophrenics, and finally the adoptive parents, is anything more than a response to the adoptive parents of schizophrenics who generally did not have schizophrenic offspring. In 1968, Wender, Rosenthal, and Kety reported that the biological parents were significantly more disturbed than the adoptive parents of schizophrenics (p<.005) who, in turn, were significantly but not greatly more disturbed than the adoptive parents of normal subjects (p<.025), a difference they felt might reflect sampling artifacts. Wynne and Singer examined the Rorschachs of these parents for evidence of communication deviance, and found that 1) they could predict with 100 percent accuracy which parents had schizophrenic children, and 2) the adoptive parents of schizophrenic children had the most deviant communication, followed by the biological parents of schizophrenics, and finally the adoptive parents of normals. Although it is unclear whether the observed communication deviance among the adoptive parents is anything more than a response to having a schizophrenic offspring, the specificity of the communication disorder for parents whose child became schizophrenic is remarkable, and suggests that psychopathology as usually defined may be a less valuable indicator of schizophrenia in the offspring than communication deviance.

Genetic Markers

An important trend in genetic research is the search for the biological and clinical markers of the genetic factors involved in the transmission of schizophrenia. Reaction time has long been known to be one of the best discriminators of schizophrenic patients. Van Dyke (1972) hypothesized, therefore, that if the poor reaction time seen in adult schizophrenics were genetically determined, it would be associated with biological relatedness to a schizophrenic parent. To his surprise, he found that on a multiple reaction time task, subjects who had been reared by schizophrenic parents performed more poorly than subjects whose biological parents were schizophrenic but who had been reared by nonschizophrenic adoptive parents. This finding confirms earlier work by Zahn et al. (1972) on identical twins discordant for schizophrenia, which indicated that the schizophrenics' slower reaction times were an index of their level of psychopathology but were not genetically determined because the nonschizophrenic twins performed as normals did.

Another interesting attempt to demonstrate a possible genetic marker of vulnerability to schizophrenia was Wyatt et al.'s (1973) investigation of monoamine oxidase activity (MAO) in blood platelets of 18 MZ twin pairs discordant for schizophrenia. They found that MAO activity was significantly lower in both the schizophrenics and their nonschizophrenic co-twins than in normal controls. Based on this finding, Wyatt et al. conclude that low platelet MAO activity may be a genetic marker of vulnerability to schizophrenia. (Results of the study are covered in greater detail in the "Biology" section; see "Enzyme Studies.") Also intriguing as a possible genetic marker are the creatinine phosphokinase elevations Meltzer (MH 16127) has reported observing in about two-thirds of acute psychotic patients, as well as about one-fourth of the first-degree relatives of acute psychotics.

Prognosis

In an attempt to correlate prognosis or course of illness with the familial occurrence of schizophrenia, McCabe et al. (1971) interviewed first-degree relatives of 53 schizophrenic patients who had been divided into good- and poor-prognosis groups; interviewers were blind to the patients' prognostic categories. Interestingly, they found that the families of the poor-prognosis schizophrenics contained significantly more schizophrenia, neurosis, and overall psychopathology but less affective disorder than the families with the good-prognosis schizophrenic member. This work confirms earlier studies indicating that the occurrence of affective disorder in the families of schizophrenics bodes well for the outcome of that individual. McCabe et al.'s findings also support indications from the Danish adoptive studies that reactive (i.e., good prognosis) schizophrenia and schizoaffective psychoses probably are not genetically related to process (poor prognosis) and borderline forms of schizophrenia (Rosenthal 1971).
Remaining Questions

Despite the impressive data that have recently accumulated from a variety of genetic studies, the basic genetic mechanisms for this disorder remain enigmatic. That is, we do not know what is inherited or its mode of genetic transmission (e.g., monogenic or polygenic). Although a variety of genetic theories have been proposed, none have been confirmed, and none have been definitively discredited. Despite the lack of answers to very basic questions, recent genetic studies seem to have had salutary effects on several related issues: They suggest a genetic predisposition to schizophrenia, but at the same time make clear that genes alone are insufficient to produce schizophrenia. This suggestion in turn has generated new interest in studies of gene-environment interaction.

Because the diagnosis of schizophrenia and borderline schizophrenic forms of disorder is so basic to genetic studies, diagnosis has begun to receive the attention it warrants. The genetic studies reviewed above focus on more subtle diagnostic questions than crude hospital-record diagnoses, with their misleading implication that schizophrenia can be assessed as either clearly present or clearly absent. In particular, the concept of a schizophrenia spectrum of disorders used by Kety et al. (1968) seems an important new variant on traditional diagnostic practices. Yet, as is so often the case with such new procedures, its use raises important problems. For example, Kety et al.'s study suggests that acute schizophrenia and chronic schizophrenia may be qualitatively different entities, with the former having little genetic component. But most clinicians have seen acute schizophrenics go on to become chronic schizophrenics—a transition that would imply similarity, rather than difference, for the two diagnostic categories. The effort to make genetic data more clinically useful by defining prognostic subgroups is another important trend in recent genetic research. Thus, our increased genetic knowledge may lead to a greater precision in the determination of relative risk for schizophrenia.

The Family

The family did not come under the scrutiny of psychiatrists until the late 1940's and early 1950's—some 40 years after social workers and child guidance clinics had begun to deal with it as an important aspect of the treatment of individual patients. Frieda Fromm-Reichmann's (1948) paper on the schizophrenogenic mother—the conceptual parent of the later hypothesized schizophrenogenic family—was the first in this vein to receive widespread attention in the psychiatric literature. Since that time, research work on and with families has been carried out at a number of American centers, principally Palo Alto, Bethesda, Philadelphia, New York, Boston, Denver, and Galveston; significant contributions have also been made by a London-based group.

The possible importance of family factors in the development of schizophrenia has been highlighted by recent developments in other research areas—for example, studies of children at risk and the genetic adoption studies. Preliminary results from both areas have pointed up the need for critical designs and sturdy variables to tease out how family factors interact with a genetic predisposition or other risk factors to trigger or suppress expression of that predisposition. The degree to which we are successful in studying these interactions will determine how well we will be able to unravel the relative contributions of nature and nurture to the development of schizophrenia. The sophistication, both in terms of hypotheses and methods, shown by the studies described below is impressive for this relatively young (about 25 years old) research area.

Friedman and Friedman (MH 11547) describe a pilot study that compared historical factors and current functioning of "normal" families with families having a schizophrenic offspring. They found that mothers of schizophrenics reported having more serious medical problems than did mothers of normals. Mothers of schizophrenic daughters had significantly more psychosomatic disorders than did control mothers or mothers of schizophrenic sons. Parents of schizophrenic patients performed more poorly and showed more evidence of thinking deficit on several tasks than control parents. Unfortunately, the control group fathers were significantly younger than the fathers of schizophrenics. Due to this and other methodological difficulties, the results must be regarded as tentative. They are consistent, however, with previous descriptions of families with schizophrenic offspring.

Reiss and Elstein (1971) have studied the perceptual and cognitive dispositions of 24 families with a psychiatrically hospitalized offspring. Based on the psychopathology of the child, the 24 family units (each consisting of both parents and the ill child) were divided into the following three groups of eight families: 1) paranoid schizophrenic, 2) nonparanoid schizophrenic, and 3) a psychiatric control group (character disorder, depressive reaction, and adjustment reaction of adolescence). The investigators report that the families of schizophrenics showed more difficulty on measures of abstraction (Shipley-Hartford Abstraction Scale); showed more frequent overexclusions using Epstein's
Inclusion Test, a measure of the extent of overinclusive and overexclusive thinking; and showed reduced reversal rates on the Reversible Figures Test. They found that, as a unit, most families with schizophrenics were unable to discern the underlying pattern or deep structure in an array of ordered stimuli. There were no significant differences between families with paranoid members as compared with nonparanoid schizophrenic members.

"Selection" of the Schizophrenic

In work with a series of MZ twins discordant for schizophrenia and their families, Leisinger (1972) explored hypotheses relating patient and parental roles and family interaction to the occurrence of manifest disturbance. The conceptual frame of reference was that shared unconscious pathology of the family system generates interlocking tensions, which are reduced by projection onto a particular member. Fragmentation of experience, identity diffusion, disturbance of motor perception, and distortion of thought and affect—some of the salient characteristics of schizophrenia—were hypothesized as being present to some degree in each member or relationship. When manifested by the patient designate, they were seen as his reflecting each member's characteristics in their most exaggerated form. To test these hypotheses, 10 families with "normal" twin pairs were compared with 20 families of MZ pairs discordant for schizophrenia (total sample of 120 individuals) on the Leary Interpersonal Checklist. Each individual described himself, his hypothetical ideal self, and each of the three other family members. Also, specialized scoring systems were used on individually administered Thematic Apperception Tests to measure 1) the level of conscious communication; 2) the level of private perception versus preconsciously symbolic representation; and 3) the level of values or ego ideal. Leisinger's data reveal that individuals in families with a schizophrenic offspring unconsciously perceive themselves as very similar—father similar to mother, child similar to parents, and parents similar to offspring. Normal family members portray themselves as different one from the other within the families, with the father particularly being perceived as exhibiting a well-differentiated role identity. This blurring of sex role and identity differences seems to lend credence to Bowen's description of the families of schizophrenics as having an "undifferentiated ego mass." Further, Leisinger found evidence consistent with Laing and Esterson's (1964) formulations that parents perceive the schizophrenic in terms that misdefine him to himself. In particular, parents tended to view the schizophrenic as globally passive and instrumentally unable to master his environment despite his efforts to be assertive or competent. These psychological-test-derived observations are consistent with earlier clinical reports on this series of discordant MZ twins that had shown that the index twin was preferentially imprinted (as compared with his non-schizophrenic co-twin) with a role expectation of incompetence and dependence from an early age.

Hoover and Franz (1972) have addressed a critical question for family research: why does one offspring in a family become schizophrenic while others do not? Attempting to answer this question, they studied 30 schizophrenic patients and their 57 siblings along three parameters: 1) degree of family entanglement, 2) degree of illness, and 3) degree of functional impairment. Using clinical interview data, the two investigators independently rated each subject on each variable. Signs of family entanglement included: use of advice, give and take in arguments, affection, dependency, conflictual ties, workable autonomy, and ability to foresee eventual differentiation in relation to the family. Degree of illness was assessed in terms of anxiety, hostility, constriction, symptoms, global clinical estimate of pathology, and diagnostic categorization. The functional impairment scale assessed the effectiveness of a subject's performance on the job or at school and in social relationships. As might be expected, the 30 patients scored significantly higher on all three variables. Almost all of the siblings (86.8 percent) demonstrated the lowest levels of functional impairment (i.e., highest social adjustment) and most (58.8 percent) demonstrated low levels of illness. There was an interesting overlap on measures of family entanglement: most of the schizophrenics (83.3 percent) showed high levels of entanglement, and a significant number of the "well" siblings (33 percent) did also. The degree of illness in the siblings did not correlate with exposure to the schizophrenic patient, since proximity in age to the index case did not significantly correlate with degree of illness. Nor could degree of illness in individual sibs be related to exposure to family-wide pathogenic processes, since there were marked variations in degree of illness within families. Six patterns of sibling/family interaction emerged from their data: by far the largest group of sibs (51 percent) was embroiled in the family but struggling to get free, and frequently demonstrated some degree of psychopathology—for example, neurosis or character disorder. The second cluster of sibs (19 percent) related well to other people, participated in a wide range of activities outside the home, and had achieved a fair amount of autonomy and individuation from the family. A third group (16 percent) isolated themselves from the family conflict,
were rigid, and formed relationships slowly. The remaining sibs (14 percent) dealt with their families in the following ways: They were 1) immersed in the family, 2) compliant and closely identified with the parents, 3) delinquent with acting-out behavior, or 4) a "near miss" for the diagnosis of schizophrenia. The authors conclude that these behavioral clusters represent some of the ways in which siblings can interact with a potentially pathogenic family to avoid schizophrenia. However, in view of the relatively small numbers of siblings in some of the clusters, the absence of a control group of normal families, and lack of evidence that preschizophrenics don't also demonstrate these coping patterns, the specificity of these patterns for "avoiding" schizophrenia remains to be established.

