Neuroleptics and the Natural Course of Schizophrenia

by Richard Jed Wyatt

Abstract

To determine if neuroleptic treatment changes the natural course of schizophrenia, 22 studies were reviewed in which relatively similar patients were or were not given neuroleptics at specific times during the course of their illnesses. Nineteen of the studies were from first- or predominately first-break populations. While there was little consensus among the authors of the studies reviewed, a re-analysis of the data indicates that early intervention with neuroleptics in first-break schizophrenic patients increases the likelihood of an improved long-term course. This finding is similar to that of earlier investigators who indicated there was a decrease in patients with the more severe forms of the illness following the introduction of convulsive therapies. Furthermore, there is evidence that stable schizophrenic patients whose neuroleptics are discontinued and have relapses may have a difficult time returning to their previous level of function. The findings described in this paper have implications for both the treatment of schizophrenia and for understanding the pathophysiological processes that determine the course of the disorder.

Following Kraepelin's (1919/1971) and Bleuler's (1911/1950) initial descriptions of schizophrenia, its natural course became the subject of considerable study and discussion. A number of diagnostic systems, including DSM-III-R (American Psychiatric Association 1987), require that deterioration occur from a previous level of function or from a projected trajectory of function, but the time during which the deterioration can take place is not well defined. Most of the longitudinal studies indicate that, to the extent that deterioration occurs, it takes place within 10 years of the initial phases of the illness, and in most cases probably over shorter periods (Bleuler 1972/1978).

Kraepelin (1919/1971), after discussing the difficulties of knowing when the morbid phenomena of schizophrenia begin, states "that as a rule, if no essential improvement intervenes, in at most two or three years after the appearance of the more striking morbid phenomena a state of weak-mindedness will be developed, which usually changes only slowly and insignificantly" (p. 210). He goes on to say that "often enough the unmistakable symptoms of dementia appear already with the first year..." (pp. 210-211) and quotes Abrect, who found that 27 percent of hebephrenic and 19 percent of catatonic patients had reached their "terminal" state within the first year.

Today, unresolved issues of diagnosis, heterogeneity of the schizophrenia syndrome, various levels of spontaneous recovery, and a possible decrease in the severity of schizophrenia since the early part of the century (Ey et al. 1957; Bleuler 1972/1978; Hare 1983) complicate our understanding of schizophrenia's natural course.

Shortly after the introduction of the convulsive therapies in the 1930's, the question (reviewed by Staudt and Zubin 1957) of whether these new treatments decreased the severity of schizophrenia beyond the interval of their administration was raised. (The role of convulsive thera-

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pies in altering the course of schizophrenia is touched only briefly in this review.) Here I examine studies that can be used to explore the possibility that neuroleptics alter the course of schizophrenia (Davis and Chang 1978). The role of neuroleptics in treating acute psychotic episodes and in maintenance therapy is covered elsewhere (Freeman 1981; Davis 1985) and is assumed here. Furthermore, I assume (and much of the data reviewed here agree) that some schizophrenic patients do well when they are not treated with neuroleptics, while other patients do poorly no matter what treatment they receive.

**Patients and Methods**

**Long-Term Course.** In each study reviewed, at least two groups of schizophrenic patients were followed. At about the same point in the development of their illness one group of patients received neuroleptics and the other group did not. As used here, long term means a time beyond the experimental or immediate period of neuroleptic treatment. In most studies long-term evaluation occurred 1 or more years following a designated period of treatment.

**Role of Maintenance Neuroleptics in Outcome.** Since it is well established that maintenance neuroleptics decrease the relapse rate of schizophrenic patients, and relapse was frequently used as the outcome measure in the studies reviewed here, it was important to be able to separate those patients who were given maintenance neuroleptics from those who did not receive them. Furthermore, it is important to make the distinction between the role maintenance neuroleptics have in preventing relapses, the immediate effects of the relapse, and the events associated with the relapse that have long-term consequences. During a relapse patients will have a decreased level of functioning. To the degree that neuroleptics prevent relapses, patients who relapse because they are not taking neuroleptics should have a lower average level of functioning than patients who take maintenance neuroleptics and do not relapse.

This review, however, is not concerned with the immediate problems associated with relapses. The question here is whether there is an association between neuroleptic treatment that limits or decreases the amount of psychosis during an initial episode or a relapse, or which prevents a relapse and promotes better functioning at a time following that treatment.

In general, patients studied in the mid-1950’s and early 1960’s tended not to receive maintenance neuroleptics, but were likely to receive neuroleptics during subsequent hospitalizations. However, patients studied in the late 1960’s and the 1970’s often received maintenance neuroleptics. Throughout this review an attempt is made to balance the percentage of patients in the control and experimental groups on the basis of whether or not they were treated with maintenance neuroleptics.

**Outcome Measures.** Ideally, comparison studies should use the same highly valid and reliable instruments. It is not surprising that this was not the case for the studies reviewed here. The studies took place over several decades while instruments measuring psychopathology, comfort, and function were being developed. The most convenient and common outcome measure used in these studies was rehospitalization. Rehospitalization has many advantages as an outcome measure. It is an objective measure of many subjective observations and may involve the integrated judgment of a number of individuals including the patient, family, community, professionals, and at times the judiciary. For statistical purposes, unfortunately, the distinction between being in the hospital and being discharged from the hospital often is not as sharp as might be expected. There are many intermediate categories that may not coincide with a discharge date, including indefinite leave and trial visits (May 1968). Fortunately, in several studies measures of function were included in addition to the need for hospitalization. When such studies were not deemed to be inconclusive, the functional level of the patients was considered.

**Types of Studies Used.** Four types of studies were used to determine if neuroleptic treatment affects the morbidity of schizophrenia. Mirror-image studies match similar patients in the preneuroleptic and neuroleptic eras and compare their outcome during a followup period. Early intervention studies make a followup comparison of patients who were treated early in their course of illness with patients whose treatment was delayed. Neuroleptic discontinuation studies examine what happens to stable schizophrenic patients who are taken off neuroleptics and have an acute exacerbation of their psychosis. Contemporaneous control group studies look at patients assigned about the same time to a neuroleptic or a nonneuroleptic treatment group. Most of these studies were initially planned to compare the short-term effects of neuroleptics with placebo (PBO), psychological, or psychosocial treatments, but circumstances
allowed investigators to follow patients over a longer time than originally planned.

Since there are no prospective studies designed to examine the long-term effect on outcome of relatively brief treatment with neuroleptics, it was necessary to rely on retrospective studies. Retrospective analyses present problems that almost always exist when trying to use data collected for a purpose other than that for which they were designed. No single study provides sufficient controls to make one comfortable with the concept that neuroleptics alter the course of schizophrenia. Fortunately, taken as a whole, the design of the studies is sufficiently different and the results sufficiently convergent to allow tentative conclusions.

While there are many problems associated with these studies, the most significant issue appears to be diagnosis. It is probable that some of the studies looking at first- or second-break schizophrenic patients included individuals who would have other diagnoses, especially affective disorder, if seen today. A schizophrenia-like illness that would be curtailed within a few weeks or months with modern treatment in the past might have persisted for 6 or more months. These patients would meet today's length of illness criteria for schizophrenia, and if the illness remained unremitted the individual might deteriorate into a chronic state. This putative change in course is addressed in part by this review.

Literature Surveyed. An extensive literature survey was performed to examine studies in which the authors followed up schizophrenic patients treated with and without neuroleptics. Since most of the informative studies could not be identified on computerized data bases, heavy reliance was placed on references in papers known to deal with the topic. It is likely, however, that useful studies were missed. Only one study (Ellsworth and Clayton 1960) that might have been used was knowingly excluded; it included an unspecified number of acute psychotic patients with explicitly diagnosed affective disorders.

Statistics. In the studies reviewed, the authors provided sufficient data to allow a statistical analysis when one had not been performed originally or when I felt that an analysis should be done differently. I have tried to provide sufficient detail for the interested reader to determine from the original papers how I derived my analyses. Unless otherwise stated, all statistical comparisons are my own, often do not reflect the opinions of the original authors (see table 17), and are one-tailed. In some studies convulsive treatments, in addition to neuroleptics, were used. When more than one form of treatment is known to have been used and the effects of the treatments cannot be disentangled, the treatments are identified.

Many of the statistical comparisons were performed using discrete measures and are presented as 2 × 2 contingency tables. Where 2 × 2 contingency tables were used, they were subjected to Fisher's exact and two-sample proportional tests. Fisher's exact tests were performed when the number of patients was less than 20 or the number of patients was between 20 and 40, with an expected frequency of less than 5. In all other situations where contingency tables were used, two-sample proportional tests were performed. The two-sample proportional test gives significance levels equivalent to a chi-square (Ingelfinger et al. 1987) but has the advantage of directly comparing one set of outcomes or proportions with the total number of subjects in the appropriate group, while the chi-square compares the two outcomes. For example, the two-sample proportional test can be used to contrast the number of patients who developed a chronic course against the total number of patients at risk for developing a chronic course in two samples (one receiving and one not receiving neuroleptics). In the same study, the chi-square might be used to compare those patients developing a chronic course with those patients not developing a chronic course.

In this article it was usually more useful to compare one category to the total number of subjects rather than two categories with each other. The two-sample proportional test also has the advantage of providing confidence intervals for any selected confidence limits (usually 95 or 99%) so that one can easily determine where a found frequency differed from the expected frequency lies within a normal distribution. A continuity correction was applied to each two-sample proportional test by subtracting 0.5 from the higher frequency and adding 0.5 to the lower frequency, thus moving the frequencies closer together by a total of 1 unit (Armitage and Berry 1987).

With one exception, when 2 × 2 contingency tables were not used, the data were analyzed with chi-squares (for contingency tables greater than 2 × 2), the nonparametric Mann-Whitney U test, and the Peto-Wilcoxon generalization of two-sample rank sum test (Lee 1984). When the chi-square was used, the continuity correction was used as described above. New data for cumulative days in the hospital from the May et al. (1981) Camarillo State
Hospital study (Wyatt and Tuma, in preparation) were analyzed by one-tailed t tests with the Satterthwaite approximation as described in Winer (1971) for unequal variances. Days on drugs and chlorpromazine (CPZ) equivalents, using conversions of Wyatt (1976), were analyzed in a similar fashion, but with two-tailed t tests.

