premorbid adjustment, paranoid status, and patterns of response to phenothiazine in acute schizophrenia*

Michael J. Goldstein

Schizophrenia research has long been plagued by a variety of methodological problems, including, for example, lack of clear diagnostic criteria, psychopathologic heterogeneity within any sample of patients labeled “psychotic,” and the effect of institutionalization on experimental results. With the introduction of the major tranquilizing agents in the early 1950’s, schizophrenia research was further complicated. While a boon to patients, these widely used drugs have proven a bane to many investigators, whose experimental results have often been confounded by drug effects. Drug withdrawal during the period of study would seem to be a logical solution to this problem, but unfortunately the phenothiazines are excreted in significant amounts for some time following withdrawal—especially if the patient had been receiving drugs over a prolonged period. Moreover, drug withdrawal may result in severely disruptive behavior, making the conduct of research even more difficult. In an effort to circumvent these problems, Dr. Goldstein chose to study “the behavioral actions of phenothiazines” on schizophrenics; i.e., what are schizophrenics on drugs like? and how do they differ from those on placebo? In the research reported below, he attempted to deal with the complicating factor of previous drug intake by separately analyzing data for patients whose urine showed low or high levels of phenothiazine at admission. In the personal essay on page 38, Dr. Ban discusses several methodological “double binds” he has encountered in clinical psychopharmacological research. Together, the two authors highlight a number of important problems in schizophrenia research.—The Editors.
Since its beginnings, experimental research on schizophrenia has been directed at understanding patterns of performance which might elucidate this complex disorder's underlying mechanisms. With the introduction of phenothiazines in the early 1950's, however, the schizophrenia researcher was confronted with the fact that these potent pharmacological agents significantly alter perception, attention, and thought—all central to any experimental program designed to understand deviations resulting from the psychotic state. Investigators were, therefore, faced with essentially two choices: to turn away from experimental studies of schizophrenics, or to attempt to understand the behavioral actions of phenothiazines. The latter course was followed in the study that will be reported here.

The need to account for the marked differences that have been noted clinically in the responses of schizophrenics to phenothiazines led to the choice of variables studied. In past experimental attempts to reduce the obvious heterogeneity in the schizophrenic group, two methods have proved useful in explaining the variations in schizophrenics' behavior and performance on experimental tasks, as well as in making prognostic judgments.

The first method divides schizophrenics according to quality of premorbid adjustment. Based largely on the work of Wittman and the Elgin group (13) and Phillips (10), some investigators have found a better prognosis for the patient whose premorbid history, particularly in his heterosexual relations, shows adequate adjustment. Another group, led by Rodnick and Garmezy (11), has found that differences in premorbid adequacy help to explain the variations in schizophrenics' behavior and performance on experimental tasks, as well as in making prognostic judgments.

The second method separates patients according to symptomatology. Numerous attempts to account for variations in schizophrenic behavior by using Kraepelinian diagnostic subtypes have produced at least one consistent finding: the value of dividing data for paranoid from that for nonparanoid schizophrenics (12). Some variations in response to drug or placebo status have been related to initial patterns of psychopathology (2, 7).

**Relationship Between Premorbid Adequacy and Paranoid Status**

It is interesting to note that research utilizing premorbid adjustment criteria has largely ignored diagnostic variation, while research utilizing the paranoid/nonparanoid dichotomy to reduce heterogeneity has generally ignored premorbid variation. In an attempt to understand whether these variables interact or correlate in any meaningful way, studies were carried out at Camarillo State Hospital by our research group; similar studies have also been carried out by Rue Cromwell and his group at Vanderbilt University (3). Our studies involved rating each new admission on the Phillips Scale of Premorbid Adjustment and comparing this rating to the patient's paranoid/nonparanoid status, based upon final hospital diagnosis. As table 1 shows, the relationship between good premorbid/poor premorbid and paranoid/nonparanoid status is a strange one: While patients with good premorbid histories are diagnosed paranoid or nonparanoid with comparable frequency, poor premorbid patients are almost exclusively diagnosed as nonparanoid. We will not speculate at this time on the basis for this relationship, but we do wish to indicate that it exists.