Praise and Censure

Since the mid-1950's, praise and censure have been reported to affect performance differentially, depending on the subject's type of preillness adjustment (i.e., relatively normal vs. impaired). Using a praise and censure reinforcement procedure which he believed to be an analog of early parent-child interactions, Klein (MH 18308) attempted to assess the impact of praise and censure on the performance of adult psychiatric patients. In addition to focusing on the relative potency of praise and censure, Klein examined the effect of three different reinforcement agents—the patient's father, his mother, and the experimenter. Contrary to expectations, preliminary data from a group of 40 nonparanoid schizophrenics and 40 nonpsychotic psychiatric controls showed that, based on scores of erroneous or delayed responses to a verbal discrimination of a nonsense syllables task, all subjects—regardless of psychopathology, type of reinforcement, or reinforcing agent—performed at the same level. This is at odds with previous reports that have characterized process schizophrenics as more responsive to censure than praise. If these findings are borne out, they will call into question the adequacy of the parent-child analog that has previously been employed in this area (or the adequacy of this experiment as a test of that analog).

Experimental Families

Many investigators of family interactive processes have reported that parents interact differently with a schizophrenic child than with his normal sibling and that, conversely, the schizophrenic child behaves differently with his parents than does a well sibling. Unfortunately, because parents and children have interacted for many years, investigators cannot be sure whether these differences are etiologically significant in the development of disorder, or simply reflect a parental response to the child's preexisting illness. Hoping to bypass this perennial problem of family research, Waxler (MH 18341) studied the following four types of “experimental” families (i.e., parents interacting with an unrelated adolescent child): experimental group 1, normal parents with a schizophrenic child; experimental group 2, parents who have a schizophrenic child with a normal child; control group 1, normal parents with a normal child; and control group 2, parents who have a schizophrenic child with a schizophrenic child. During the experimental session, each pseudofamily was asked to complete an abstract 20-questions problem-solving task: First, each individual worked alone on the 20-questions task; next, the experimental family worked together as a group to solve three trials of the task; and finally, each individual once again worked alone. Individuals and “families” were compared across time (i.e., before, after, and during the group sessions) for change in level of performances. In addition, the causal agent (the person whose cognitive performance remained relatively more stable) and the affected person (the person whose performance changed across time) were identified. Control group 1 (normal parents, normal child) showed significantly greater influence of one person over another and more instances of mutual influence. By contrast, in control group 2 (parents of a schizophrenic child with an unrelated schizophrenic child), only the mother was a significant causal agent. She influenced the schizophrenic child to use an abstract strategy consistently different from her own. Parents in experimental group 1 (normal parents, schizophrenic child) succeeded in influencing the child to use cognitive problem-solving strategies like theirs. In experimental group 2 (parents of a schizophrenic interacting with a normal child), parents had an indirect or passive effect upon this usually influential adolescent, so that he lost effective influence. The effects of normal family members (whether parent or child) on parents of schizophrenics or schizophrenics were much more consistent than the effects of schizophrenics or parents of schizophrenics on normals. Unfortunately, the experiment provides some support for both the etiologic and responsive hypotheses, since both parents and children were "causal" agents. The finding that cognitive deficits of schizophrenics can be reversed by interaction with normal parents may have important practical application to treatment.
Communication Deviance

Some of the difficulties with replication studies (perhaps explaining why they are not often done) are found in a recent effort by Hirsh and Leff (1971) to repeat Singer and Wynne's (1965) work distinguishing parents of schizophrenics from parents of offspring with other psychiatric disturbance and normals by means of communication deviance scores (based on such characteristics as peculiar language, overexactness, and blurred meanings). Using Singer and Wynne's (1966) Rorschach manual, these investigators compared the communication deviance scores of families of a sample of English schizophrenics and neurotics. Subjects were tested and scored blindly, and the scoring was shown to be reliable. Hirsh and Leff were able to demonstrate statistically significant differences in communication deviance scores between the two groups but were unable to replicate Singer and Wynne's finding of almost no overlap in the distribution of scores between parents of schizophrenics and parents of neurotics. These investigators relate the discrepancies between their findings and those of Singer and Wynne to 1) not completely replicating Singer and Wynne's testing and scoring methods, 2) differences in the ways subjects were obtained, and 3) differences in diagnostic practices between the two countries. Although this study well illustrates their difficulties, replication studies are crucially important to the growth and development of the field of family research.

Some Conclusions

Developments in family study methodology are making it increasingly possible for investigators to address the critical questions confronting the field: Is the family implicated as a causative agent in schizophrenia, or are parental abnormalities merely a response to prolonged contact with an offspring's unfolding schizophrenic disorder? What distinguishes the offspring who becomes schizophrenic from his sibling who does not? Are the intrafamilial communication disorders that have been reported specific to schizophrenia, or are they more general phenomena associated with any number of psychopathological conditions? Singer and Wynne believe, for example, that deviant communication in the parents is specific to the occurrence of schizophrenia in the offspring, because their data show little overlap in scores between families with a schizophrenic and families with a neurotic offspring. Nevertheless, the possibility that communication deviance represents an extreme parental reaction to extreme disorder in the child cannot be ruled out, since Singer and Wynne's neurotic control group is less severely ill than their schizophrenic group. To disentangle aspects of the data that reflect severity from those specific to schizophrenia will require other types of controls (e.g., equally severe nonschizophrenic psychosis) or other research approaches (e.g., experimental families).

Family studies are difficult for two major reasons: 1) the great number of potentially influential variables over which the experimenter has little control and 2) the serious ethical issues these studies raise. Many feel family studies are efforts to blame parents, invade privacy, or manipulate child-rearing practices. These concerns must be taken seriously and dealt with if family studies are to continue to be conducted. The family is without a doubt the single most powerful socializing influence in anyone's life. This fact, taken in conjunction with increasingly community-based (i.e., family) treatment, draws attention to the need for studies of the family's impact on recidivism and community adjustment in the discharged schizophrenic.

Several types of family research appear to be especially needed at this time:

- Naturalistic, hypothesis-generating studies of families designated vulnerable to the occurrence of schizophrenia (i.e., high risk families), of families containing a discharged schizophrenic, and of families with a schizophrenic in remission; it would be especially important to study the schizophrenic and his family in their natural habitat (i.e., the home), since most family studies have been clinic or laboratory based.

- Use of high risk and experimental families to help unravel the etiologic from the responsive explanations of the evidence implicating family factors in this disorder.

- Careful comparative studies of sibs in families with various types of manifest psychopathological disorders; such studies can give us important clues about operant familial factors that lead to coping and competence, as contrasted with the dysfunction found in the labeled patient.

- Replication (within and across cultures) of findings that seem to indicate specific types of communication patterns in both lower- and middle-class families having schizophrenics as compared with other types of disordered offspring.

Studies of Populations at High Risk

For the past several years we have reported growing interest in the high risk method, in which persons
believed especially vulnerable to schizophrenia—usually the offspring of schizophrenics—are studied before the occurrence of manifest disorder. The burgeoning popularity of this research strategy leads us to sound a cautionary note. Although the method has many unique advantages, it should not be seen as providing a quick cure for the traditional difficulties inherent in research on schizophrenia. Now that a number of major projects are under way, the high risk field is beginning to encounter methodological snags. Primary among these is the fact that the investigator, having once discovered a distinguishing characteristic of subjects at risk, must still demonstrate that his finding is correlated with a schizophrenic denouement that may not eventuate until many years after the conclusion of his initial studies. Therefore, it would be unrealistic to expect that the high risk method will speedily fulfill its ultimate goal—distinguishing persons who go on to develop schizophrenia from those who do not. Lest disappointment over the failure of the method to yield a quick payoff lead to a premature loss of interest in high risk studies, it should be remembered that these studies can significantly enhance our knowledge of invulnerability and normal child and family development. The possibility of health-related contributions should be kept clearly in mind as research derived from this method’s use is assessed over the next several years.

Last year, we (Mosher, Gunderson, and Buchsbaum 1973) reported that, based on preliminary findings of ongoing high risk studies, the following characteristics seemed to distinguish high risk from low risk children: 1) inattention, withdrawal, and lack of positive affect in the preschool age; 2) psychiatric referral; 3) unsocialized aggression among boys and overinhibited hyperconformity among girls during high school; 4) absence of intimate peer relationships in early adolescence; 5) evidence of neuropathology under age 11; 6) frequent ill health during childhood; and 7) disorganized, disruptive families, including parental loss. During the past year, several new differentiating factors have been reported and are reviewed below. It should be pointed out that the prognostic validity of these factors remains to be established from longitudinal studies.

**Psychophysiological Studies**

Based on digital computer analysis of the electroencephalogram (EEG), Itil (MH 20801) and his associates found statistically significant differences between EEG patterns of 31 children of schizophrenic mothers and 50 controls with normal parents. The EEG's of the risk children were characterized by low amplitude, increased variability, more slow delta waves, less slow alpha waves, more high frequency activity, and variability in high frequency activity. Interestingly, a very careful clinical (i.e., not computer-analyzed) study of the EEG’s failed to show significant differences between the two groups of children. Itil and his associates conclude that the striking similarity of their previously reported digital computer period analysis EEG data from adult schizophrenics to the results obtained in children of schizophrenic mothers suggests physiopathological factors related to schizophrenia may be present long before the onset of schizophrenic illness. Because only 10 to 15 percent of this sample are expected to develop schizophrenia, these investigators point out that it is important to search for additional factors that discriminate those risk children who eventually develop schizophrenia from those who develop other problems or develop normally.

Mednick and Schulsinger (1972), two pioneers of risk research, have previously reported that 207 offspring (aged 10 to 20) of schizophrenic mothers demonstrated autonomic instability compared to 104 control children. In a 5-year followup, they compared a group of 20 risk children who had developed severe psychiatric disturbances with a matched group from the risk sample who thus far showed no signs of mental disorder. Looking back at data originally collected in 1962, they found that the disturbed group had shown significantly more deviant autonomic responsivity at that time than members of the risk group who did not go on to develop psychopathology. They also found that the disturbed group had had significantly longer periods of separation from their mothers during early development. Mednick and Schulsinger currently are conducting a 10-year followup assessment on a variety of psychological and physiological variables in this sample. They have tentatively concluded, meanwhile, that early evidence of autonomic dysfunction may predict serious adult psychopathology. This conclusion remains the focus of much research attention and controversy. There is a need for confirmatory replications before its significance can be properly weighed.