**Results of Specific Studies**

**Mirror-Image Studies**

**Northeast Scotland Study.** McWalter et al. (1961) reported a 3-year outcome study of two groups of first-break schizophrenic patients admitted to a hospital in northeast Scotland. The first hospitalization for the preneuroleptic group was between 1949 and 1953; the neuroleptic group was admitted between 1954 and 1957. For the 3 years that the patients were followed, outcomes were classified by whether they had had just one admission and were discharged, had more than one admission in 3 years (relapsing), or were not discharged within 3 years (chronic). Some patients in the preneuroleptic and neuroleptic groups were treated with electroconvulsive therapy (ECT) and/or insulin. When neuroleptics were used with the second group they were used sparingly, usually only after ECT and insulin were found to be ineffective. While 16 percent of the preneuroleptic patients (table 1) had a chronic course, only 4 percent of the patients had a similar fate after neuroleptics had been introduced (two-sample proportional test, \( p = 0.003 \)).

The authors speculated that the improvement may only have been apparent; the patients who would have been chronic in the preneuroleptic era had become "revolving door" patients. Inspection of their data, however, indicates that while there was a 6-percent shift toward multiple admissions from chronic hospitalizations after the introduction of neuroleptics, there was also a 5-percent increase in one-time admissions. Thus, not only were patients more likely to be released from the hospital after the introduction of neuroleptics, but they were also more likely to stay out of the hospital after they were released. Since this study was performed before the introduction of maintenance neuroleptics, the use of maintenance neuroleptics probably does not explain the change.

**All Norway Study.** Ødegård (1964) compared preneuroleptic-era schizophrenic patients whose first hospital admission took place between 1948 and 1952 with neuroleptic-era schizophrenic patients whose first hospitalization took place between 1955 and 1959. His standards for long-term improvement were relatively stringent. To be classified as improved, patients could not be readmitted during the year following discharge.

Nevertheless, there was a strong statistical trend toward improvement (two-sample proportional test, \( p < 0.06 \)), even if only 3 percent of the patients showed this improvement (table 2). Although there had been little change in Norwegian psychiatric care other than the introduction of neuroleptics between 1948 and 1959, Ødegård felt that pooling all patients with the diagnosis of func-

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### Table 1. Number of first-break schizophrenic patients developing chronic course (not released within 3 years of admission to a northeast Scotland hospital prior to [1949-53] and after [1954-57] the introduction of neuroleptics)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>( n )</th>
<th>( % ) of patients with chronic course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preneuroleptic</td>
<td>128</td>
<td>16 (21)</td>
</tr>
<tr>
<td>Neuroleptic</td>
<td>93</td>
<td>4 (4)</td>
</tr>
<tr>
<td><strong>Two-sample proportional test</strong></td>
<td></td>
<td>( p = 0.003 )</td>
</tr>
</tbody>
</table>

*Note.—Other than providing means, the original report presented no formal statistics. Data adapted from McWalter et al. (1961).*

### Table 2. Comparison of number of preneuroleptic-era (1948–52) and neuroleptic-era (1955–59) first-admission schizophrenic patients in the All Norway Study, not readmitted during the year following discharge

<table>
<thead>
<tr>
<th>Treatment</th>
<th>( n )</th>
<th>( % ) discharged and not readmitted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preneuroleptic</td>
<td>2,514</td>
<td>1,166 (46)</td>
</tr>
<tr>
<td>Neuroleptic</td>
<td>1,979</td>
<td>966 (49)</td>
</tr>
<tr>
<td><strong>Two-sample proportional test</strong></td>
<td></td>
<td>( p &lt; 0.06 )</td>
</tr>
</tbody>
</table>

*Note.—Data adapted from Ødegård (1964).*
tional psychosis was more reliable than using the more specific diagnosis of schizophrenia, because diagnostic procedures could have changed in a nonsystematic manner from year to year. Of the patients who had a functional psychosis and who had been discharged within 2 months of their admission, using the same improvement criterion, Ødegård found that 112 of 1,000 patients with a functional psychosis improved in the preneuroleptic era compared with 145 of 1,000 who improved after the introduction of neuroleptics.

The Anoka schizophrenia cohort. Peterson and Olson (1964) compared a cohort of 170 schizophrenic patients following their first admission to Minnesota's Anoka State Hospital with a cohort of first-admission schizophrenic patients from Pennsylvania's Warren State Hospital. (The Minnesota sample included an unspecified number of patients who had been treatment failures or had had recurrences and who had been previously treated at other hospitals.) The Anoka patients were admitted from 1956 to 1958 ("the earliest period providing extensive drug therapy" [Peterson and Olson 1964, p. 137]) and the Warren patients were admitted from 1936 to 1945. All patients were followed for at least 5 years after admission. Although the Anoka patients probably had a more chronic illness on admission than the Warren patients, by the end of 5 years, 89 percent of the Anoka patients had never left the hospital (two-sample proportional test, \( p < 0.001 \)). The Anoka patients who were discharged required a number of readmissions and, after 5 years, 10 percent of the original group were in the hospital as readmissions. Unfortunately, the number of patients from Warren State Hospital who required readmission is unknown. Nevertheless, when those patients never discharged from Warren are compared with the group of patients never discharged plus readmitted from Anoka, the difference is still highly significant (two-sample proportional test, \( p < 0.001 \)).

Table 3. Comparison of number of schizophrenic patients never discharged during 5 years after first hospitalization to Warren State Hospital (1936-45, preneuroleptic era) and patients never discharged plus those readmitted at 5 years to Anoka State Hospital (1956-58, neuroleptic era)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Treatment opposite</th>
<th>( n ) first-admission patients</th>
<th>( n ) patients never released</th>
<th>( n ) patients never released plus those readmitted at 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preneuroleptic era (Warren State)</td>
<td></td>
<td>4,254</td>
<td>1,659 (39)</td>
<td>1,659 (39)</td>
</tr>
<tr>
<td>Neuroleptic era (Anoka State)</td>
<td></td>
<td>170</td>
<td>19 (11)</td>
<td>36 (21)</td>
</tr>
<tr>
<td>Two-sample proportional test</td>
<td></td>
<td>( p &lt; 0.001 )</td>
<td>( p &lt; 0.001 )</td>
<td></td>
</tr>
</tbody>
</table>

Note.—Data adapted from Peterson and Olson (1964).

Patients never released from hospital.
pears to have begun at the time of the introduction of convulsive treatments in the mid- to late 1930's.

The Israel and Johnson (1956) report provides data for a mirror-image comparison of discharge rates for the preneuroleptic era nearer to the time the neuroleptic-treated patients were studied than the data used by Peterson and Olson (1964). There were 1,789 schizophrenic patients admitted for the first time to Warren State Hospital between 1943 and 1952. (Not all of these patients were followed for 5 years because the study ended in 1955.) Of these, 491 (27.5%) had not been discharged after 5 years of hospitalization. Only 11 percent of Anoka State Hospital patients had not been discharged during the same length of time (two-sample proportional test, \( p < 0.001 \)). At the end of 10 years (again, many of the patients were not followed for a full 10 years), 231 of the previously discharged Warren State patients were back in the hospital. When these patients are added to the Warren patients never discharged (although the time periods are not the same), a total of 722 (40.5%) of the first-admission patients from Warren were in the hospital compared with 21 percent of the Anoka patients (two-sample proportional test, \( p < 0.001 \)).

The Oslo Gausted Hospital Study. Astrup and Noreik (1966) compared two groups of first-admission schizophrenic patients. The first group included 1,102 patients admitted to Oslo's Gausted Hospital between 1938 and 1950. The second group of 706 patients was admitted between 1951 and 1957. In the second group, 237 patients were treated on admission with neuroleptics. At followup (at least 5 years), the patients were determined to be in one of five functional levels—recovered, improved, schizophrenic personality change, slight schizophrenic deterioration, or severe schizophrenic deterioration. The recovered group had no psychotic illness during the 5 years of followup, and the improved group had periodic psychotic episodes during followup. The severe schizophrenic deterioration group had a very poor outcome with characteristics such as severe catatonia or shallow and silly hebephrenia.

Five or more years after their first hospital admission, 9 percent of the neuroleptic-treated patients were found to be in the severe schizophrenic deterioration group, compared with 16 percent of the preneuroleptic era patients (table 4). Those neuroleptic-treated patients who ended up in the severe schizophrenic deterioration group had a longer duration of illness (2 or more years), more emotional blunting, and more schizophrenic thought disturbance, and they were more likely to have below-average intelligence than the preneuroleptic-treated patients who at followup were similarly deteriorated (i.e., the neuroleptic-treated patients who were in the worst group at followup had deteriorated before their first admission). Because the study took place shortly after the introduction of neuroleptics, it is unlikely that this difference in the proportion of patients developing a severe course was due to the use of maintenance neuroleptics.

While neuroleptic treatment made a substantial change in prognosis, the authors (Astrup and Noreik 1966) point out that in general, "The more acute the illness, the more variable the course, and the more limited the defect, the more changeable the condition" (p. 131). Where there was a long-lasting defect, the possibility of improvement was decreased, but where the course of the illness was such that neuroleptics could blunt the psychosis, there was a chance that the prognosis could be altered for the better.

The Maudsley Hospital Study. In a retrospective study at the Maudsley Hospital, Pritchard (1967a, 1967b) followed two groups of schizophrenic patients, most of whom were admitted for the first time. The groups were from the preneuroleptic (1952–53) and the neuroleptic (1956–57) eras. Although about half of the preneuroleptic patients received ECT and insulin and did better than patients who did not receive them, only 29 of 50 patients had improved by the time of discharge. (Many were discharged to another hospital.) Following the introduction of neuroleptics, 17 of 18 patients given CPZ, CPZ plus ECT,

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>% (n) patients with severe deterioration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preneuroleptic</td>
<td>1,102</td>
<td>16 (176)</td>
</tr>
<tr>
<td>Neuroleptic</td>
<td>237</td>
<td>9 (21)</td>
</tr>
<tr>
<td>Two-sample proportional test</td>
<td></td>
<td>( p = 0.003 )</td>
</tr>
</tbody>
</table>

Note.—Data adapted from Astrup and Noreik (1966).
CPZ plus insulin, or CPZ plus reserpine improved (Fisher's exact test, $p = 0.003$), and 8 of 9 patients given only CPZ improved (Fisher's exact test, $p < 0.08$).