**Table 1. Paranoid/nonparanoid status of good and poor premorbid patients in 3 samples.**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Premorbid status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Good</td>
</tr>
<tr>
<td>Paranoid</td>
<td>22</td>
</tr>
<tr>
<td>Nonparanoid</td>
<td>28</td>
</tr>
</tbody>
</table>

**Premorbid Adequacy, Paranoid/Nonparanoid Status, and Drug Response**

Thus far, we have carried out two studies (the second of which will be reported here) which explored the value of premorbid adjustment and paranoid/nonparanoid status in understanding patterns of response to phenothiazines; both studies utilized similar patient selection proce-
dures, psychological test battery, and experimental design. In the first study (4), a significant interaction between premorbid and drug status was frequently found for measures of skin-resistance responsivity, word association, film comprehension, and perceptual defense. Typically, the pattern for the poor premorbid patient followed clinical expectation, while that for the good premorbid patient did not. For example, if we examine the poor premorbid patient’s skin-resistance responsivity to a tension-arousing film (see figure 1), we can see that phenothiazine administration was associated with reduction in autonomic responsiveness, while a placebo regimen was associated with increased responsiveness. If we assume that a reduction in responsivity is likely to be associated with less agitated and disturbed behavior, while the reverse is true for increased responsivity, then these data conform to expectations based upon phenothiazine’s clinical action. Following this line of reasoning, however, it is difficult to interpret the reverse trend illustrated in figure 1 for the good premorbid group. A number of possibilities suggest themselves: (1) that phenothiazines are not particularly effective agents for schizophrenics with good premorbid histories; (2) that they are effective but evoke different patterns of response in good and poor premorbid schizophrenics; or (3) that this particular phenothiazine (thioridazine) is not the “right” drug for good premorbid patients but is appropriate for poor premorbid patients.

In an effort to gain a clearer understanding of issues (1) and (2), a second study was carried out at Camarillo State Hospital. The research involved two levels of data: (1) results of experimental procedures designed to understand the behavioral mechanisms underlying drug response; (2) clinical ratings designed to index patterns of behavioral change in the psychotic patient. It was felt that comparisons between these two levels of concurrently gathered data could contribute to an understanding of how premorbid and paranoid status might relate to patterns of response to pharmacological treatment.

Methods

All newly admitted male patients who satisfied the NIMH collaborative study criteria (9) for schizophrenia were assigned to a special ward at Camarillo State Hospital and placed immediately on a placebo regimen. Each patient remained on placebo for 7–8 days for a modified “drying out” period. Half of the patients were then assigned to an active phenothiazine (thioridazine, 100 mg. Q.I.D.), and half remained on placebo for the succeeding 21 days. After a total of 28 days, the patient was released from the study and placed on medication or not as the physician desired. A total of 54 patients were seen throughout the period of study.

Psychological Measures

At the end of the 7-day drying out period and again at the 28-day point, each patient received the following battery of psychophysiological and behavioral measures:

Psychophysiological Measures

Basal skin resistance and reactions to a startle stimulus (phone bell), tension-arousing film, and standardized interview concerning the patient’s comprehension of the film were measured. This procedure has been described in detail elsewhere (4).

Figure 1. Means of 3 largest skin-resistance responses of schizophrenic patients to a tension-arousing film viewed 28 days after admission.

Film Comprehension

Following the film, the patient was interviewed by a research assistant concerning his reaction to the film and, based upon this interview, the

1Clinical ratings were not obtained in the first study.
patient’s comprehension was rated on a 5-point scale.

**Word Association**

A 50-item word association test was orally administered to the patient, whose responses were scored on a 7-point scale in which 1 represented statistically popular associations and 7 represented associations never given by a normal comparison group and which were difficult to relate to the stimulus word. (The association data served as the basis for selection of the stimulus words for the procedure described below.)