One specific outgrowth of Mednick and Schulsinger's research is Schachter's (MH 22840) study of psychophysiological responsiveness in infants at risk. By studying neonates, Schachtzer hopes to eliminate the confounding effects of maternal separation which were also found to be significantly related to galvanic skin resistance (GSR) responsiveness in the Mednick-Schulsinger study. Analysis of heart rate responses to auditory stimuli from 112 newborns, including 23 with a schizophrenic mother, indicates that the following two
types of physiological characteristics distinguish the offspring of schizophrenic mothers: 1) A marked increase in heart rate acceleration over the test session was seen in four newborns whose mothers had had high levels of medication for delivery. 2) Two infants showed both an abnormally low heart rate increase and an abnormal EEG response when presented with the loudest auditory stimuli. Neither of these findings could be accounted for by differences in the emotional state of the mothers during pregnancy, by differences in complications of pregnancy, labor or delivery, or by differences in several other perinatal factors studied. The followup portion of this study focused on whether the offspring of schizophrenics who showed distinguishing characteristics at birth actually exhibited more deviant development during early childhood. Schachter and his colleagues have attempted to isolate and evaluate factors in the environment that might aggravate a tendency toward deviant development. Followup of 32 infants (14 with schizophrenic mothers) at 5 to 8 months of age indicated that offspring of schizophrenic mothers showed deficiencies in physical growth and health. They also tended to exhibit more developmental problems. Since the nurture and care provided by the schizophrenic mothers seemed substantially less adequate than that provided in families free of schizophrenia, the investigators concluded that it is not possible to determine the degree to which the deficiencies in physical development were a function of inadequate nurturing care or an expressed genetic predisposition to schizophrenic disorder. As in Mednick and Schulsinger's work, the confounding effects (on any genetic/constitutional factors) of poor maternal care became apparent.

Influence of Rearing by a Psychotic Parent

Recognizing the importance of this factor, Grunebaum (MH 13946) and his group have focused specifically on the quality of care psychotic women provide for their offspring. After comparing psychotic mothers to a matched sample of normal mothers on specially constructed measures of maternal attitudes and character development, they reported that the psychotic mothers, as a group, tended to deny rather than acknowledge normal child-rearing concerns, had difficulty in seeing the mother-child relationship as reciprocals, and showed inappropriateness in establishing closeness to and distance from their children. Grunebaum and his group believe these findings, if further pursued, will eventually allow investigators to specify more precisely the pathogenic aspects of the global concept, "poor mothering."

Preventive Intervention

As risk studies begin to focus on environmental factors, such as the disturbed family situation, as well as on biogenetic factors, the possibility of preventive intervention assumes immediate significance. Two risk projects have incorporated interventions into their research design and now have some preliminary data about the effectiveness of these programs.

Grunebaum (MH 13946) and his associates, as part of a study of mothering in psychotic women, have developed an intensive child-oriented nursing aftercare program in the homes of 25 psychotic mothers. Although the mothers tended to rely heavily upon the nurse as a source of support and counsel, the preschool-aged children showed few differences from control children (also born to psychotic mothers) for whom nursing care was not available.

Manfred Bleuler (1974), drawing from his unique experience as a family psychiatrist, has described the life courses of the 184 offspring of 206 schizophrenic parents he treated and followed systematically since 1938. He found that, although 10 children to date have developed schizophrenia, their course of illness and presenting symptomatology bore no resemblance to that of their schizophrenic parent. More surprisingly, he found a higher frequency of normality (approximately 72 percent) in these offspring than has been reported in other studies (33 to 50 percent). He explained this difference in results in two ways: First, although diagnostic criteria for schizophrenia may vary somewhat from study to study, the diagnosis of nonschizophrenic disorders (e.g., schizoid psychopathy) and of "normality" is even less reliable. Second, his diagnostic evaluations were done on people he knew closely over time, as contrasted with other studies in which the subjects were evaluated by relative strangers for strictly diagnostic purposes. Having observed that normal development can take place in the face of severe neglect, "teaching of irrationality," and parental degeneration, Bleuler concludes that the effect of prolonged immediate contact with an overtly psychotic parent is insufficient to explain the subsequent development of schizophrenia. Nevertheless, early childhood suffering was associated with poorer levels of adult functioning among these offspring. Finally, he showed that, for the majority of the offspring who were not schizophrenic, the chances of their children (i.e., the grandchildren of schizophrenics) developing schizophrenia were very little or no greater than for the population at large.
Anthony (MH 14052) has evaluated 138 grade-school-aged children (6 to 11 years old) from 46 families with a psychotic parent on four clinically derived variables which seemed relevant to the lives of these children: logical thinking (the ability to make sense), reality testing, identity (involving differentiation of the self and others), and organizational competence (including intelligence). Using a variety of psychological tests, Anthony found that the children of psychotic parents could be discriminated on all four variables from matched and unmatched samples of children whose parents were not psychotic. Reasoning that these scores provide a measure of the child's vulnerability, Anthony devised the following four intervention programs through which he hoped to influence the children's scores: 1) The compensatory program provided children with many supportive, recreational, and creative opportunities outside the home; 2) the classical program offered individual and group therapy; 3) the cathartic program emphasized family interviews during times of psychotic illness of the parent; and 4) the corrective program included demystifying or reality-testing sessions with the child. Preliminary results suggested that the amount of intervention in man hours correlated with the change in vulnerability score. The classical program was associated with the greatest changes in vulnerability scores, but since the program also involved the greatest number of man hours, it is difficult to say whether its success stems from the particular therapeutic techniques used or from the substantial amount of time spent with the children. Cathartic procedures, which seemed efficacious early in treatment, did not appear to have much lasting impact. Finally, there seemed to be some relationship between the extent of change in a child's vulnerability score and the extent of change in the organizational structure and function of the family as rated independently by a social worker visiting the family at home. Unfortunately, it is difficult to say whether these family changes were brought about by the intervention programs. Although the four interventions appeared to have lessened vulnerability, only very tentative conclusions can be drawn from Anthony's study, since no untreated control group was used.

Ongoing high risk studies continue to add new details to the still sketchy picture of the preschizophrenic. But each new descriptive detail should not be automatically endowed with etiological significance. It must be remembered that, although we are learning to describe preschizophrenic children, no definite etiologic factors have yet been established. Thus, intervention programs are necessarily symptomatic—that is, dealing with these children's immediate difficulties, which might or might not relate to the development of schizophrenia in adulthood. Interestingly, however, if symptomatic treatment is shown to be effective in preventing schizophrenia, it will facilitate the development of more specific, refined etiologic hypotheses.

Research on the vulnerable child seems to be in an era of high activity (in terms of data collection) but low productivity (in terms of analysis and publication). We applaud this trend, as premature publication of unjustified claims might do great harm to the field and to the children and parents who are its subjects. Statements that might prove unsupportable over the long run could lead to unwise attempts at drastic intervention, stigmatization, and a variety of unnecessary iatrogenically generated problems. Backlash from this situation could effectively prevent further research in this very critical area.

Childhood Schizophrenia and Autism

We must begin this section with a caveat: The section's title, "Childhood Schizophrenia and Autism," is not meant to imply that these terms are either mutually exclusive or all inclusive. Given the abundant disagreement about almost all aspects of severe mental disorder of childhood, especially its categorization, we prefer, and will very often use in our editorial remarks, the more general term childhood psychosis. As will be noted at the end of the section, comparisons of the ways in which terms are used and achievement of consensus as to how they should be used remains a major impediment to progress in this area.

Studies reported here fall into two major categories: 1) efforts to delineate basic descriptive and etiologic factors defined in psychological, biological, and neurological terms and 2) efforts to improve the treatment of these disorders.

Descriptive Studies

The lack of professional consensus in diagnostic terminology for severely disturbed children is endemic to the field. But although diagnostic terminology is widely disputed, child psychiatrists and psychologists generally agree that a crucial problem confronting such a child is his or her apparent inability to relate normally to other people. Some theorists attribute problems in human relatedness to preexisting problems in the environment—particularly disturbances in mothering relationships. Believing that such an interpretation is oversimplified, Reichler and Schopler (1971) recently attempted to demonstrate that human relatedness is a
multidimensional, complex construct that can be analyzed in terms of simpler, more basic functions. These investigators used a 14-point diagnostic scale to evaluate 66 psychotic children, and subjected their findings to a factor analysis, which revealed a clustering of variables concerning human relatedness and perceptual functions at various levels of complexity (i.e., auditory, visual, and near-receptor responsiveness, verbal and motor imitation, body awareness, and relation to nonhuman objects). The most parsimonious interpretation of this result, Reichler and Schopler believe, is that human relatedness is but one aspect of the organism's total ability to relate to his external environment and, further, that impairment in human relatedness appears to be largely due to impaired perceptual functions. Thus, they conclude that much inappropriate maternal behavior may be a response to preexisting disturbances in psychotic offspring—rather than (as has often been supposed) vice versa. Reichler and Schopler concede, however, that inappropriate maternal behavior—even if itself responsive—may have an amplifying effect on the child's already disturbed behavior.

Based on research conducted at the Ittleson Center in New York City, Goldfarb (MH 5753) believes that there is a disturbance in neurological integrity in some children diagnosed schizophrenic, but adds that these children characteristically show errors in communication and thought as well. Because Goldfarb's recent work has confirmed the presence of a great many and varied speech and language difficulties, he believes that approaches focusing exclusively on some one communication fault—for example, echolalia—may be too narrow. Indeed, Goldfarb has sometimes found opposite kinds of language problems—for example, too much or too little stress on particular syllables—in the psychotic children in his sample. Goldfarb concludes that the range of communication disturbances observed is best explained by a core disturbance in the organizing and integrative process of the ego.

DeMyer and her group (1971) in Indiana have reported a new biological abnormality in a group of psychotic children. They found that baseline free fatty acid (FFA) levels were highly variable in 15 psychotic children compared to 14 emotionally disturbed and 49 normal children. Despite these variable baselines, the psychotic children demonstrated a normal lowering of FFA in response to intravenous insulin injection (this contrasts with a paradoxical rise noted in some adult schizophrenics); moreover, their response to glucose ingestion, as expressed in FFA and glucose levels, was comparable to that of the two control groups. DeMyer et al. speculate that FFA variability in psychotic children may reflect a defect in neurogenic or cellular level regulation. As with other biological correlates of this disorder, baseline FFA abnormalities are variably present, and their interpretation is confounded by a number of uncontrolled variables (e.g., psychological set, diet, exercise, and hospitalization). Furthermore, FFA levels are the end result of complicated internal control factors involving both the endocrine and nervous systems.

As part of an ongoing investigation of the possible disturbances of the vestibular system in autistic children, Ornitz (MH 13517) has studied the effect of vestibular and auditory stimulation on eye movements during the rapid eye movement (REM) or dreaming phase of sleep. He introduced a vestibular stimulus (rocking) to groups of both normal and autistic children during sleep and studied the effect on the spontaneous eye movement activity. He found, based on all-night sleep recordings, that the variability and organization of REM bursts increased in response to rocking in normal children, whereas among autistic children, REM activity either showed no response or decreased during the course of the night. REM response to auditory stimulation was in the same direction as, but less clear-cut than, the response to vestibular stimulation. Since extensive animal studies have shown that eye movement activity occurring during REM sleep depends upon the normal functioning of central connections of the vestibular system, the results suggest that the central vestibular connections are less responsive to stimulation in autistic than in normal children. Ornitz believes this finding provides new evidence of vestibular dysfunction in autistic children.