Following discharge, 41 of the preneuroleptic- and 47 of the neuroleptic-treated patients were followed for 3 years. Neither group received maintenance neuroleptic treatment. While the readmission rate was about the same for the two groups, there was a substantial difference in the amount of time required for subsequent hospitalizations. During the 3 years following their initial discharge, the patients in the preneuroleptic era who had received neither ECT nor insulin spent a mean of 9.3 months back in the hospital, while the patients treated solely with CPZ required only 4.0 months of rehospitalization. This is not a statistically significant difference.

At the end of 3 years, the 21 patients in the preneuroleptic era who were unimproved at discharge had spent a total of 756 months back in the hospital, while the patients treated solely with CPZ required only 4.0 months of rehospitalization. This is not a statistically significant difference.

Pritchard (1967b) points out that following their initial hospitalizations, both groups of patients were probably treated with neuroleptics when they were rehospitalized. (Insulin and ECT may have also been used.) The second and later group, however, is more likely to have received neuroleptics than the earlier group and their rehospitalization time would be expected to be shorter. Pritchard argues that because the readmission rate was the same for both groups (56% for the preneuroleptic vs. 50% for the neuroleptic group, representing one more patient rehospitalized in the preneuroleptic group), neuroleptics had no effect on the long-term course of the illness.

Pritchard did not take into account, however, that the two groups had different at-risk periods for rehospitalization. The preneuroleptic group was rehospitalized for a mean of 9.3 months compared with 4.0 months for the neuroleptic-era patients. The difference of 5.3 months indicates that the neuroleptic-treated patients were at risk of rehospitalization for 32 months while the preneuroleptic patients were at risk for 26.7 months. If the neuroleptics had no effect on the rehospitalization rate, there should have been a 20-percent greater rehospitalization rate for the neuroleptic patients than for the preneuroleptic patients, which there was not.

Kanazawa University Hospital Study. Two reports (Shimazono and Torü 1968; Shimazono 1973) describe a Kanazawa University Hospital followup study comparing readmission rates between two preneuroleptic groups of schizophrenic patients whose first admissions occurred between 1943 and 1950 and between 1951 and 1954, and another group whose first admissions occurred between 1960 and 1962 (neuroleptic-treated). At the time of followup (3 years), patients were classified in one of four groups: those who were completely recovered, those with a slight defect, those with a moderate defect, and those who had a severe defect or had deteriorated. There was a trend for patients to shift from the severe and moderately severe groups into the slight defect or fully recovered groups (Fisher's exact test, $p = 0.07$) after the introduction of neuroleptics. The major neuroleptic-related shift (table 5), however, was from the severe defect into the slight defect group (Fisher's exact test, $p = 0.03$).

Tokyo Musashino Hospital Study. Murakami (1971) looked for a relation...
relationship between neuroleptic treatment and rehospitalization in all first-break schizophrenic patients admitted for the first time to the Tokyo Musashino Hospital in 1951 and in 1965-66. (Another group admitted in 1958-59 was also studied, but these patients received a combination of ECT and neuroleptics.) Ninety-six percent of the 1951 group received ECT and 94 percent of the 1965-66 group received neuroleptics. The 1965-66 group probably had a poorer premorbid history because the patients tended to have had a longer length of illness before admission \((p = 0.05, \text{two-tailed } t\text{ test using means and standard deviations from author's table 5}),\) as well as more simple and hebephrenic schizophrenic patients in it. Nevertheless, there was a weak trend for the neuroleptic-treated patients to have a total hospitalization of less than 3 years at followup compared with preneuroleptic-era patients. (This trend was based on Fisher's exact test, \(p = 0.22, \text{ data from author's table 10,}\) comparing patients hospitalized for less and more than 3 years following their first admission.)

The Bonn University Psychiatric Study. Huber et al. (1979, 1980) studied 500 patients whose first psychiatric hospital admission took place between 1945 and 1959. The patients were systematically followed between 1967 and 1973. As seen in table 6, during their first admission 287 patients were treated with neuroleptics, ECT, or both, and 213 patients received neither. At followup the patients who were treated with neuroleptics or ECT during the first admission were doing considerably better than those who were not treated with these modalities (two-sample proportional test, \(p < 0.001)\). In addition, Huber and colleagues found that patients whose initial treatment took place within 1 year of onset (including those with prodromal symptoms) had a significantly better long-term prognosis than patients whose first treatment took place after they had been ill for 1 year or longer.

St. Johns Hospital Study. Shepherd (1957) examined the case records for St. Johns Hospital, the only psychiatric facility for a catchment area serving 500,000 people living 50 miles north of London. Five-year followup information was obtained for the two groups of first-admission schizophrenic patients admitted between 1931 and 1933 and between 1945 and 1947. These cohorts were compared with a third group of schizophrenic patients whose first admission took place over a 20-month period from 1973 to 1974 (Watt et al. 1983). In each successive cohort there was an increasing percentage of discharged but not readmitted female patients, but there was no improvement for male patients. Thus, for first-admission female schizophrenic patients, the introduction of convulsive treatments and then of neuroleptics appears to have been associated with decreased morbidity.

Early Intervention Studies
Tochigi Prefectural Hospital Study. Aritome (1978) examined 82 patients still living 16 years after their first hospitalization for schizophrenia (1959-60) and compared their outcome with that of patients described in the literature by others as treated before the introduction of neuroleptics. As a group, the patients did no better than the preneuroleptic patients reported in the literature. At followup 17 patients were in remission (no psychotic symptoms and good adaptation to family and work). Thirteen of these (one-sample proportional test, \(p = 0.01)\) were hospitalized within 1 year of the onset of symptoms. (The study is not included in the mirror-image studies because the authors did not match their patients with a specific group of comparable patients either from the same hospital or from the literature. Furthermore, it is not clear from the article how many of the patients in the study were given neuroleptics. In a similar Japanese study from the Tokyo Musashino Hospital, [Mura-kami 1971] covering the same period, only 16 percent of first-break schizophrenic patients were placed on neuroleptics.)

There was information about the premorbid temperaments of 12 of the patients who were in complete remission. Nine had cyclothymic premorbid personalities; the other three were schizothymic. It is unclear how the length of symptoms before hospi-

<table>
<thead>
<tr>
<th>Neuroleptic or ECT</th>
<th>(n)</th>
<th>% ((n)) patients in complete remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>287</td>
<td>28 (80)</td>
</tr>
<tr>
<td>No</td>
<td>213</td>
<td>14 (31)</td>
</tr>
</tbody>
</table>

Note.—Adapted from Huber et al. (1980), authors' table 18.
talization and premorbid personalities were related, but the larger number of patients in remission who had cyclothymic premorbid personalities suggests that having a good premorbid cyclothymic personality may be more important than when treatment was initiated. Unfortunately, the unclear nature of the patients' premorbid personality makes interpretation of this study and that of Crow et al. (1986), described below, difficult.

Northwich Park Study. Crow et al. (1986) followed a group of 120 first-episode schizophrenic patients who were discharged from full or partial hospital care and were maintained out of the hospital for at least 30 days (tables 7 and 8). Following their initial treatment, the patients were randomly assigned to a maintenance neuroleptic or PBO group and monitored until relapse during a 2-year period. As expected, patients treated with neuroleptics had a longer time until relapse than patients treated with PBO. In both neuroleptic- and PBO-treated groups, patients symptomatic for less than 1 year before their first admission had a longer time to relapse than those who were symptomatic for a year or more before their first admission. Unfortunately, it is unclear if there was a difference in the premorbid personalities of the patients who had been ill for less than 1 year and those ill longer than 1 year.

Tokyo University Study. Anzai et al. (1988) followed 62 patients with a DSM-III (American Psychiatric Association 1980) diagnosis of schizophrenia after their initial neuroleptic treatment. There were 14 poor-outcome patients who were unable to resume their social roles. These poor-outcome patients tended to be disorganized, had an earlier onset, and were excluded from further study. Forty-eight patients remained in the study. The followup began when the patients were able to resume their social roles and continued for 5 more years. As shown in table 9, patients who had had symptoms for longer than 1 year before entering treatment were more likely to relapse than patients who were treated within 1 year of developing symptoms.

**Table 7. Actuarial percent relapse-free time between first (n = 31) and second (n = 22) episode in neuroleptic-treated schizophrenic patients in the Northwich Park Study**

<table>
<thead>
<tr>
<th>Time between onset and first treatment</th>
<th>Months after treatment began</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 1 year</td>
<td>6 12 18 24</td>
</tr>
<tr>
<td>More than 1 year</td>
<td>76 33 26 18</td>
</tr>
</tbody>
</table>

Note.—Peto-Wilcoxon generalization of two-sample rank sum test (Lee 1984); \( \chi^2 = 4.47, df = 1, p = 0.03 \). Raw data from Crow et al. (1986) authors' table 2. For the actuarial statistic, patients relapsing within 6 months were considered to relapse at 1 month. Followup patients whose last time of followup was not stated in text were considered to have dropped out evenly across the followup period. Times of relapse for other patients were considered to occur at 6, 12, or 18 months.

**Table 8. Actuarial percent relapse-free time between first (n = 51) and second (n = 13) episode in placebo-treated schizophrenic patients in the Northwich Park Study (all patients treated with neuroleptics until out of hospital for 1 month)**

<table>
<thead>
<tr>
<th>Time between onset and first treatment</th>
<th>Months after treatment began</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 1 year</td>
<td>6 12 18 24</td>
</tr>
<tr>
<td>More than 1 year</td>
<td>23 8 0 0</td>
</tr>
</tbody>
</table>

Note.—Peto-Wilcoxon generalization of two-sample rank sum test (Lee 1984); \( \chi^2 = 11.64, df = 1, p = 0.003 \). See Note, table 7, for details.