Lovaas and his colleagues (Lovaas et al. 1971 and Lovaas and Schreibman 1971), a team of investigators who, like Ornitz, are based at UCLA, have reported that autistic children characteristically respond to only one component of a complex stimulus. They characterize this tendency as stimulus overselectivity or overselective attention (see, also, Koegel and Wilhelm, in press). In recent research, Lovaas and his group have found that overselective attention occurs within as well as between modalities; that the tendency interferes with the autistic child's learning in environments where there are additional stimulus inputs; that attentional difficulties are also apparent in social situations (i.e., recognizing people on the basis of such nonessential cues as pieces of clothing rather than the face); and that overselective attention is related to the psychotic child's characteristic difficulty in generalizing learning from one situation to another.
In the preceding four studies, perceptual, cognitive, biochemical, neurological, communicational, and attentional deficits have been described in children variously called childhood psychotics, autistic children, or childhood schizophrenics. In her cohort of similar children, labeled childhood schizophrenics, Fish (1971) notes many of the same deficits. Attempting to integrate these many findings, she notes that the neurological features of schizophrenia in infants and young children bridge the gap between the neurophysiological and psychological studies of this disorder. She postulates that in infancy inadequate central nervous system (CNS) integration disturbs growing organizational alertness, activity, muscle tone, vestibular function, proprioception, and autonomic stability. This results in a fluctuating and erratic pattern of development. She suggests that the fluctuating level of integration in childhood schizophrenia is itself a part of a basic integrative disorder of CNS functioning and can be related to the fluctuating states of attention and arousal that have been observed.

All of these hypotheses about the core deficiency in childhood psychoses remain speculative. They all include, or allow for, an underlying neurological, biological, and genetically determined substrate. As yet, little is known about the nature of the hypothesized substrate. It is worthy of note, however, that both Fish and Goldfarb describe the core disturbance as a failure of integration. Whether this basic failure of integration is primarily neurological or ego psychological remains an empirical question.

**Treatment**

It has often been noted that a therapist's etiologic theories—even if loosely held and unarticulated—influence his clinical practice. An interesting illustration of this phenomenon can be seen in the therapeutic approaches of four investigators (Schopler, Goldfarb, Lovaas, and Fish) whose attempts to identify the basic deficit in childhood psychosis have been described above. Not surprisingly, the treatment programs developed by these investigators are, to some extent, an extension of their formulations of the childhood psychotic's basic deficits.

Reflecting their view that the social withdrawal of autistic children is not a product of unhealthy parental influences, Schopler and Reichler (1972a and 1972b) have used parents as teacher/therapists. Attempting to erase doubts about the ability of parents to be objective, the investigators recently compared parental evaluations of their children's developmental level in six different areas of function (mental function, self-sufficiency, social skills, motor function, language, and overall development) with assessments of the same functions obtained from batteries of psychological tests. They found that correlation coefficients between the psychometric and the parental assessments were significantly high, indicating that parents were aware of their children's developmental functions. Through systematic and repeated assessments of each child's areas of achievement or failure, at-home treatment programs are tailored to his or her needs. These programs focus on using parents as teachers of the specific cognitive and perceptual skills lacking in the child. In addition to their programs employing parents as therapists, Schopler and Reichler have found a number of other helpful treatment techniques, including operant conditioning, special education methods, and occasional drug interventions. Based on their research, Schopler and Reichler have concluded that the success of specific treatment techniques largely depends upon the following characteristics of the overall treatment program: 1) the practice of frankly sharing with parents the available diagnostic information about their child, 2) the diffusion of expertise through the use of paraprofessionals, 3) the recognition that behavioral interventions are only effective if they can be carried over into the home environment, and 4) the preservation of parental authority. The promising results of Schopler and Reichler's program and its popularity with parents have resulted in an expanded statewide program in North Carolina; the program includes three centers in which individualized management and educational strategies are worked out with parents and in conjunction with special education classes in the public schools.

Goldfarb's ego-integrative theory of the core difficulty in schizophrenic children has led him to develop psychotherapeutically oriented residential treatment programs. He and his co-workers evaluated schizophrenic children at admission and 3 years later in terms of the following characteristics: educational attainment, social competence, neurological integrity, perceptual and conceptual response, intelligence, psychomotor ability, orientation, communication, startle behavior, and response to delay in auditory feedback (confronting the child with his disordered communication). He reports that, as a group, the children improved on 35 of 40 behavioral dimensions during the 3-year period. Individual decline in this sample was a rarity. There were, of course, distinct variations among subgroups when the children were subdivided by sex, age of admission to treatment, neurological integrity, social
classification, and intelligence level, but the overall improvement achieved was impressive.

Lovaas, whose theoretical orientation is primarily behavioral, has reported on the evaluation of 20 autistic children treated with behavior therapy (Lovaas et al., in press). Since research on this treatment first began in 1964, Lovaas and his group have made comprehensive pretreatment, posttreatment, and followup behavioral assessments. The results of this evaluation are summarized below:

- Inappropriate behavior (echolalia and self-stimulation) decreased, while appropriate behavior (appropriate speech, play, social nonverbal behavior, IQ scores, and Vineland Social Quotient scores) increased.
- There were no exceptions to the improvement, but some of the children improved more than others.
- Followup measures taken 2 years after treatment showed large differences, depending on the posttreatment environment. Children whose parents were trained to carry out the behavior modification techniques continued to improve, while children who were institutionalized regressed.
- A brief reinstatement of behavior therapy could reestablish original therapeutic gains in the institutionalized children.

These findings confirm both Goldfarb's report of overall improvement and Schopler's data which indicate that parents are useful extra-institutional therapeutic agents.

The search for effective drug treatment of psychotic children stems partially from the belief that these children have a CNS disease. Fish's conceptualization of autism as a neurologically based disease has led her group to treat these children with various psychoactive drugs. Magda Campbell, a co-worker of Fish's, recently reported a controlled trial of tri-iodothyronine ($T_3$—a very rapidly acting thyroid hormone) in a limited number of severely disturbed 3- to 6-year-old childhood schizophrenics (Campbell and Fish MH 4665). The investigators state that the drug appears to have both stimulating and antipsychotic properties without serious side effects. The children showed stimulation in terms of lessened withdrawal and increased language production and vocabulary. They played more after treatment and their affect was more responsive. Moreover, children who had tended to daydream excessively became alert, while overactive children quieted down. This treatment approach may be a promising lead—but one that must be regarded as tentative and certainly not understood.

Each of the studies reported above provides important data on changes observed in patients after treatment—data against which claims of efficacy of other approaches can be compared. Unfortunately, however, because there were no matched untreated or differently treated control groups in the Schopler, Goldfarb, and Lovaas studies, it is difficult to establish whether the changes observed were treatment related or were simply developmental changes that might have taken place even in the absence of treatment. Moreover, the generally positive results reported must be seen in proper perspective to avoid fostering unwarranted optimism. The long-term outcome of these children is not known. The changes that occurred by no means resulted in the children's being able to lead normal lives. Further, the data we presented from the Indiana group in our 1972 report (Mosher, Gunderson, and Buchsbaum 1973) are sobering. DeMyer and her associates found relatively little change in their autistic children. Why other investigators have gotten more favorable results remains a question. It is likely that differences in the types of subjects studied and measures used account for much of the discrepancy. However, more definitive answers await carefully designed studies that employ the same sampling, diagnostic, and assessment procedures.

Hingtgen and Bryson (1972) have noted that recent investigations have been characterized by renewed interest in the development of treatment procedures, in the description of perceptual process, intelligence, and language, and in the search for neurobiological correlates. The studies reported here confirm this trend but underscore the fact that relatively little progress toward finding specific etiological factors has been made despite the considerable research activity in the area. The variety of basic deficits viewed as significant and the range of treatment practices that grow out of the various etiologic theories seem to reflect the failure of any one viewpoint to provide a totally satisfactory explanation of either the etiology or proper treatment of childhood psychosis. It is, moreover, difficult to make cross-study comparisons because of a lack of shared diagnostic criteria and evaluative methodology across centers. If our understanding of childhood psychosis is to be enhanced, greater cooperation, collaboration, and compromise among investigators may be a necessary precondition. This is especially true since childhood psychosis is a relatively rare disorder. It may be that, until a generally accepted diagnostic scheme is implemented, the principal advances in this area will remain political. In this respect, the National Society for Autistic Children is working to pass Federal legislation that will provide non-mental-health-related medical and educational
resources for these children. That leadership in this campaign comes from a parent group with a bias against the implication of nonorganic factors in the disorder may reflect the inability of the professional community to relinquish idiosyncratic, provincial, and affectively charged viewpoints in favor of dispassionate scientific ones. Until professionals can give up dogma in favor of science, it seems unreasonable to expect parents, who are confronted daily with children who engender guilt and despair, to do so.

### Biology

A biological theory of schizophrenia is predicated on the belief that an etiologically significant biological difference exists between schizophrenics and others. Unfortunately, in the past, the possible relationship between the hypothesized biological abnormality and clinical state variables (e.g., the effects of institutionalization) generally received less attention than, in retrospect, seems to have been warranted. This not infrequently led investigators to draw premature causal conclusions that all too often proved, on closer scrutiny, to be correlative. Increasingly, however, we are seeing biological research that attempts in a highly sophisticated way to correlate biological factors with phenomenological or clinical aspects of schizophrenia. Today, in contrast to 5 years ago, it is rare for investigators to seek a biochemical phenomenon, a psychophysiological observation, or an observed electroencephalographic finding as the cause of schizophrenia. One example of the increasing sophistication of biological research is the tendency to study relatively homogeneous diagnostic subgroups of patients instead of studying a heterogeneous group of patients characterized by the global term “schizophrenia.” Recent studies have also attempted to correlate specific symptomatology with biological and/or psychophysiological findings. It is encouraging to see how increased sophistication in both the biological and clinical spheres is now being applied in a mutually facilitative way to attempt to understand the schizophrenic conundrum.

#### Biochemical Studies

**The Model Psychosis**

The so-called “model psychosis” approach to schizophrenia is being used increasingly by biochemical investigators. This method correlates biochemical abnormalities with clinical state across a variety of psychotic conditions: for example, acute schizophrenia, amphetamine psychosis, and LSD reactions. Clinically, amphetamine psychosis closely resembles an acute schizophrenic psychosis with symptoms of paranoid delusions, auditory hallucinations, volatile and inappropriate emotions, and compulsive and stereotyped behavior. Amphetamine psychosis differs from the acute, paranoid schizophrenic psychosis in that there is no thought disorder and there are nonspecific signs of arousal, restlessness, and loss of appetite.

In an attempt to elucidate the mechanism of action of amphetamines, Snyder (1972) noted the structural similarities between amphetamine and the neurotransmitters, dopamine and norepinephrine. He hypothesized that the clinical picture of amphetamine psychosis could be explained by the effects of amphetamine on these neurotransmitters. In basic rat-brain biochemical analyses, he found that amphetamine inhibited the neuronal reuptake of dopamine and norepinephrine, thereby making more of these neurotransmitters available at nerve synapses. Snyder also found that dextroamphetamine (amphetamine that rotates polarized light to the right) was 10 times more powerful than levoamphetamine in inhibiting the reuptake of norepinephrine and that the two forms were equally effective in inhibiting reuptake of dopamine. Attempting to examine the behavioral effects of these substances, Snyder demonstrated that dextroamphetamine caused greater motor activity than levoamphetamine and that both forms were equally effective in producing stereotyped behavior. He concluded that the brain’s dopamine tracts may be responsible for repetitious, stereotyped behavior and that norepinephrine tracts are responsible for the arousal and restlessness seen in amphetamine users. These investigators hypothesize that, if the effects of amphetamine on the brain’s norepinephrine tracts could be eliminated, then amphetamine’s effects on the dopamine tracts would more closely approximate an experimental model of acute schizophrenic psychosis. It is possible to hypothesize that an even better model might be a combination of actions such as increased dopamine activity plus decreased norepinephrine activity. This model could account for the mood changes and withdrawal frequently seen in schizophrenic psychoses.

#### Transmethylation

The transmethylation hypothesis, simply stated, postulates that the body is capable of endogenously producing hallucinogens by methylation of normally occurring compounds and that these hallucinogenic
compounds cause the physiological or psychological abnormalities seen in schizophrenic individuals. Indoleamines (serotonin) and catecholamines (epinephrine, norepinephrine) are the brain chemical transmitters of nerve impulses in the central nervous system. The presence of enzymes necessary for their methylation (into hallucinogens) has been demonstrated in human brains. Although extremely provocative, this finding raises a number of serious questions:

- Are the methylating enzymes (or increased amounts of the methylating enzymes) found only in schizophrenic individuals?
- If not, why do only some people become psychotic?
- Given the presence of the necessary enzyme, can it be further demonstrated that endogenous hallucinogens are actually formed?
- Is there a compound necessary to activate the reaction?
- Is there a compound normally present that inhibits the reaction and that, when decreased, allows the reaction to occur?
- Normally, are the postulated endogenously formed hallucinogens rapidly destroyed?

Attempting to answer the first of these questions, Domino (MH 11846) compared overall activity of the N-methyltransferases in different areas of brains from deceased chronic schizophrenic patients, organic brain syndrome patients, and normal individuals. Varying degrees of enzyme activity were found in all areas assayed. No differences in activity between gray matter and white matter were found, and the activity of brain N-methyltransferase in different regions of the brain was similar in the three groups studied.

Using thin-layer chromatography, Narasimhachari, Plaut, and Himwich (1972) have found that none of 11 normals, 6 of 7 acute schizophrenics, and 13 of 18 chronic schizophrenics showed spots isographic with bufotenine or 5-methoxy-N: N-dimethyltryptamine (5-MeODMT). Wyatt et al. (1972) measured dimethyltryptamine (DMT) using gas-liquid chromatography and highly refined mass spectrometric techniques, but were unable to show that DMT was differentially present in the plasma of schizophrenics. These studies illustrate some of the problems encountered in biochemical research: Although an enzyme capable of forming DMT from tryptamine and monomethyltryptamine has been identified in human platelets (Wyatt et al. 1972), it remains to be demonstrated that a reaction not only can but does occur (in vivo) and that it discriminates schizophrenics from other patient groups.

**Indolamine Studies**

One group of neurotransmitters under study is the indolamines, principally serotonin and tryptamine and their products. Two of the normal metabolic pathways pertinent to these studies are schematically represented in figure 3.

Most of the indolamine studies reported here rest on the hypothesis that serotonin and/or tryptamine are abnormally methylated to form hallucinogenic compounds such as DMT, bufotenine, and 5-MeODMT, which are causatively related to schizophrenia. The
Figure 4. Hypothesized formation of hallucinogenic compounds by abnormal methylation.

\[
\text{serotonin} \rightarrow \text{N-methylserotonin} \rightarrow \text{bufotenine} \\
\text{serotonin} \rightarrow \text{?} \rightarrow \text{?} \rightarrow 5\text{-methoxy-DMT} \\
\text{tryptamine} \rightarrow \text{N-methyltryptamine} \rightarrow \text{N,N-dimethyltryptamine (DMT)}
\]

hypothesized chain of reactions is schematically represented in figure 4.

Mandell et al. (1972) have reported that an enzyme indole (ethyl) amine-N-methyltransferase (IENMT) in the human brain can convert serotonin into a hallucinogenic compound, DMT. This same enzyme reportedly can also convert tryptamine into DMT. IENMT, which seemingly produces DMT when there is a decrease in monoamine oxidase (MAO), is found in normals as well as in schizophrenics. Mandell et al.'s belief in the body's capacity to restore homeostasis led them to hypothesize that, normally, the brain's compensatory mechanisms would soon restore systemic balance and prevent a hallucinogenic product of a brain enzyme such as IENMT from singlehandedly producing long-term disruptive effects in brain function. In an attempt to test this hypothesis, they injected 6-hydroxydopamine, a drug that selectively destroys transmitter nerve endings, directly into the ventricles of the brain of rats. When a followup injection of norepinephrine was given, the rats displayed marked hyperactivity with the infusion of amounts that previously had been ineffective. Having thus demonstrated that compensatory hypersensitivity can develop, Mandell et al. hypothesized that the schizophrenic may have a decreased synaptic adaptive capacity to excess or to false neurotransmitter substances. The potential importance of this study is underscored by Wyatt et al.'s (1973) report concerning MAO activity in some schizophrenics (see below under "Enzyme Studies").

Hypothesizing a functional deficit of serotonergic activity within the brains of at least some schizophrenics, Wyatt et al. (1972) developed a combined clinical and biochemical research program to test their notion. In one study, 14 phenothiazine-refractory chronic schizophrenic patients were studied after being off phenothiazines for up to 5 months. During this period they were given a constant number of identical capsules containing either placebo or active drug. Eleven subjects received 5-hydroxytryptophan (L5HTP, a precursor of serotonin) plus MH-386 (a peripheral decarboxylase inhibitor that blocks the conversion of 5HTP to serotonin outside the brain, thereby increasing the amount of 5HTP available for conversion to serotonin within the brain). Based on behavioral assessments by nursing staff, seven patients improved, two got worse, and two remained unchanged on this regimen. If one assumes that the L5HTP increased CNS serotonin levels, the improvement of these patients appears to support Wyatt et al.'s hypothesis of a functional deficit of serotonergic activity in some schizophrenics. The hypothesis is weakened, however, by results of an earlier study in which they gave three subjects alpha-methyl-5-hydroxytryptophan (αMSHTP), a compound that, since it is apparently unaffected by normally occurring brain MAO, should be converted to serotonin, a conversion that, in turn, should result in symptomatic improvement. But since the behavior of all three patients treated with this compound worsened, the serotonin-deficit theory found no support.

**Catecholamine Studies**

Another major group of neurotransmitters under study is the catecholamines, principally dopamine and norepinephrine and their products. The main metabolic pathways pertinent to these studies are schematically represented in figure 5.

The catecholamine study reported here rests on the hypothesis that dopamine, norepinephrine, and/or epinephrine are abnormally methylated to form hallucinogenic compounds such as dimethoxyphenethylamine (DMPEA) and mescaline derivatives.

Friedhoff (MH 08618) has demonstrated that a dopamine metabolite, N-acetyl-3-hydroxy-4-methoxyphenethylamine (i-NAMT) can be transformed enzymatically to N-acetyl-3,4-dimethoxyphenethylamine (NADMPEA) by a variety of mammalian tissues. This dimethoxy derivative is capable of producing behavioral changes in rats at a dose of 5 mg/kg. Friedhoff's present data present presumptive evidence that NADMPEA is catalyzed by an enzyme that is different from other O-methyltransferase systems. NADMPEA is rapidly 4-O-demethylated by liver microsomal preparations in the
Figure 5. Main metabolic pathways of catecholamine neurotransmitters.

presence of NADPH. He also reports that a liver fraction can enzymatically transform 4-hydroxy-3,5-dimethoxyphenethylamine (4-desmethymescaline or 4-DMM) to mescaline (3,4,5-trimethoxyphenethylamine) and N-acetyl-4-hydroxy-3,5-dimethoxyphenethylamine (N-acetyl-4-desmethymescaline or NA-4-DMM) to N-acetylmescaline. Neither the mescaline nor the dimethoxy compounds seem to be formed through the action of any of the O-methyltransferase systems described by other investigators. Although these enzymes have not been demonstrated to have in vivo activity, their existence raises questions about their possible physiological functions, as well as their possible involvement in the pathogenesis of psychosis.

Protein Abnormalities

For several years Bergen (MH 09252) has attempted to replicate Heath's findings of electroencephalographic (EEG) changes in monkeys injected with the gamma G immunoglobulin (IgG) fraction of serum from acute schizophrenics. Using Heath's DEAE Sephadex A-50 extraction procedure, Bergen has isolated IgG. When the isolated fraction is injected into the anterior ventricles of monkeys and EEG responses are measured, using cortical and depth electrodes, Bergen has shown that the serum fractions from the schizophrenic patients, when injected into monkeys, produced more frequent EEG abnormalities than did the serum fractions from controls (13 of 23 schizophrenics, 4 of 23 controls) ($\chi^2 p<0.01$). There are several questions raised by this work. Heath has reported that once a schizophrenic is judged "positive" by this procedure, he remains positive. In Bergen's research, however, serum samples from the same subject do not consistently produce EEG abnormalities. Why isn't the test positive in all schizophrenics? Why do serum fractions from some nonschizophrenics produce EEG abnormalities? Work is continuing in an attempt to relate protein abnormalities to clinical symptomatology and family history and to characterize further the controls whose sera produced changes in monkey EEG's.

Frohman and Gottlieb's (1972) investigation of another abnormal protein postulated to be related to schizophrenia has been widely, and often uncritically, reported in the lay press. Frohman and Gottlieb are investigating an alpha-2 globulin (plasma factor) found
in the serum of some schizophrenic patients. Incubation of serum with chicken erythrocytes produces an increase in the ratio of lactate to pyruvate concentration (L/P ratio) if this plasma factor is present. Frohman and Gottlieb hypothesize that the increased ratio is due to stimulation of cellular uptake of amino acids, notably tryptophan. They further postulate that the plasma factor correlates with the alpha helical form of the alpha-2 globulin since, using optical rotatory dispersion (ORD), they have found increased levels of alpha-2 globulin in serum from patients with a high plasma factor. In comparison, patients with a low plasma factor have less alpha helical protein, and controls have a predominance of beta or random coil configuration of their alpha-2 globulin. Because methodology reported by Frohman and Gottlieb is sketchy and attempts by other investigators to replicate their findings have been unsuccessful, the significance of this work is speculative at the present time.

**Enzyme Studies**

Wyatt et al. (1973) measured MAO activity in blood platelets in 18 monozygotic twin pairs discordant for schizophrenia and compared this with activity in platelets of 23 nontwin normal controls. All of the schizophrenic twins had been hospitalized at least once, but at the time of the study only one was hospitalized and five were considered to be in remission. Six of the 13 schizophrenic co-twins were currently on phenothiazines. Except for one nonschizophrenic co-twin whose psychosocial functioning was considered borderline, none of the co-twin controls had ever been hospitalized for a behavioral disorder and all were generally functioning well.