**Table 9. Early neuroleptic treatment and relapse in 48 first-break schizophrenic patients in Tokyo University Study after 5-year followup**

<table>
<thead>
<tr>
<th>Time to neuroleptic treatment after first symptoms</th>
<th>Relapsed</th>
<th>No relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 1 year</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>More than 1 year</td>
<td>13</td>
<td>2</td>
</tr>
</tbody>
</table>

Fisher's exact test: \( p = 0.03 \)

Note.—Data adapted from Anzai et al. (1988).

*Authors' statistics used.
Investigators thought they were good candidates for drug discontinuation, so they are probably not representative of all patients with schizophrenia. Most of the studies did not address the consequences of the relapses when they did occur. There are, however, several studies which do focus on these consequences.

Curson et al. (1985) traced a group of 64 chronic schizophrenic outpatients who were followed for 7 years after a comparison study that showed that a long-acting depot neuroleptic was superior to PBO in reducing relapses. At the end of the comparison study, all patients were given a depot neuroleptic until they were stable for 8 weeks. Only patients considered to be compliant were placed in the study, but 40 percent of the patients presented compliance problems at least once during the 1-year followup period. Patients who failed to comply with medications during the followup period had relapses sooner and in greater numbers than compliant patients. At the end of 7 years of followup, patients with a greater number of relapses had a worse (p < 0.003, authors' statistics) social adjustment. The authors concluded that the largest part of their sample comprised “patients who do show some response to maintenance neuroleptic drugs and, provided they comply with medical treatment, acute relapses are reduced and social deterioration is limited” (p. 478). They also stated that social performance improved slowly and may continue to improve long after resolution of florid symptomatology.

One problem in interpreting this naturalistic study is the inability to determine the causality: whether failure to take medication caused the relapse, or whether the patients stopped taking their medication because they were relapsing.

The slow recovery of social performance was demonstrated in a more deliberate, better controlled neuroleptic-withdrawal study by Johnson et al. (1983). They studied the outcome of 56 chronic schizophrenic patients whose neuroleptic medication was discontinued after they had been living in the community and were psychiatrically stable for 12 to 48 months. These patients were compared with a similar group of 60 patients continuously given neuroleptics. Not surprisingly, 80 percent of the neuroleptic-discontinuation patients relapsed, compared to only 23 percent of neuroleptic-maintenance patients. For both groups, most relapses occurred in the first year of followup. If a patient did relapse, the relapse was much more severe in the neuroleptic-discontinuation group than in the neuroleptic-maintenance group. The neuroleptic-discontinuation group had more antisocial behavior, more self-injury, and required more compulsory admissions. When patients off neuroleptics at the time of relapse were placed back on neuroleptics, they required more medication, not only for stabilization, but for at least 6 months after they had relapsed. The patients in the neuroleptic-discontinuation group had poorer social adjustment than the patients remaining on neuroleptics. After 18 months of followup, only 23 percent of neuroleptic-discontinuation patients had good social adjustment, compared with 57 percent of the patients who had been maintained on continuous treatment (two-sample proportional test, p < 0.001).

Three of the neuroleptic-maintained group and nine of the neuroleptic-discontinuation group relapsed during months 12-18 of the study, or within 6 months of the time when the estimate of social adjustment was made. This acute disruption is likely to have biased the social adjustment ratings against the neuroleptic-discontinuation group (i.e., relapsed patients in the process of recovering might not have had a chance to stabilize). In table 10, I have assumed that these patients would have had good social adjustment if they had not relapsed during the last 6 months of the study. Assuming these patients would have had a good response and adding their number to those rated as good-

### Table 10. Patients with overall good social adjustment in previously stable neuroleptic-medicated chronic schizophrenic patients whose medications were either continued or discontinued 18 months earlier

<table>
<thead>
<tr>
<th>Neuroleptic status</th>
<th>n</th>
<th>n (%) patients with good adjustment</th>
<th>n (%) patients with good adjustment plus patients relapsing during the last 6 months of study [n]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintained</td>
<td>56</td>
<td>32 (57)</td>
<td>35 (62) [3]</td>
</tr>
<tr>
<td>Discontinued</td>
<td>60</td>
<td>14 (23)</td>
<td>23 (38) [9]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Three-sample proportional test p &lt; 0.001</td>
</tr>
</tbody>
</table>

Note.—Data adapted from Johnson et al. (1983).

* Assumes that the added patients would have had good adjustment if they had had longer recovery periods.
adjustment patients, there is still a substantial difference between the two groups. The neuroleptic-mainte-
nance group had a higher proportion of good-adjustment patients than the discontinuation group ($p < 0.01$). Thus, even after a minimum of 6 months' reinstitution of neuroleptics for patients who had relapsed, the neuroleptic-discontinuation group had not recovered to the social adjust-
ment level they would have had if their neuroleptics had been main-
tained.

Contemporaneous Control Group Studies

Minneapolis Veterans Administra-
tion Study. Wirt and Simon (1959) may have published the first random-assignment controlled study demonstrating that the initial form of treatment has an effect on the subsequent course of newly diagnosed schizophrenia. They divided 80 never-treated, DSM-I (American Psychiatric Association 1952) diagnosed acute schizophrenic male pa-
tients into four treatment groups. The clinical judgment group was given a variety of somatic treat-
ments, which often included CPZ, at the discretion of the treating psychia-
trist. The CPZ group received a minimum of 200 mg, and an average of 400 mg of CPZ per day. A third group received reserpine and is not considered here. The hospital routine group received only routine hospital care without somatic intervention.

Eight years after the initial hospitaliza-
tion the investigators (Simon et al. 1965) were able to interview 72.5 percent of the original sample. Fifty percent of the patients were rated as worse in their psychiatric and occupa-
tional adjustments compared with the condition before their first hospitaliza-
tion. Thirty percent of the patients were unchanged. The investiga-
gators found no distinguishing differences on prognostic or social factors for those patients who improved or became worse. When the treatment groups were examined sepa-
ately, 20 percent of the hospital discharged either to outpatient status or to another facility. One year fol-
lowing discharge the patients were again examined. Patients doing the best at 1 year were in the initial clinical judgment and CPZ groups. Table 11 demonstrates the combined 1-year followup results for the clinical judgment and CPZ groups combined compared with the hospital routine group. The patients who received the initial treatment given in either the clinical judgment or the CPZ group did better ($p < 0.01$) than those patients provided only routine hospital care without somatic intervention.

Four years after the initial hospi-
talization the investigators (Simon et al. 1965) studied chronic schizo-
phrenic patients who had been in a State hospital for more than 5 but less than 10 years. The study began in 1956, shortly after neuroleptics had become available, and the patients had had relatively little previous neuroleptic exposure: about half had been on phenothiazines and another 15 percent on reserpine for 5 to 6 months before the study. A few patients had had lobotomies and many had received ECT and/or insulin therapy. All patients who had been given medications were kept neuroleptic-free for at least 1 month before entering the study. Because of assumed poor prognosis, patients over 50 years of age and those with the subtype diagnosis of hebephrenia or simple schizophrenia were omitted. The study was designed to examine the effects of the interaction of neuroleptics plus social therapies (milieu) over a 6-month period. The patients were divided into four groups

<table>
<thead>
<tr>
<th>Initial treatment</th>
<th>1-year followup$^2$ (mean social rating)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital routine (nonsomatic)</td>
<td>19</td>
</tr>
<tr>
<td>Somatic plus CPZ groups</td>
<td>40</td>
</tr>
</tbody>
</table>

\[ \chi^2 = 14.0, \quad p < 0.01 \]

Note.—CPZ = chlorpromazine. Data adapted from Wirt and Simon (1959).

$^1$The patients' initial 30-day treatment was either the hospital routine (a nonsomatic therapy), CPZ, CPZ plus a somatic therapy, or a somatic treatment without CPZ (clinical judgment).

$^2$Followup ratings are based on letter values from authors' Appendix XII (A = 1; B = 2; C = 3; D = 4; E = 5). Lower mean social adjustment is in the direction of health.
of about 30 patients each. One group of patients was transferred from two large State hospitals to an active teaching hospital (MMHC) and treated with neuroleptic medications—primarily CPZ at 300 mg/day for males and 150 mg/day for females. Another group was transferred to the same hospital, but was given only social therapies. The other two groups remained in the State hospitals and are not considered further since they were not treated similarly in the followup period. (Patients who were given neuroleptics in the State hospitals during the experimental period tended to stay on them while those not treated with neuroleptics tended to remain neuroleptic-free [carryover effect].)

Not surprisingly, after 6 months the MMHC-medicated patients improved more, as determined by a mental status examination, than the patients treated without neuroleptics. Following the 6-month experimental period, 85 percent of MMHC patients who were in the initial drug-free group were immediately placed on medications while only two-thirds of the patients initially treated with medications were maintained on neuroleptics.

Table 12 shows the number of patients from each group who had been discharged 30 months after the initial phase of the study. Thirty months after the experimental period, 12 of 13 patients who were living outside a hospital had been in the initial neuroleptic group (Fisher’s exact test, \( p = 0.002 \)).

The Maudsley Study. The Maudsley preneuroleptic-versus neuroleptic-era study was discussed in the earlier section on mirror-image studies. As part of the same investigation, Pritchard (1967b) examined a group of schizophrenic patients in the neuroleptic era (1956 and 1957) who were nonrandomly assigned to be treated with either CPZ or no somatic treatment. For 78 percent of the patients the index hospitalization was the patient’s first. As can be seen from table 13, there was a trend for patients treated initially with CPZ to spend less time rehospitalized. Since the patients had equal access to neuroleptics when they were rehospitalized, and maintenance neuroleptics were not yet being used, this trend was probably not related to these factors.