The MAO activity in platelets was as follows:

- **Normals**: $6.4 \pm 2.7$ nmol/mg of protein per hour.
- **Schizophrenic twins**: $3.9 \pm 2.3$ nmol/mg of protein per hour.
- **Nonschizophrenic twins**: $4.7 \pm 2.9$ nmol/mg of protein per hour.

The MAO activity in the schizophrenic twins was significantly lower ($p<.005$, t test) than that in the normals. When the nonschizophrenic co-twins were compared to the normals, the difference was significant at the $p<.05$ level. The difference in MAO activity between the schizophrenic and the nonschizophrenic twins was significant ($p<.01$). A “blind,” forced-rank order was made between numerical ratings of severity of impairment in the schizophrenic co-twin (scale 1 to 5) and compared to levels of MAO activity. The more severe patients had significantly lower MAO activity ($p<.05$). Four twin pairs who contributed heavily to the lower values of MAO activity also contained four of the sickest schizophrenic patients. The authors conclude that low platelet MAO activity may be a genetic marker for the vulnerability to schizophrenia, although not to the disorder itself, since the twin pairs were discordant for schizophrenia. They suggest further studies to determine

- Whether platelet MAO activity indicates a generalized deficiency in MAO (or one of its isoenzymes);
- Whether platelet MAO activity is correlated with brain MAO activity; and
- Whether platelet MAO activity is genetically determined.

Meltzer (MH 16127 and MH 18396) continues to report increased serum creatinine phosphokinase (CPK) and aldolase activity in 50 to 75 percent of acute schizophrenic patients, as well as in patients with other types of acute functional psychoses. Elevations of serum CPK have been confirmed by other investigators in the United States and England. In a few patients studied, the increases preceded the appearance of overt psychotic symptoms by 1 to 4 days, suggesting that CPK elevations might be a useful predictor of impending decompensations. In addition, Meltzer reports that some patients whose clinical status falls somewhere between the acute-remitting and chronic-unremitting groups also have increased CPK activity during acute exacerbations of their illness. In a collaborative venture with Strauss and Carpenter of the NIMH Intramural Research Program, Meltzer has demonstrated that the degree of “cognitive disorganization,” as defined by a group of mental status items, correlates closely with elevated serum CPK and aldolase (Strauss, Meltzer, and Carpenter 1972).

Attempting to understand the pathophysiology leading to increased serum CPK, Meltzer has performed skeletal muscle (the principal source of CPK) biopsies on psychotic patients. These reveal extensive pathology in a few patients and subtle, low-level pathology in nearly half. These abnormalities most commonly appear to be scattered atrophic fibers and Z-band streaming. Meltzer believes these abnormalities may be of neurogenic origin and that the study of etiology of the muscle abnormalities in psychotic patients might lead to an understanding of central nervous system abnormalities in this disorder.

**Trace Minerals**

In a long-term study of blood levels of zinc, copper, magnesium, and calcium, Simpson, Cooper, and Lifshitz...
(1972) found that the levels in schizophrenics were within the range found in normals, when 2 SD's from the mean were used as the level of significance. These findings do not support an earlier reported finding of Pfeiffer, who claimed that 11 percent of schizophrenics had low zinc levels and 20 percent had high copper levels (see Mosher, Gunderson, and Buchsbaum 1973).

**Psychophysiological Studies**

Zahn and his collaborators (1972) have investigated differences between schizophrenics and normal control subjects in autonomic responsivity to various stimuli, the relationship of autonomic activity to adequacy of performance and to psychiatric condition, and the possible genetic determinants of autonomic activity. Peripheral measures of autonomic functioning, such as galvanic skin resistance (GSR), heart rate, finger pulse volume, respiration and skin temperature, are recorded during several sessions in which stimuli are presented and tasks of various levels of complexity are performed. Psychophysiological data are then correlated with biochemical and psychiatric assessments. These procedures have been applied to identical twins discordant for schizophrenia and their parents and to adoptive and biological parents of schizophrenic patients to determine if genetic factors in schizophrenia are expressed in autonomic functioning. Studies of the psychophysiology of the twins discordant for schizophrenia (regardless of which twin was studied) have shown consistent negative correlations—that is, as autonomic arousal increases, urinary biochemical measures of the precursors and metabolites of epinephrine and norepinephrine (dopamine, metanephrine, and normetanephrine) decrease. These studies also suggest that overall autonomic function (i.e., arousal levels, variability and responsivity) may have a significant genetic familial component. Performance measures and the autonomic response to experimental demands, however, do not show appreciable genetic influence, since differences found between schizophrenic and nonschizophrenic co-twins were similar to those found between unrelated schizophrenic and normal subjects. Although both the index and normal co-twins showed equal autonomic responsivity to meaningless stimuli, the schizophrenics were significantly hyporeactive to more meaningful stimuli; and whereas the nonschizophrenic control twins showed a greater increase in arousal under the mild stress of task performance, the schizophrenics showed higher arousal levels under nondemanding conditions. Correlations between autonomic performance and behavioral variables suggest that schizophrenics with high arousal levels have poorer performance and more severe symptomatology than those with lower arousal levels. Schizophrenics who showed more task arousal tended to have less severe symptomatology than those who did not show changes in arousal levels. Unlike Mednick, who hypothesizes that schizophrenia is caused by a hyperactive and irregularly controlled autonomic nervous system, Zahn et al. have concluded that there is no generalized deficit in autonomic reactivity in schizophrenia, but that when such a deficit appears, it is specifically in response to meaningful or demanding stimuli.

In a study using evoked potentials, Roth and Cannon (1972) like Zahn et al. found greater differences between 21 schizophrenics and 21 age-matched normal controls when responses to a rare (therefore meaningful) stimulus were compared. Using $P_3$ with an amplitude of 3.20 $\mu$V in the first 2.5 minutes as a dividing point, Roth and Cannon correctly classified 35 of the 42 subjects as either controls or schizophrenics. The control group demonstrated a larger $P_3$ amplitude in evoked responses to infrequent stimuli than did the schizophrenics. Evoked response latencies did not distinguish the two groups.

Like Roth and Cannon (1972) and Zahn et al. (1972) Small and Small (1971) report that patient-normal differences are greatest when task-related responses are being studied. Investigating a group of 40 acutely disturbed, unmedicated psychiatric patients (14 schizophrenics, 12 manics, and 14 depressives) and 10 normals, Small and Small focused on the slow wave potential response. This wave was chosen for study because it is believed to be a cerebral response in anticipation of either motor or mental performance, it is responsive to semantic and subjective cues, and it is affected by attentiveness and distraction. The subjects were given a warning stimulus (flash) followed by an imperative stimulus (click) after which they were to push a button. Small and Small were able to identify statistically significant differences between patients and normals, but not among groups of patients. In normals, a typical contingent negative variation (CNV) response, expectancy wave, or E wave, appeared in the preparatory interval between flash and click stimuli with positive potential shifts occurring after button pushing. The manics and depressives showed lower amplitude with little or no differentiation between the resting, expectancy, and response intervals; wave forms in the schizophrenics were more variable, with negative potential shifts occurring after the motor response. Because these slow wave potentials are felt to reflect the subject's focusing his attention on the task, it would appear that
patienthhood, independent of diagnostic category, is associated with an inability to attend.

Shagass (MH 12507) continues to measure evoked potential responses produced by painless stimulation of the median nerve at the wrist. He has reported that there are significant sex differences in the evoked responses of male and female chronic schizophrenic patients but not in nonpatients. Chronic female schizophrenics tended to be more responsive than chronic male schizophrenics under all conditions (in contrast, the responses of normal females tended to show less responsiveness than those of normal males). This result differs from earlier reports of restricted responsiveness in schizophrenic patients that were based on male subjects only: that conclusion still holds for males, but Shagass concluded it does not pertain to females. The wave-shape stability index of the evoked potential (a measure of CNS excitability), computed for the first 100 msec of stimulation, was significantly higher in chronic schizophrenics than in a variety of control groups, including acute or latent schizophrenics, personality disorders, and nonpatients. The heightened stability cannot be wholly explained by the heightened amplitude of response, so Shagass attributes it to a more consistent subcortical modulation of cortical responsiveness in the chronic schizophrenics. He speculates that such structures as the reticular formation may be sending a less variable stream of impulses to the cortex of these patients. Shagass believes the apparent differences between his findings and the findings of other researchers (Callaway, Jones, and Donchin 1970), who had reported increased variability, reflect the fact that they were measuring later components of auditory and visual responses. This illustrates some of the difficulties in comparing results across studies.

A study that may reflect, from another vantage point, Shagass’ finding of increased evoked potential stability in chronic but not acute patients has been reported by Sugerman et al. (1971). These investigators found abnormally low variability in the time course of EEG amplitudes of chronic schizophrenic patients, although absolute amplitudes were not significantly different from normal. The low EEG variability noted in chronic schizophrenics appears to reflect heightened cortical arousal and can be normalized by treatment with antipsychotic medication. This hypovariability is similar to that seen in normal subjects who have received stimulants or hallucinogens. In a recent study, these investigators studied differences in amplitude between the two sides of the brain. The usual finding of greater amplitude on the right hemisphere in normal subjects did not appear in recently admitted psychiatric patients.

Fifty-eight percent of 67 normal volunteers showed a left-right ratio of amplitudes indicating relative right-hemisphere dominance, as compared to only 36 percent of 173 patients (the investigators did not control for handedness). In all-night sleep recordings of the EEG’s of normal subjects, Sugerman et al. observed that striking shifts of amplitude dominance from right to left side occurred in parallel with shifts in rapid eye movement (REM) sleep episodes. Sugerman et al. interpret this as a possible predominance of right-hemisphere functioning during REM sleep and in certain waking psychiatric patients.

The finding of differences between schizophrenics and normals in EEG hemispheric asymmetry is of interest, since Bigelow and Rosenthal (1972) have discovered anatomical differences between schizophrenics and nonschizophrenics in the corpus callosum, an important structure in interhemispheric communication. In a controlled double-blind comparison of the dimensions of various brain structures in autopsy material from 10 hospitalized control and 10 schizophrenic brains, Bigelow and Rosenthal found that, of 10 structures studied, only the corpus callosum was significantly thicker (p<.001) in the schizophrenics than in the controls. Studies of differences between the right and left hemispheres in schizophrenic patients assume further significance when considered in the light of Laitinen’s (1972) report that lesions placed in the corpus callosum can cause a decrease in schizophrenic symptomatology.

Some Conclusions

The material covered in this section accurately reflects two phenomena: the complexity of neurobiology and the tremendous technical achievements of the last 10 to 15 years. Many of the enzymes whose functions are discussed here had not even been identified 15 years ago. The roles of various substances in neurotransmission were mostly hypothetical at that time. Now we have sophisticated and sensitive methods to assay them. Similarly, evoked potential studies have been made possible by the development of highly sophisticated computer technology.

Scientific progress usually has depended on creative ideas and the availability of techniques to test them. Biological research in schizophrenia has never lacked hypotheses. Rather, these have often proved untestable by the available techniques. But, today, an increasing number of intriguing hypotheses (e.g., transmethylation) appear to be testable. Moreover, current notable advances in research technology will undoubtedly facilitate
the generation of new hypotheses. Whether or not future studies demonstrate the relationship of a biological factor or factors to schizophrenia, they will prove immensely valuable in providing us with the kind of basic neurobiological data that may eventually enable us to understand the normal, or abnormal, workings of the human brain.

Treatment

The increasing prospects of legislation enacting a national health insurance plan and the concurrent possibility of more rigorous cost accountability procedures are drawing attention to the need to evaluate treatment efficacy. Yet research on treatment is confronted by several major difficulties. First, it must try to keep pace with rapidly changing clinical practice. Unlike research on the etiology or phenomenology of schizophrenia, which builds upon the results of previous studies, research on treatment often does not proceed in an orderly fashion, largely because the changes that occur in clinical practice are frequently unrelated to evaluative efforts. Thus, a research project demonstrating the benefits of inpatient treatment may be ignored by clinicians whose current practice is concentrated in the community. Likewise, attempts to evaluate a currently popular therapeutic practice such as family therapy may be foredoomed to irrelevancy if, by the time findings are published, family therapy has been replaced by some new treatment innovation—say, nuclear commune therapy (which itself already shows signs of being displaced by extended commune therapy).

Another major problem in research on treatment revolves around the inadequacy of currently available methodologies. For example, despite the differences between their treatment approaches, both psychopharmacologists and psychotherapists face similar difficulties in attempting to evaluate their respective techniques. Some of the major questions they must satisfactorily answer are the following:

- Why does drug treatment (psychotherapy) work? What can its mode of action tell us about schizophrenia?
- What are the limitations of drugs (psychotherapy)? Are there subgroups of responders and nonresponders?
- What are the effects of long-term drug administration (psychotherapy)? At what point can treatment be discontinued?
- How and when should drug (psychosocial) treatment be accompanied by psychosocial (drug) intervention?
- How does drug treatment (psychotherapy) affect the patient's view of himself and the subjective experience of living?

The majority of the studies discussed below attempt to confront at least some of these questions. Not surprisingly, whether the treatment is drugs or psychotherapy, the two most difficult questions to answer are also among the most basic—why does the treatment work, and how does it affect the internal experience, or brain processes, or those who receive it? Because effects of drugs on the living brain are not easily measured, behavioral changes are generally relied upon as an index of the drugs' effectiveness. Likewise, because the psyche cannot be examined under a microscope, psychotherapists must depend upon patients' overt behavioral changes to reflect the more subtle, internal changes they are striving to effect. So both psychopharmacologists and psychotherapists have the same problem: they must depend upon indirect measurement of therapy's effects. It is generally conceded, however, that this problem is more pronounced in studies of psychosocial interventions, where the treatment being given is itself poorly defined (as compared with a drug). Accordingly, the efficacy of drug treatment is at present much better established than that of psychosocial interventions.

Laboratory Studies

For some years, Merlis (MH 18465) has studied the metabolism of chlorpromazine in chronic schizophrenics. Of interest is his recent finding of a fairly constant rate of elimination of chlorpromazine, regardless of the exact time or frequency of medication. There is no evidence of a marked rise in the amount of chlorpromazine excreted within a few hours of drug administration. In addition, with few exceptions, the proportion of the various metabolites observed using gas chromatography remains fairly constant across dosage schedules. Merlis feels that it may eventually be possible for clinical laboratories to use his method to determine whether a patient receives more or less than the prescribed amount of chlorpromazine. Using gas chromatography, Merlis found that the plasma of chronic schizophrenics contained almost no metabolites other than chlorpromazine and its sulfoxide; the plasma of acute schizophrenics, however, also showed considerable amounts of mono- and di-desmethylated chlorpromazine. Because of the differences between acute and chronic patients, Merlis concluded that enzyme induction may play a role in the metabolism and effects of chlorpromazine. He hopes to find ways of using early
metabolic responses to predict drug responsiveness. If such predictive techniques can be developed, he believes much time, and even functional impairment, may be spared patients who need treatment other than drugs.

In another laboratory, Spirites (in press) recently reported an improved method for gas chromatographic extraction of serum chlorpromazine. This technical development should add validity to efforts to correlate both red blood cell and serum concentrations of chlorpromazine and other antipsychotic compounds with clinical response in human subjects. In addition, the possibility that certain “drug refractory” chronic schizophrenic patients do not properly absorb chlorpromazine may now be more reliably evaluated.

**Clinical Drug Practices**

Among the current controversial issues in clinical practice are 1) proper dosage schedule (i.e., rapidly increasing dosage until side effects become bothersome versus gradually increasing dosage), 2) the pros and cons of prophylactic or maintenance antiparkinson drugs, and 3) at what point, if ever, maintenance phenothiazines should be discontinued.

Some recent research suggests that lithium may be a useful treatment for agitated behavior in schizoaffective patients (Heninger MH 18949) and that fluphenazine enanthate (injectable Prolixin) may be valuable in acute schizophrenics as well as in chronics (Chien and Cole 1973a). Another study, done in England, has shown that discharged chronic schizophrenics who were treated monthly with injectable fluphenazine were less symptomatic and less likely to suffer relapses than a matched group of patients receiving placebo injections (Hirsch, Gaind, and Rohde 1972). It may be that future drug treatment of schizophrenia will increasingly involve injectable or other forms of long-term medication, since many discharged schizophrenics are known to take themselves off drugs prematurely.

Among the few recent efforts to introduce new methods of drug treatment, the most publicized contender has been an approach called orthomolecular psychiatry. The orthomolecular, or megavitamin, approach was first advocated in the 1950's by Hoffer et al. (1957) on the basis of extensive clinical experience and their own controlled trials. In this approach, large doses of vitamins (initially vitamin B₃, niacin, but more recently including vitamins B₄, C, and sometimes others) are used to treat schizophrenia. In addition, “usual” treatments (e.g., phenothiazines, electroshock therapy, and hospitalization) are also employed.

Last year, three controlled studies showing that niacin or nicotinic acid had no value when added to the “usual” treatment of schizophrenia (i.e., phenothiazines) were included in this report. Some advocates of the megavitamin treatment of schizophrenia suggested that these results must be considered preliminary until more long-term effects on rehospitalization have been studied. Hoffer et al., the possible role of such nonspecific factors as the interest and enthusiasm of the drug givers, and the possible role of nonspecific factors as the interest and enthusiasm of the drug givers has become apparent. Unless the indications for the use of vitamins become more clear-cut, they should be used only as an adjunct to other better established forms of treatment and then only cautiously, with full attention to possible side effects. In view of the accumulating evidence about the inefficiency of this approach, the sweeping public claims made by megavitamin enthusiasts are dangerously misleading and seem destined to cause bitter disillusionment.

**Drug Limitations**

A major new thrust of clinical drug research is the attempt to delineate the limitations of drugs. One aspect of this focus has been heightened concern about the side effects of the phenothiazines. In particular, tardive dyskinesia has repeatedly been reported to occur in a significant (estimates vary from 1 to 41 percent) number of patients on long-term, high-dose phenothiazines (Kazamatsuri, Chien, and Cole 1972). Because this
neuromuscular disorder is often masked by continued high dosage and its appearance is irreversible, the FDA this year required pharmaceutical companies to adopt a more specific warning about this complication.

The concern over side effects like tardive dyskinesia has been one motive for finding ways to discontinue long-term maintenance medication. The use of routine maintenance chemotherapy is widespread—estimates of its frequency being 70 to 90 percent in State hospital populations. The following three studies attempt to work out better alternatives to such maintenance practices.

A recent report from a multihospital collaborative project now sheds some light on which chronic schizophrenics can safely be taken off their maintenance medications. This study attempted to identify subgroups of hospitalized chronic schizophrenics with a sufficiently low probability of relapse to warrant discontinuation of medication. Major emphasis was placed on the possible predictive value of such variables as length of hospitalization, age, severity of illness, and type and dose of previous medication. In all but one of the seven participating hospitals, patients who had been receiving low doses of medication before the study was initiated had a lower relapse rate on placebo than patients who had been receiving moderate or high doses. The results indicate that the large majority of schizophrenics who have been hospitalized for more than 15 years and who are receiving low doses of tranquilizing medication can remain off drugs for 6 months without deleterious effects. Short-stay patients and/or patients receiving higher doses of drugs, however, show relatively high relapse rates. It was concluded that more attention should be paid to chronic schizophrenics and that a workable dose-reduction program could result in sizable financial savings for the hospital and less risk of toxicity for the patient (Prien, Levine, and Switalski 1971).

Another effort to avoid side effects of maintenance phenothiazine therapy has been to find alternative drugs. One such drug is pimozide, the first long-acting piperidine to be tested in this country. A preliminary study in five severely ill chronic schizophrenic patients (all of whom relapsed within 2 weeks of withdrawal from standard antipsychotic medication) showed that small doses of pimozide could be substituted for large amounts of other drugs without damage to these patients’ mental state (Sugerman 1971). If future double-blind, larger scale studies confirm this initial impression, pimozide, which can be given in a single small daily dose, may prove to be a maintenance medication that has fewer side effects than those presently available.

**Drug Interaction with Psychosocial Interventions**

The routine practice of maintenance chemotherapy for chronic patients has been criticized in a recent report by Paul, Tobias, and Holly (1972). They note that drugs are continued on the assumption that they either control bizarre behavior and/or render patients more responsive to other forms of treatment. However, in their study, in which none of the participants were aware that a drug study was taking place, no differences at all were found between equated groups of chronic patients who continued to receive drugs and those who were abruptly withdrawn from active drugs and given inert capsules (placebos), except that the drug-maintained patients were initially slower to respond to newly introduced active treatment programs. During this same time period, two different active socioenvironmental milieu programs reduced bizarre behavior for all patients by over 50 percent. The study suggests that maintenance medication may be a poor substitute for active milieu treatment in chronic patients. Indeed, in patients who fail to respond to drugs, the continuation of drugs may not only cause unnecessary side effects but actually retard the effectiveness of other treatments.

Hogarty (MH 15829 and MH 15830), in collaboration with the Psychopharmacology Research Branch at the National Institute of Mental Health, is analyzing the effects of drug treatment (chlorpromazine) and major role therapy (MRT)—which basically consists of social casework with some vocational rehabilitation—on 374 recently discharged schizophrenic patients. Subjects are placed into one of four treatment groups (placebo alone, placebo plus MRT, drug alone, and drug plus MRT) and evaluated for mental status, evidence of relapse, work, and social adjustment. Data for the entire 2-year study have been collected and relapse rates have been analyzed. By 1 year, relapse rates on placebo (67 percent) are twice that of those on drugs (31 percent). MRT also lowers relapse rates, but only after the first 6 months. At 12 months, the drug and sociotherapy effects are additive (i.e., both have their own effect), although the drug effect is larger than that of MRT. By 2 years, relapse on drugs (47 percent) remains significantly lower than relapse on placebo (80 percent), and the MRT effect on relapse observed after 6 months continues throughout the 24-month period. Although drugs emerge as the most important factor in determining outcome, this study’s affirmation of an unequivocal usefulness for supplemental psychosocial intervention is also noteworthy.
When Hogarty's results are contrasted with the interactive effect seen in the Paul, Tobias, and Holly study above, one must conclude that the interaction between drugs and psychosocial intervention is not a simple matter. It would seem to be influenced by factors such as the type of patient population, the setting in which the treatments are given (e.g., inpatient vs. outpatient), the duration in time, and perhaps the skill and enthusiasm with which each is given. These studies raise broader issues of how best to integrate drug treatment with other concurrent or sequential psychosocial therapies. The issue has changed from drugs versus other therapies, as it was seen in the early 1960's, to the issue of drugs plus what other therapies. The following series of studies address some of the issues involved in adding other therapies to drugs.