Table 12. Number of patients discharged at 30 months after initial 6-month neuroleptic or no neuroleptic treatment from the Massachusetts Mental Health Center Study

<table>
<thead>
<tr>
<th>Initial 6 months of treatment</th>
<th>n patients discharged 30 months after experimental period</th>
</tr>
</thead>
<tbody>
<tr>
<td>No neuroleptic</td>
<td>27</td>
</tr>
<tr>
<td>Neuroleptic</td>
<td>33</td>
</tr>
<tr>
<td>Fisher’s exact test</td>
<td>12</td>
</tr>
<tr>
<td>( p = 0.002 )</td>
<td></td>
</tr>
</tbody>
</table>

Note.—Data adapted from Greenblatt et al. (1965).

Table 13. Months of hospitalization during 3 years after discharge of patients receiving no somatic treatment and treated with chlorpromazine (CPZ)

<table>
<thead>
<tr>
<th>Initial treatment</th>
<th>n</th>
<th>Months (mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No somatic treatment</td>
<td>13</td>
<td>10.4</td>
</tr>
<tr>
<td>CPZ</td>
<td>18</td>
<td>5.5</td>
</tr>
<tr>
<td>Mann-Whitney U test</td>
<td>( p = 0.1 )</td>
<td></td>
</tr>
</tbody>
</table>

Note.—Adapted from Pritchard (1967b). In the published article mean lengths of hospitalization were presented in table 3 (p. 1355). Also presented was the number of patients in each group who were hospitalized for nil time, for up to 18 months, and for more than 18 months. No statistical comparison between groups, however, was presented. I assumed that patients who had nil hospitalizations actually were hospitalized zero days, those hospitalized less than 18 months were hospitalized 9 months, and those hospitalized for more than 18 months were hospitalized 9 months. The 9- and 27-month values are medians between 0 and 18, and 18 and 36 months, respectively. The published no somatic treatment and CPZ means were 9.8 and 4.0, respectively, somewhat shorter than my interpolated means. Using the Fisher’s exact test, \( p = 0.19 \) comparing patients spending nil plus less than 18 months hospitalization postdischarge with those hospitalized longer than 18 months without somatic treatment or treated with CPZ. If the preneuroleptic-era patients who were not treated with a somatic treatment are added to the control group in the neuroleptic era and compared with the CPZ-treated group, \( p = 0.14 \), Fisher’s exact test. When patients who received CPZ, insulin, ECT, or reserpine were compared with patients who did not receive any of these in the neuroleptic era, \( p < 0.06 \), Fisher’s exact test.
Each group consisted of about 100 patients. At the end of the 6-week trial, patients given neuroleptics had substantially improved compared with their own admission ratings and compared with the patients given PBO. One year after the patients were discharged, 254 patients were living in the community (Schooler et al. 1967). It is unclear if these were proportionally distributed between the neuroleptic- and PBO-treated patients who finished the comparison study, but the PBO-treated patients in the initial trial had fewer readmissions than those who had been given neuroleptics during the first 6-week trial.

There are several problems in interpreting this study. One third of the PBO-assigned patients compared with 2 percent of neuroleptic-treated patients had to be removed from the study before the 6-week trial was over. The selective omission of the most difficult patients from the PBO group makes it difficult to evaluate the comparison. Furthermore, the PBO-treated patients, on average, spent 6 more weeks in the hospital than the neuroleptic-treated patients after the 6-week formal trial was over. During that extra time, the authors speculate, the staff gave them special care including, presumably, neuroleptics. Finally, there are no data comparing the administration of maintenance neuroleptics between the groups.

Camarillo State Hospital Study. May (1968) compared several modes of treatment for first-break schizophrenic patients and found that compared with psychotherapy alone or milieu therapy, neuroleptics and ECT increased the rate of release from the hospital, reduced the length of hospital stay, and decreased the need for sedatives and hydrotherapy. Patients were considered successes if they were released from the hospital after less than 1 year of treatment. These "successful" patients became the subjects of the Camarillo followup study (May et al. 1976a, 1976b).

Upon discharge, the form of treatment was not further dictated, but patients tended to receive the same treatment as in the original study (May et al. 1981). Only the patients who were treated with ECT in the hospital, however, received a statistically significant decrease of neuroleptic during the followup period. For 3 years following their release after the initial hospitalization, the patients who had been treated with neuroleptics, neuroleptics plus psychotherapy, and ECT were rehospitalized an average of 90 to 105 days (table 14). The patients who had been initially treated with psychotherapy alone were rehospitalized about 205 days and the milieu group about 155 days. Patients in the milieu group tended not to be released within the 1-year period and fewer of them were entered into the followup study (data from authors' figure 9, May et al. 1976b). While the difference between the groups seems large, the only statistically significant difference occurred 2 years after release; the psychotherapy group had a statistically significant increase in days rehospitalized compared with the ECT group (authors' statistics). Since the ECT patients were the only group to receive statistically significantly less neuroleptics during the followup period, and since they required the fewest rehospitalizations, it seems unlikely that the trend toward a difference between those patients who received neuroleptics in the initial hospitalization and those who did not receive neuroleptics was due to a carryover effect, that is, patients on drugs tended to remain on drugs.

Not only did patients who received neuroleptics in the hospital spend less time rehospitalized than the psychotherapy patients, but their symptoms were less severe (May et al. 1981). Perhaps the most objective measure used was the proportion of time that the patients were working for pay. Two years after all patients were released from the hospital the neuroleptic-treated patients were spending about twice as much time working for pay as the psychotherapy patients. The psychotherapy plus neuroleptic group was second, con-
considerably behind the neuroleptic-only group, but slightly ahead of the ECT group and the milieu group.

In the published followup study (May et al. 1981), all patients discharged within 1 year of their initial hospitalization were included. Dr. Tuma and I are in the process of further evaluating the contribution of neuroleptic treatment to patient outcome following initial discharge from the hospital. We felt it might be important to look at those patients hospitalized for a shorter period of time. Today, few patients would have 1 year of continuous hospitalization following their initial schizophrenic episode. Perhaps more important, there may have been a subgroup of patients with spontaneous remission who did very well after their initial hospitalization. For this comparison we used only those patients hospitalized 6 months or less who were followed for at least 3 years after discharge and for whom we also knew the total days rehospitalized, the total number of days they were prescribed neuroleptics, and the names and doses of neuroleptics. There were 65 patients in the initial neuroleptic and neuroleptic plus psychotherapy groups who fit these criteria, but only 14 patients in the psychotherapy and milieu groups.

Table 15 shows a strong trend during years 1, 2, and 3 (year 3, \( p < 0.01 \)) for the patients initially treated with neuroleptics to spend fewer days rehospitalized than those patients given psychotherapy and milieu therapy. There was a strong trend for the total days on neuroleptics (year 1) and total neuroleptic in CPZ equivalents (year 1, \( p < 0.01 \); year 2, \( p < 0.05 \)) to be increased during the first and second year following discharge in the group treated with neuroleptics in the hospital. By the third year, however, this trend was reversed.

NIMH Study. Carpenter et al. (1977a) followed up a group of acute schizophrenic patients who were originally brought to NIMH to be studied without neuroleptics. The patients were selected because they had reasonably adequate social and work function before the onset of their current psychotic episode. They also had to be willing to participate in research, which as a rule meant they were living with a responsible family member. Patients were seen in psychoanalytically oriented psychotherapy two to three times a week. All patients also had group and family therapy. While for the most part the patients were treated without neuroleptics, occasionally neuroleptics were needed. The mean patient stay was 4 months, with no patient staying at NIMH more than 4.5 months. Patients requiring further hospitalization were transferred to other institutions.

At followup the former NIMH patients were compared with the first 73 patients admitted to a local community hospital. This comparison group had been treated with the usual hospital care of the late 1960's. The community hospital patients' mean outcome score 2 years after admission was 11.1, while the NIMH drug-free patients had a 12.8 score 1 year after admission (higher score = better social function). Because the outcome followup periods were unequal for the two groups, the authors examined a subgroup of the NIMH patients 24 to 30 months after admission and found that they improved with further distance from the index hospitalization, suggesting the unequal comparison periods did not bias the study in favor of NIMH patients.

While the authors state that there were no significant differences in prognostic scores between the two groups, the published table reveals that the NIMH patients were in a higher social class (17 of 49 were social classes I and II, while only 7 of 73 community patients were in these two classes; Fisher's exact, \( p < 0.001 \)). This observation about social class was made in a letter to the editor (Kane 1977). When this was brought to their attention, Carpenter

<table>
<thead>
<tr>
<th>Initial treatment with neuroleptics</th>
<th>( n )</th>
<th>1 Mean (SD) days hospitalized</th>
<th>2 Mean (SD) days hospitalized</th>
<th>3 Mean (SD) days hospitalized</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>65</td>
<td>24.8 (51.0)</td>
<td>62.1 (105.9)</td>
<td>75.9 (133.2)</td>
</tr>
<tr>
<td>No</td>
<td>14</td>
<td>45.3 (77.2)</td>
<td>130.3 (148.0)</td>
<td>170.1 (170.0)</td>
</tr>
<tr>
<td>One-tailed ( t ) test</td>
<td></td>
<td>( p &lt; 0.16 )</td>
<td>( p &lt; 0.06 )</td>
<td>( p &lt; 0.01 )</td>
</tr>
</tbody>
</table>

Note.—Data from original records of May et al. (1981). I am grateful to Phyllis Lathers and Louis Jolyn West for helping to retrieve these data.
et al. (1977b) reanalyzed their data and found no relationship between social class and outcome.

There are other indications, however, that community-treated patients were probably not a good comparison group. The community-treated patients were older (23.7 ± 7.8 years [mean ± SD] for NIMH, 28.9 ± 8.3 years for community; two-tailed t test, t = −3.5, p < 0.0001) and as indicated below may have had a more chronic illness at the time of admission than the NIMH patients. The community-treated patients were part of the World Health Organization (WHO) International Followup Study, and more details are presented in a monograph about that study (World Health Organization 1979). The admission criteria for the WHO study very likely allowed for inclusion of patients who had a poorer prognosis than the patients in the NIMH study. In the WHO study, patients were admitted who had been psychotic for up to 3 years, had been hospitalized for up to 2 years, and could have had an IQ as low as 70. At the 2-year followup period, 47 percent of WHO comparison patients were still psychotic and had never recovered from the index episode, and only 1 percent of these patients had remained out of the hospital for more than 25 percent of the time since the index admission. Finally, because of the manner in which services were provided in the Washington, DC, area in the late 1960's, only the patients in the WHO community setting with built-in social and personal resources were likely to continue treatment and have an active social life. Having a family who could participate was one of several criteria for admission to the NIMH research program.