**Psychosocial Aftercare Intervention**

O'Brien and his co-workers (1972) studied 100 consecutively admitted schizophrenic patients who were randomly assigned at hospital discharge either to group therapy or to individual therapy. Both treatments were of the supportive type (sessions on a once-weekly, biweekly, or monthly basis) and were administered by young psychiatrists, medical students, or social workers. Follow-up evaluations based on a social effectiveness scale and other psychiatric ratings indicated that the group receiving group therapy did significantly better. Rehospitalization rates, however, did not differ significantly between the two groups. This apparent advantage of group therapy was not readily explained by the nature of the therapists, since, although the group therapy sessions had more psychiatrists than medical students as leaders, the medical students showed a trend toward greater therapeutic effectiveness! O'Brien points out that group therapy with schizophrenics has been generally confined to inpatient treatment and suggests that it may be useful as an aftercare practice as well, since it seems to be differentially effective in enhancing social functioning.

Chien and Cole (1973b) have developed and evaluated a program to move long-term mental patients into landlord-supervised cooperative apartments in the community. At first, the landlord-supervisor oversees the routine chores of the patient's daily life, but the patient is encouraged gradually to gain autonomy. The patient's incentive comes in part from having to apportion a limited welfare check according to how much he does for himself. Chien and Cole report that 186 homeless patients now have been placed in such cooperative apartments, and over 80 percent have not required readmission. They report that almost all of the patients who live in these apartments for more than 3 months like the arrangement, that the patients are considered much improved by their landlord-supervisors, and that the program costs considerably less than the alternative community aftercare facilities currently in use, including halfway houses, family-care homes, and nursing homes.

In another effort to evaluate aftercare programs for chronic psychotic patients, Weinman (MH 15008) searched for predictors of recidivism and adjustment in the community in more than 150 chronically psychotic patients from the Philadelphia State Hospital. In this program, indigenous members of the community, specially trained to help newly released patients deal with the everyday problems of life outside the hospital, were assigned therapeutic roles of two types—"live-in enablers" who took patients into their own homes, and "visiting enablers" who regularly visited patients in their apartments. These two groups of patients were further subdivided into those who received direct supervisory aid from the professional staff at the hospital (home visits, group therapy, and audio-feedback in conjoint meetings with other patients and the enablers) and those who had minimal direct contact with hospital staff; in the second subgroup, the enablers received the same types of direct supervision from the hospital staff that the patients received in the first group. Weinman now reports that all four experimental conditions were associated with significantly less recidivism than the controls, that is, the hospital-based milieu therapy program and the traditional discharge outlets not using enablers. Although all four conditions seemed more effective than the control treatments, it appeared that the patients who achieved the best community adjustment were those assigned live-in enablers who received hospital supervision (as opposed to the patient being supervised directly by hospital personnel). The investigators also found that certain clusters of attitudes and expectations before the start of the program were associated with different trends in recidivism. Three prediction scales have been developed, based on the patients' attitudes and expectations: 1) expectations of success, 2) self-reports of autonomous behavior, and 3) perception of the psychiatrically sick role. The third factor was the single most potent predictor of outcome in this sample of patients, regardless of the time it was assessed during the course of the 16-week treatment, since patients who saw themselves as sick tended to do worse than those who saw themselves as well. The effect of the treatment program was to increase the importance of the patients' expectations of success relative to the other two measures.
In Great Britain, Scott (in press) has attempted to relate the outcome of schizophrenic patients to family attitudes toward illness at the time of admission. He first studied the 2-year outcomes of a group of schizophrenic patients who were admitted from their parental homes. He found a bimodal distribution in which approximately 70 percent of these patients spent less than a third of their time in the hospital ("community centered") and the other 30 percent spent over two-thirds of their time in the hospital ("hospital centered"). Using a family relationship test, Scott independently assessed parents and patients' attitudes toward each other in 34 families and correlated them with hospital or community centeredness at 2 years. He found that if the patient saw himself as sick and his parents as well, and this agreed with the parents' assessment, the patient was able to return home and remain community centered. If the patient saw the parents as disturbed while the parents saw the patient as sick, then the return home was untenable and such patients became hospital centered. Scott concludes that doctors may unwittingly be playing into family pathology when they give official sanction to the family's need to designate one member as "sick"—thereby ignoring the interpersonal context from which the patient came. The finding that patients who see themselves as sick seem to do better when they return to their families does not contradict Weinman's (MH 16999) study where patients (generally long removed from their families) who viewed themselves as sick did worse. In Scott's view, seeing oneself as the sick member of a family is a pathological adaptation that is not conducive to actual improvement.

Another English study addressing factors in the schizophrenic's family after he returns home was carried out by Brown, Birley, and Wing (1972). Their basic hypothesis was that a high degree of negatively expressed emotion (EE) would characterize the families of schizophrenics who relapsed. One hundred and one schizophrenic patients between the ages of 18 and 64 and their families were assessed on several occasions for the presence of EE and other factors. The number of critical comments, presence of hostility, and presence of emotional overinvolvement, all indices of EE, were significantly associated with relapse even after length of illness and type of severity of previous symptomatology were taken into account. Presence of typical schizophrenic symptoms, male sex, rejection of admission, lack of regular medication, and much close contact in the home were also associated with higher rates of relapse, but the association between EE and relapse was independent of these factors. The past history of most of the patients (75 percent) revealed that they had either been disturbed while living with relatives with a high degree of EE, or had been relatively undisturbed while living with relatives with a low degree of EE. Two-thirds of the patients who were disturbed or had work difficulties lived with a relative with a high level of EE, while only 14 percent without such behavior did so. Warmth expressed by the family toward the patient showed a curvilinear association with relapse; patients in the middle range had the lowest relapse rates. Relatives who were given a high rating on warmth tended to be emotionally overinvolved, while a low rating on warmth usually implied a high level of critical comments. On the other hand, marked warmth free from these unfavorable factors was associated with a low rate of relapse. These results suggest that negatively expressed emotions in the families to which discharged patients return greatly heighten the chance of relapse. The authors state that this factor is mitigated to some extent by 1) regular phenothiazine medications and 2) avoidance of "too-close" contact (>35 hours per week with a highly emotional relative).

In other studies, Weinman has investigated the effect of videotape feedback on the self-image of chronic schizophrenics. Those who viewed themselves performing on videotapes tended to increase task-oriented verbal behavior and to improve their performance. Patients who viewed others performing as models on videotapes, however, were unable to use the model to improve their own behavior. The videotape feedback was also used to help chronic patients recognize and express their emotions. Weinman found that the effectiveness of videotape feedback depended on how it was presented to the patient and concluded that the therapist should be present to help the patient deal with his self-confrontation experience.

Some Conclusions

We see a movement in the research on treatment of schizophrenia away from a focus on hospital treatment and onto community alternatives. The change in focus has been made possible, if not necessary, by the acceptance of psychopharmacological agents in the treatment of most schizophrenics. With this background, new and major research questions continue to need answers: 1) What is the cost to the community of early discharge? 2) What are the relative merits of various aftercare treatments? 3) What are the advantages of returning to one's parental home versus alternative
residential settings? 4) How do family and social attitudes affect community adjustment in discharged patients? 5) Is short-term intensive inpatient care (e.g., 10-30 days) better than longer term care (e.g., 60-120 days)?

This changing focus of research seems to parallel the changing focus of clinical needs and clinical practice. The interaction of psychosocial treatments with drugs is a complicated, subtle problem requiring a great deal more attention in the years to come. Yet even the complications of this problem pale in comparison to the difficulty and significance of studies attempting to identify the healing ingredients in interpersonal relationships.

Problems and the Future

The complexity and diversity of the research results reviewed in this year's report—as in previous years—defy easy summarization. As in the past, we cannot report that either of the major etiological models, biological or social, have carried the day. On the contrary, both models have found further confirmation and provoked new questions. It remains for the highly touted high risk studies to provide more definitive clues about etiology. There is every reason to believe that some biological predisposition—as yet unknown—will be found to interact with social factors—as yet undefined—to cause some fraction—as yet undetermined—of what is now called "schizophrenia." Just as surely, in the meantime, advocates of either model will continue to seek confirmation for their viewpoint in research studies and will continue to pose stimulating and sometimes irritating questions to those with other interpretations.

Of more immediate concern to therapists and persons diagnosed schizophrenic is whether research results will lead to more successful treatment. Like the etiological models, treatment models tend to be polarized towards either biological (for example, drugs) or psychosocial (for example, psychotherapy) approaches. Many of the studies reported here underscore the need for focusing greater attention on the interaction and sequencing of various treatments for the appropriate subgroups within the broad heterogeneous category labeled "schizophrenia." Until more data on these crucial treatment issues become available, it is likely that dogma, with its attendant use of advocacy, will continue to be used by proponents of one or another treatment approach.

Two of the year's best publicized studies highlight the ongoing schisms in the field and the role of research in shedding light on these schisms. Megavitamin enthusiasts have long captured headlines by the hope they engender in clinician and patient alike for a rapid and more effective treatment of schizophrenia. This year's report summarizes the generally negative results of Wittenborn, Weber, and Brown's (1973) study of long-term niacin therapy in schizophrenia. Because of the controversy generated by advocates of megavitamin therapy about the usefulness of this treatment method, these results have potential for immediate impact on clinical practice. In addition, it is reassuring to see that research—sober, objective research—can provide answers to highly emotionally charged, but very practical, questions.

Yet, that the field is not always so able to be objective and neutral is underscored by Rosenhan's (1973) recent study. In this study, graduate students sought admission to a variety of mental hospitals because of a single auditory hallucination. They were admitted, diagnosed as suffering from schizophrenia, treated for an average 19 days, and discharged with a diagnosis of schizophrenia in remission. This occurred despite the patient impersonators' having specifically told ward staff the day after admission they no longer had their symptom. This study, focused on the biases and prejudices so frequently encountered by persons designated schizophrenic, serves to remind us how cautious we must be in viewing the results of research on a disorder fraught with controversy, disagreement, and perplexity. We have attempted to report results that are objective and valid. Nevertheless, it should be kept in mind that, although we know much more now than we have ever known before, we still have a long way to go in sorting out bias and prejudice from objective fact with regard to this most uniquely human disorder.

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available from nimh

A new publication on schizophrenia, Utilization of Mental Health Resources by Persons Diagnosed with Schizophrenia: Mental Health Statistics Series B, No. 3 (DHEW Publication No. [HSM] 73-9110), has been published by the National Institute of Mental Health. The report examines schizophrenic patient care during 1969, with special attention to such characteristics of patients and treatment as age, sex, modality of treatment, type of facility in which care was received, and patient care episodes. The recent use of psychiatric facilities by schizophrenics is carefully analyzed, and an attempt is made to predict future patterns of use for these facilities. Detailed charts and tables are included. Single copies of the report may be obtained from the Public Inquiries Section, NIMH, Room 15C17, 5600 Fishers Lane, Rockville, Md. 20852.