Agnews State Hospital Study. Rappaport et al. (1978) reported on 127 acute male schizophrenic patients who were randomly assigned to be treated with PBO or CPZ. Seventy-four percent of the patients had no or only one previous hospitalization. Patients treated with PBO and CPZ (300 to 900 mg/day) spent the same number of days (45.0 vs. 42.2, respectively) hospitalized, but the CPZ group was significantly more improved on discharge. (Surprisingly, the difference was only significant at the 0.05 level using a one-tailed t test. Also, there was no difference on a measure of functional disturbance between the groups at discharge.) At regular intervals for up to 3 years following discharge, the patients were rated and asked about their medication history since discharge (treatment following discharge was not assigned). The patients were then divided into four groups based on their being in the CPZ or PBO group in the planned part of the study, and the patients reported medication status at last contact after their initial discharge: CPZ in hospital but off medication at their last visit (CPZ-Off); CPZ in hospital, on medication at the last visit (CPZ-On); PBO in hospital, no medication at last visit (PBO-Off); and PBO in hospital and medication at last visit (PBO-On).

There is no indication that the groups were followed for equal time periods or that any attempt was made to determine the reliability of patient-provided information. Nevertheless, the PBO-Off group had greater improvement from admission to followup than did any of the other groups. There was no difference among the other three groups. The PBO-Off patients also had the fewest number of rehospitalizations, and again there were no differences between the other groups. (See table 16.)

It is of some interest that at followup 74 percent of the CPZ group but only 54 percent of the PBO group could be located. (It appears that, for reasons not explained, the original assignment to groups was unequal with 75 patients assigned to the PBO group and 53 patients assigned to the CPZ groups.) The authors noted that there was a direct relationship between the proportion of patients with good premorbid histories in each group and the improvement scores, and that this differential attrition had added a bias. (There was a substantially greater proportion of good premor-

Table 16. Relationship of good premorbid history, improvement, hospital treatment, and treatment at last visit in Agnews State Hospital Study

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Improvement since admission</th>
<th>% patients with good premorbid history</th>
<th>Premorbid history difference from PBO-OFF¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBO-Off</td>
<td>0.92</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td>CPZ-Off</td>
<td>0.52</td>
<td>71</td>
<td></td>
</tr>
<tr>
<td>CPZ-On</td>
<td>0.48</td>
<td>59</td>
<td>p = 0.12</td>
</tr>
<tr>
<td>PBO-On</td>
<td>0.29</td>
<td>47</td>
<td>p = 0.04</td>
</tr>
</tbody>
</table>

Note.—PBO = placebo, CPZ = chlorpromazine. Data adapted from Rappaport et al. (1978).

¹Fisher's exact test.
bid history patients in the PBO group at followup; poor premorbid PBO-group patients were not available for followup.) When the authors attempted to equalize the groups by dropping the patients in the CPZ-treated groups with the smallest improvement scores, they found no difference between the groups at followup.

Perhaps the most important finding of this study regarding treatment of patients during the early phase of their psychotic illness is that patients treated in the hospital with PBO and who were found to be taking neuroleptics at followup comprised the one group that had not improved upon discharge from the hospital or at followup. Assuming that there was no systematic bias in the way the patients were treated in the followup period, this finding has several likely explanations. One interpretation is that the long-term outcome for this group of patients would have occurred regardless of whether neuroleptics had been given during the hospitalization and those patients who did not improve without neuroleptics had no further benefit once neuroleptics were given. Another interpretation is that some patients who were allowed to go unmedicated during the hospitalization became more difficult to treat, and once neuroleptics were introduced they had become poor responders. In part, the latter explanation seems pertinent since the patients in the PBO-On group with good premorbid personalities did the worst of any of the patients with good premorbid personality during the followup period.

*Soteria House Study.* Matthews et al. (1979) compared the 24-month postdischarge risk of relapse for first- and second-admission schizophrenic patients treated a mean of 21 days in a Community Mental Health Center (CMHC), which primarily used neuroleptic medications, with similar patients treated for a mean of 159 days in Soteria House, a small community homelike facility. Soteria House patients were not given neuroleptics during their first 6 weeks of treatment, and thereafter neuroleptics were used only minimally. While the patients were not randomly assigned to treatment settings, they appeared to be well matched for acute versus insidious onset as well as for other parameters thought to predict outcome. In contrast to most studies examining the effects of maintenance neuroleptics, the CMHC-treated patients, who received considerably more maintenance neuroleptics than the Soteria House patients, were rehospitalized at a faster rate than the Soteria House patients (p ≤ 0.05 at 12 months but not significant at 18 or 24 months; authors' statistics using a life-table analysis).

This study adds support to the considerable evidence that some schizophrenic patients do well when treatment methods other than neuroleptics are used. The study, however, probably does not help answer the question of whether neuroleptics alter the course of schizophrenia. The Soteria House patients were institutionalized an average of 138 days (between 4 and 5 months) more than the CMHC patients before discharge. In the context of the above question, this difference makes any comparison between the groups difficult to interpret. Twenty percent of CMHC patients relapsed within the first month after discharge and approximately another 18 percent relapsed by the fifth month postdischarge (Matthews et al. 1979, figure 1). In contrast, by the fifth month postdischarge, only about 25 percent of Soteria House patients had relapsed. By the 15th month, however, all the CMHC patients who were going to relapse had relapsed, while relapses were still occurring for the Soteria House patients. At the end of 24 months there was no statistically significant difference between the groups.

A possible explanation for the early difference between the two groups is that the Soteria House patients were still institutionalized at the time the majority of the CMHC patients were relapsing; if the CMHC patients had been allowed to return to the community more gradually, they might have fared better. In retrospect, it is unfortunate that a randomly assigned medication control group from Soteria House was not made part of this study.

For the purposes of this article, it would be useful to compare subgroups of both CMHC and Soteria House patients who were not maintained on neuroleptics after discharge from their treatment sites. Twenty-six Soteria House patients were given no neuroleptics during the 2-year followup period while 18 CMHC patients discontinued their neuroleptics (reason not specified) at some point during the followup period.

The CMHC patients not maintained on neuroleptics had the same probability of not relapsing as the Soteria House patients not given neuroleptics during the followup period. The CMHC patients, however, were discharged 110 days, or almost 4 months, sooner (32 vs. 142 days) than the Soteria House patients. It appears that the CMHC patients treated with neuroleptics during their hospitalization, but subsequently withdrawn from neuroleptics, had 110 more days out of an institution than the Soteria House patients who were neither treated with neuroleptics while they were inpatient residents nor after discharge. Thus, this subgroup of neuroleptic-treated acute
schizophrenia patients appears to have required less institutionalization than the Soteria House nonmedicated patients with about the same rate of relapse.

**Comments**

Twenty-two studies have been reviewed, from first-break or predominantly 19 first-break populations (table 17). The conclusions of some original study authors are consistent with the view that neuroleptic intervention given relatively early in schizophrenia improves the course of the disorder. On the other hand, none of the authors of the studies reported here concluded that neuroleptic treatment in the early phases of the disorder makes the course of schizophrenia worse.

A number of investigators would argue, however, that some patients do not need to be placed on neuroleptics. This view is consistent with the published results of several studies that indicate that some patients do well when they are not given neuroleptics early in the course of their illness. While it is clear that some patients do recover without neuroleptic treatment, collectively the analysis of the data presented here indicates that some patients do well when they are not given neuroleptics early in the course of their illness. While it is clear that some patients do recover without neuroleptic treatment, collectively the analysis of the data presented here indicates that some patients do well when they are not given neuroleptics early in the course of their illness. While it is clear that some patients do recover without neuroleptic treatment, collectively the analysis of the data presented here indicates that some patients do well when they are not given neuroleptics early in the course of their illness.

Mirror–Image Studies. Random patient assignment is probably the most critical element missing from mirror-image studies. Random assignment, however, was not common in any group of studies. For example, only four contemporaneous control-group studies used random assignment (Wirt and Simon 1959; Schooler et al. 1967; Rappaport et al. 1978; May et al. 1981). It is more likely that those mirror-image studies examining eras chronologically closest together used similar criteria for procedures, admission, and discharge. The study of Peterson and Olson (1964), which examined patients from one Pennsylvania hospital in the preneuroleptic era and from another hospital in Minnesota during the neuroleptic era, might have introduced the greatest diversity of patients and treatments. Nevertheless, in these studies, exposure to ECT and other nonneuroleptic somatic treatments probably decreased the likelihood of neuroleptic effect since these treatments seem to have affected the morbidity of schizophrenia. For example, Manfred Bleuler (1972/1978), summarizing his

<table>
<thead>
<tr>
<th>Study</th>
<th>First- or predominantly first-break populations</th>
<th>Authors’ conclusion</th>
<th>My conclusion (degree of effect)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wirt and Simon 1959</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes (H)</td>
</tr>
<tr>
<td>(Simon et al. 1965)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McWalter et al. 1961</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes (M)</td>
</tr>
<tr>
<td>Ødegård 1964</td>
<td>Yes</td>
<td>No</td>
<td>Yes (L)</td>
</tr>
<tr>
<td>Peterson and Olson 1964</td>
<td>Yes</td>
<td>No</td>
<td>Yes (H)</td>
</tr>
<tr>
<td>Greenblatt 1965</td>
<td>No</td>
<td>Yes</td>
<td>Yes (M)</td>
</tr>
<tr>
<td>Astrup and Noreik 1966</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes (H)</td>
</tr>
<tr>
<td>Schooler et al. 1967</td>
<td>Yes</td>
<td>No</td>
<td>Inc</td>
</tr>
<tr>
<td>Pritchard 1967a, 1967b—I</td>
<td>Yes</td>
<td>No</td>
<td>Yes (L)</td>
</tr>
<tr>
<td>Pritchard 1967b—I</td>
<td>Yes</td>
<td>No</td>
<td>Yes (L)</td>
</tr>
<tr>
<td>Shimazono and Toru 1968</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes (M)</td>
</tr>
<tr>
<td>Murakami 1971</td>
<td>Yes</td>
<td>No</td>
<td>Yes (L)</td>
</tr>
<tr>
<td>May et al. 1976, 1981</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes (M)</td>
</tr>
<tr>
<td>Carpenter et al. 1977</td>
<td>Yes</td>
<td>No</td>
<td>Inc</td>
</tr>
<tr>
<td>Aritome 1978</td>
<td>Yes</td>
<td>No</td>
<td>Inc</td>
</tr>
<tr>
<td>Rappaport et al. 1978</td>
<td>Yes</td>
<td>No</td>
<td>Inc</td>
</tr>
<tr>
<td>Matthews et al. 1979</td>
<td>Yes</td>
<td>No</td>
<td>Inc</td>
</tr>
<tr>
<td>Huber et al. 1980</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes (H)</td>
</tr>
<tr>
<td>Johnson et al. 1983</td>
<td>No</td>
<td>Yes</td>
<td>Yes (H)</td>
</tr>
<tr>
<td>Watt et al. 1983</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes (H)</td>
</tr>
<tr>
<td>Curson et al. 1985</td>
<td>No</td>
<td>Yes</td>
<td>Yes (H)</td>
</tr>
<tr>
<td>Crow et al. 1986</td>
<td>Yes</td>
<td>Yes</td>
<td>Inc</td>
</tr>
<tr>
<td>Anzai et al. 1988</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes (H)</td>
</tr>
</tbody>
</table>

Note.—Yes = improved; No = not improved; Inc = inconclusive; H = high effect; M = moderate effect; L = low effect.

1in females.
longitudinal studies with patient groups who became probands in 1928–29 and ending with patients who became probands in 1942–43, stated: “Intensified therapeutic methods applied in recent decades [before the introduction of neuroleptics] have been able to combat with considerable success the catastrophe-schizophrenias” (p. 191). (Catastrophe-schizophrenias are schizophrenic patients with acute onsets that became severe chronic states without remission.) Bleuler does not believe, however, that the therapeutic methods introduced in the 1930’s affected the unfavorable outcomes of patients whose schizophrenia began with more gradual courses. (See table 18.)

The differences between eras revealed by the mirror-image studies might be due to systematic changes that occurred in the neuroleptic era, such as better nutrition. The improved social climate in which the patients were treated during the neuroleptic era could also account for the improvement found in the mirror-image studies. Again, since most of the preneuroleptic- and neuroleptic-era patients were studied within a few years of each other, it seems unlikely that these improvements happened quickly enough to explain the differences found.

Finally, the effects of maintenance treatments are probably not a major problem for the studies reported here. While use of maintenance neuroleptics is now commonplace, when the neuroleptic-era patients entered into the mirror-image studies during the mid–1950’s, maintenance neuroleptic treatment was not commonly used for first-admission patients. The use of maintenance treatment began only after it became apparent that most patients relapsed following their initial discharge.

Early Intervention Studies. The results of the three studies comparing patients treated within 1 year of the onset of their illness and patients treated 1 year after the symptoms began are consistent with many long-held ideas about schizophrenia. In the 1930’s, Langfeldt (1969) and others attempted to determine if the newly introduced insulin and metrazole treatments produced a long-term benefit in schizophrenic patients. He concluded that some of the claims for these therapies were being made for patients who would have improved without these specific therapies. Patients who responded well were described as having a schizophreniform psychosis. Similarly, after the introduction of ECT, it was observed that schizophrenic patients who were ill for less than 1 year before treatment did much better than patients ill for longer periods of time (Gralnick 1946).

In subsequent reports, these patients were often referred to as reactive schizophrenic patients, patients with a sudden onset and often a good prognosis, compared to process schizophrenic patients who had a gradual onset and poorer prognosis (Stephens 1970). In part, because the reactive/process dichotomy implies more about the etiology of schizophrenia than is justified, this terminology is now in disfavor. Today much of what was called reactive schizophrenia would be called schizophreniform, brief reactive psy-

Table 18. Number of patients having acute schizophrenic onset with severe end state (catastrophe-schizophrenias) before introduction of somatic treatments (1929–30 and 1933–36) and after the introduction of somatic therapies (1942–43)

<table>
<thead>
<tr>
<th></th>
<th>Presomatic treatment era patients</th>
<th>Somatic treatment era patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At risk</td>
<td>Acute onset to severe state (%)</td>
</tr>
<tr>
<td>All probands</td>
<td>65.0</td>
<td>5.0 (8)</td>
</tr>
<tr>
<td>Schizophrenic relatives of probands</td>
<td>122.0</td>
<td>14.0 (11.5)</td>
</tr>
<tr>
<td>All probands and their schizophrenic relatives (presomatic), siblings (somatic)</td>
<td>187.0</td>
<td>19.0 (10)</td>
</tr>
</tbody>
</table>


^1Fisher’s exact test.
chosis, atypical psychosis, schizophrenic disorder, or manic depressive illness. In future studies comparing early versus late intervention, it will be important for investigators to more comprehensively describe patients before their first treatment, to follow the patients for a period sufficiently long to make a rigorous diagnosis, and to make comparisons across patient groups with a similar prognosis to the degree possible in naturalistic studies.

The Anzai et al. (1988) study, while small, attempted to compare early and late treatment in patients with similar prognoses. By excluding patients who did not return to their previous level of function following treatment, they should have eliminated patients with a poor premorbid history. If a similar outcome is found in larger studies where premorbid history is more tightly controlled, it would indicate that early intervention is of greater importance than is commonly accepted.

It is of interest that Ey and colleagues (1957) compared two groups of acute psychosis patients with a "schizophrenic tendency" who were treated with somatic therapies (ECT, insulin, and lobotomy) to patients treated with psychotherapy. When the patients were followed up 12 years after the onset of illness, the group of patients who had received the somatic treatments were less likely to have had a chronic course than those patients who had not received somatic treatments (two-sample proportional test, \( p = 0.02 \)). (See table 19.)

### Table 19. Percentage of patients with chronic course at follow-up 12 years after somatic treatment or no somatic treatment for acute psychotic delusional illness with schizophrenic tendencies

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>n</th>
<th>% patients developing chronic course (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No somatic treatment</td>
<td>43.0</td>
<td>35 (15)</td>
</tr>
<tr>
<td>Somatic treatment</td>
<td>76.0</td>
<td>18 (14)</td>
</tr>
</tbody>
</table>

Note.—Data adapted from Ey et al. (1957).

\(^1\)Somatic treatments included electroconvulsive therapy, insulin, and lobotomy.

Neuroleptic Discontinuation Studies. The neuroleptic discontinuation studies address an issue related to the major question posed in this article. While the other kinds of studies ask whether neuroleptics given early in schizophrenia alter the course of the disorder, the discontinuation studies raise the question of whether allowing an individual to have repeated psychotic relapses causes loss of function beyond the time of the exacerbation of the psychosis itself. This is different from the question usually asked by maintenance-treatment studies, the results of which indicate that neuroleptics can prevent relapses. Maintenance-treatment studies have not yet resolved the question of whether maintenance neuroleptics can decrease patient deterioration when compared with patients who are not provided maintenance treatment. A series of studies, however, are currently being undertaken that may add new information to this subject.

The results of a preliminary study (Herz et al. 1982) suggested that some schizophrenic patients who had been stably maintained on neuroleptics could be treated by lowering or discontinuing neuroleptics if these patients were carefully watched for signs of decompensation. It is noteworthy that Herz et al. (1982) stipulated that the neuroleptic should be raised or restarted at the first sign of decompensation.

Carpenter et al. (1987) published the first controlled study comparing continuous- versus targeted-neuroleptic treatment plus psychosocial intervention. Forty-two schizophrenic and schizoaffective disorder patients who recently had been psychotic and were in an intermediate stage of recovery entered the study. Neuroleptics were continued for 4 to 8 weeks, then the patients were taken off neuroleptics for 4 more weeks. The patients were then randomly assigned to be treated either with continuous-neuroleptic or a targeted-neuroleptic intervention using a stratification procedure matching for gender, age, and prognostic status. Those patients who failed to remain drug-free during the drug-free period were admitted to the study on medications. When patients required it, they were hospitalized and treated in the normal fashion. On discharge they were returned to their previously assigned group unless they required more than 6 months of hospitalization.

The continuous-treatment group was given at least 300 CPZ equivalents per day and monitored with brief visits every other week. The targeted patients were given neuroleptics when they seemed to be developing early signs of psychosis, but
they were also seen for 45 minutes each week, at which time prodromal symptoms were discussed, environmental stressors were identified, and support was given for minimizing the impact of the stressors. Also, early in the treatment, family members were seen to identify stressors and offer practical suggestions for decreasing the impact of the stress.

During the first year the targeted-symptom groups required more hospital admissions than the continuous-treatment group, but during the second year there was only a slight difference in the number of hospitalizations (the continuously medicated group needed fewer). No data were given for number of days in hospital or for patients dropped from the study because they required more than 6 months of hospitalization. The targeted-patient groups used less medication than the continuous-medication group. At the end of 2 years the psychosocial functioning was nearly the same for the two groups.

Recently, Carpenter and associates (1990), using a slightly different design, reported on an attempt to replicate their earlier findings. Again, the targeted-neuroleptic patients received less neuroleptic over the 2 years of the study. Unfortunately, however, when the targeted intervention was applied to this larger and probably more diverse group of schizophrenic patients, the targeted-treatment patients required more hospitalizations, in addition to having decreased social functioning on the eight measures examined. In the authors' table 5, continuously treated patients were higher (higher scores meant better function) in frequency of social contacts, quality of social relationships, extent of employment, quality of employment, symptoms, ability to meet basic needs, fullness of life, and degree of impairment, although statistical analysis showed that only the extent of employment and quality of employment were by themselves significantly different between the groups. These results were present even though only 49 percent (compared with 81% of the continuously treated group) finished the 2-year study.

In a similar study, Jolley and Hirsch (1989) reported on a group of stable schizophrenic outpatients assigned to depot neuroleptic or intermittent neuroleptic treatment for a period of 2 years. While the intermittent group had fewer extrapyramidal side effects, their social function was not different. The intermittent-treatment group did, however, have four times as many relapses as the continuous-treatment group, even though patients were referred to the study if they had been stable on depot neuroleptics for 6 months and were not thought to present a danger to themselves or others if they should have a relapse. Even after meeting these criteria, 60 percent of patients referred to the study were not included because the investigators did not feel they could be managed off medications.

If patients in the targeted neuroleptic-treatment strategies continue to have poor outcomes, perhaps a better result will occur when low doses of neuroleptics are combined with some of the same psychosocial interventions used for the targeted neuroleptic-treatment groups. For example, Goldstein et al. (1978), using some of the same psychosocial interventions as Carpenter et al. (1987) but in combination with neuroleptic drugs, found that there was an additive effect of the two treatments in preventing relapses for at least 6 months after the initial hospitalization for acute schizophrenia.

The issue of preventing relapses is underscored by an observation of Ciompi (1980). In his 37-year follow-up study of 228 schizophrenic patients treated before the introduction of neuroleptics, Ciompi found that 48 percent had acute onsets. Of those patients with acute onsets, about 25 percent had one or more relapses followed by excellent remissions. Yet for patients who had a subsequent relapse, there was often a moderate or severe increase in baseline symptoms. Similar observations have been made by others (Bleuler 1972/1978; Watt et al. 1983).

Contemporaneous Control Group Studies. In practice, contemporaneous control-group studies should provide the opportunity to match patients on a number of important factors. Surprisingly, however, of all the published studies that might be used to determine the long-term effects of neuroleptic intervention on the course of schizophrenia, only the study of May et al. (1981) used a large number of randomly assigned patients, provided great detail about the nature of the study and follow-up, and did not lose a disproportionate number of one group.

The authors of three studies (Carpenter et al. 1977a; Rappaport et al. 1978; Matthews et al. 1979) indicated that schizophrenic patients fared better when they were not given neuroleptics during one of their early admissions than when they were given neuroleptics. For reasons discussed here under the descriptions of the individual studies (above and below), the studies cannot be used to indicate that the majority of such patients should be treated without neuroleptics.

The Agnews State Hospital Study was complicated by an uneven assignment of patients and a high attri-
Conclusions and Implications

Some psychotic patients with an acute onset do well even though no neuroleptic or other somatic treatment is used. Bockoven (1956), for example, examined records of Worcester State Hospital from 1833 to 1852 and found that 71 percent of patients who had been ill for less than 1 year before their first hospitalization were discharged as recovered or improved, while only 45 percent of those who had an illness which lasted for more than 1 year before their first hospitalization were discharged as recovered or improved. It is of interest that a substantial number of those patients did not require rehospitalization at a subsequent date. Depending on the duration of illness, such patients might be diagnosed schizophreniform by DSM-III-R, acute schizophrenic epi-
Neuroleptics in some acute psychotic illnesses. Objective measures, such as increasing the number of rehospitalizations, including abating relapses and decreasing the number of rehospitalizations, were the most common criteria used. Presumably the symptoms that are most likely to cause rehospitalizations are ones that other people find disruptive. However, the specific symptoms altered by early intervention have not been well delineated. The follow-up study of Ciompi (1980) suggests that deficit symptoms may develop after several psychotic relapses. Perhaps early intervention also helps decrease these fairly intractable symptoms by reducing the number or severity of psychotic relapses. The decrease in severe deterioration (catastrophic schizophrenia) associated with the introduction of somatic treatments (Bleuler 1972/1978) and neuroleptics (McWalter et al. 1961; Astrup and Noreik 1966; Shimazono and Torü 1968; Huber et al. 1980) appears to be consistent with this notion. Finally, the findings of May et al. (1981) that patients treated with neuroleptics during their first hospitalization were spending about twice as much time working for pay as the psychotherapy patients suggests that the initial treatment may decrease symptoms other than those which cause hospitalization.

Neuroleptic intervention may improve more than the long-term morbidity of patients who have acute psychotic symptoms. The MMHC study (Greenblatt 1965) indicates that schizophrenic patients who have been ill for a number of years may still receive long-term benefits from neuroleptics. Paradoxically, in the MMHC study, patients whose onset was more gradual did better than patients with an acute onset. The MMHC patients who had been hospitalized for more than 5 years before entering the study. Many of these patients had previously received ECT and other somatic treatments without much long-term benefit. It seems likely that the acute-onset patients who would have benefited from neuroleptics would have been discharged before being entered into this study; those acute-onset patients who were still in the hospital were no longer amenable to treatment. Another possibility, related to the theme of this review, is that a prolonged state of intense psychosis might render a person refractory to treatment.

A publication from the Chestnut Lodge long-term outcome study (Fenton and McGlashan 1987) indicates that the length of time a patient is psychotic does influence discharge and rehospitalization. In the Chestnut Lodge study some schizophrenic patients with good premorbid histories who were hospitalized for more than 3 years, but psychotic for less than 1 year before their Chestnut Lodge admission, were discharged and remained out of the hospital for an average of 15 years without neuroleptic treatment. Patients who had been hospitalized for a similar length of time but had been psychotic for more than 1 year did not fare as well, even though they were treated with neuroleptics while at Chestnut Lodge.

The most detailed contemporaneous control study (May 1968) indicated no benefit from milieu therapy or from adding psychotherapy to neuroleptic treatment; other studies, however, suggest that nonpharmacological treatment can be important. For example, the MMHC study provided evidence that combining active psychosocial treatments with neuroleptics is useful. In addition to the patients transferred to MMHC, a group of patients was randomly assigned to remain at the original State hospitals. Half of these patients were given neuroleptics while the other half was not. The patients remaining in the State hospitals who were given...
neuroleptics did better than those not given neuroleptics. They did not, however, do as well as the MMHC patients given neuroleptics plus milieu therapy. At the end of 36 months, 12 of 33 patients originally at MMHC were discharged while only 5 of 32 patients from the State hospital were discharged (Fisher's exact test, \( p = 0.05 \)). This difference cannot be explained by more MMHC patients receiving neuroleptics following the 6-month experimental period, since at 36 months 78 percent of the State hospital patients were receiving neuroleptics compared to only 68 percent of the MMHC patients.

In recent years a number of studies have demonstrated that a combined program of neuroleptic administration and stress-reducing psychotherapy decreases the incidence of relapse in patients with schizophrenia. Falloon (1989) demonstrated a decrease from an expected rate of schizophrenia of 7.4 cases per 35,000 to 1 case per 35,000 after introducing a screening program that examined patients for prodromal signs of schizophrenia. If prodromal signs were present, aggressive intervention was initiated with low-dose neuroleptics together with education for the patient and family about managing stress. The neuroleptics were continued until all symptoms were gone, while the stress management was continued until the stress was removed from the family, or the family was able to manage the stress proficiently.

The concept that initial psychosis and later relapses might have long-term effects on morbidity suggests that greater consideration should be given to the usual clinical practice of taking patients off neuroleptics after they have recovered from an acute psychosis and appear stable. Even patients who have been stable for some time may be at significant risk for further relapses when neuroleptics are discontinued. For example, Johnson (1979) concluded that patients whose psychosis had remitted for 3 years had no better chance of not relapsing than patients who had remitted for 5 years if neuroleptics were discontinued. A similar conclusion was reached by Cheung (1981), who followed a group of fully remitted schizophrenic patients maintained on neuroleptics for 3 to 5 years before discontinuing the neuroleptic. During the ensuing 1.5 years, 2 of 15 patients remaining on neuroleptics had relapses while 8 of 13 patients who were given benzodiazepines as a substitute had relapses (\( p = 0.01 \)). Nevertheless, since neuroleptics have numerous side effects, and one of the most serious (tardive dyskinesia) appears to be related to the length of time a patient is given neuroleptics, the effect of a relapse and the possible long-term morbidity associated with that relapse is only one of many factors that must be considered for a given patient.

The studies discussed here do not address why patients treated with neuroleptics and perhaps other somatic treatments have better long-term outcomes than patients who are allowed to remain psychotic. The steplike loss of function described by many authors (Bleuler 1972/1978; Shimazono 1973; Ciompi 1980; Watt et al. 1983) in patients with multiple psychotic exacerbations, as well as the lengthy periods of reintegration following psychosis described by Johnson et al. (1983) and Curson et al. (1985) are indications that something associated with being psychotic is responsible for the long-term morbidity.

Is there something about being psychotic that is toxic to the individual beyond the immediate psychotic episode? An example from another area of medicine might be instructive. In ischemic heart disease, a distinction can be made between the pain or arrhythmia associated with a specific ischemic episode and the cumulative effect of several ischemic attacks toward the development of chronic heart failure. Treatments that decrease the physical injury associated with ischemic attacks have a benefit beyond the time of their application and help prevent chronic heart failure. Decreasing the ischemia decreases the amount of scarring.

The thrust of this article is that some patients are left with a damaging residual if a psychosis is allowed to proceed unmitigated. While psychosis is undoubtedly demoralizing (Miller 1989) and stigmatizing, it may also be biologically toxic (Wyatt 1985, 1986; Wyatt et al. 1989). The latter appears to occur in manic depressive disorder in which episodes, when untreated, become worse over time, a phenomenon that has been attributed to kindling (Post et al. 1986).

While it is far from clear what kind of scar prolonged or repeated psychoses might leave (some possibilities include biochemical alterations, gross pathological or microscopic scars, and changes in neuronal connections), there is ample evidence that some patients have structural brain changes as seen on pneumoencephalograms, and computed tomographic and magnetic resonance imaging scans. While in some patients these brain alterations appear to precede evidence of psychosis (Weinberger et al. 1980), in others there may be progressive brain changes associated with the changes in symptoms (Woods and Wolf 1983). Furthermore, glial scarring, while not universally found in the brains of
schizophrenic patients, has been described on a number of occasions (Stevens 1982).

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World Health Organization. Schizophrenia: An International Followup


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