**Perceptual Defense**

The perceptual defense procedure provided a means of assessing the patient’s method of coping with threatening and neutral stimuli, presented tachistoscopically. Three anxiety-linked and three neutral words were selected for each patient, as determined by his reaction times for the word association test. The anxiety words were selected as having the longest reaction times and the neutral words, which had short reaction times, were prematched in length, starting letter, and frequency of usage.

**Clinical Measures**

**Behavior Ratings**

*Nurses Observation Scale for Inpatient Evaluation (NOSIE):* The NOSIE (5), a 30-item, 5-point scale designed to describe patient behavior on a ward, was administered at the end of the 7-day drying out period and again on the 28th day of the study. After the patient’s release from the study, nurses continued to collect NOSIE data throughout his stay in the hospital.

*Inpatient Multidimensional Psychiatric Scale (IMPS):* The IMPS (8) is a 75-item rating scale designed to be used by psychiatrists and psychologists to describe patient behavior in an interview situation. Quantified indices are provided of 10 symptom areas; e.g., excitement, hostility, and perceptual distortion. Interviews took place on the 7th and 28th days of the study.

**Ratings of Premorbid Adjustment and Paranoid/Nonparanoid Status**

*Premorbid adjustment:* After the second (28-day) experimental session was completed, each patient was interviewed using questions derived from the Phillips Scale of Premorbid Adjustment. For those patients too disturbed or hostile to be interviewed, ratings of premorbid adjustment were based on data available in the patient’s file. A patient was defined as “good premorbid” if his Phillips Scale score was 15 or below and “poor premorbid” if his score was 16 or above.

*Paranoid/nonparanoid status:* Using final hospital diagnosis, patients were divided into paranoid and nonparanoid groups. To qualify as paranoid, a patient must have received a diagnosis of schizophrenic reaction, paranoid type. Nonparanoids were distributed among all other diagnostic categories, but most received the “chronic undifferentiated” subdiagnosis.

The mean age, Phillips Scale scores, and number of prior admissions for good and poor premorbid patients subdivided into paranoid and nonparanoid groups are presented in table 2.

**Urine Tests**

During the patient’s first day on the experimental ward, a urine specimen was collected and read using the universal phenothiazine test (1). The common assumption that patients enter a State hospital with varying levels of medication was borne out in our sample; at admission, approximately half the patients gave no evidence of phenothiazine in their urine, and the other half showed high readings.

In order to determine whether these high and low urine groups differed on some index of psychopathology, word association data collected on day 7 were analyzed. The word association data were selected for analysis because they reflect one of the most significant signs of schizophrenia: remote and personalized associations. These responses were scored using a 7-point scoring system in which 1 represented statistically popular and 7 represented highly personalized and rare association. Analysis of variance of the average score on this system revealed an F of 11.60, p < .01, for initial urine level; a greater number of schizophrenic-type associations were shown by the group whose urine showed high levels of phenothiazine on admission (readings of 2 or greater) than the low urine group (0 or 1 readings). The means for each group are presented in figure 2 below; in each subgroup the
Figure 2. Schizophrenic-like word associations for high and low urine groups of good and poor premorbid patients. (All data obtained 7 days after admission.)

high urine patients revealed more remote associations, on the average, than the comparable low urine patients.

Because of these word association differences, it was questioned whether the placebo regimen was sufficient to equate for marked differences in level of medication on admission. For this reason and because high and low urine groups might represent extreme and moderate groups on a schizopathology continuum, data for these two groups were analyzed separately.

Results and Discussion

The analysis of our data concerning the effects of phenothiazines involved an initial comparison of good vs. poor premorbid groups, followed by a comparison of paranoid and nonparanoid subjects within the good premorbid group only. Since the majority of our findings revealed significant differences between the two premorbid groups, we will refer to the paranoid/nonparanoid comparisons only for those variables in which reliable differences were found. All subjects were divided into those whose urine showed high levels (the high urine group) and those whose urine showed low levels (the low urine group) of phenothiazine at admission. Because most significant findings occurred in the low urine group, the data reported below refer to subjects in the low urine group unless otherwise stated; findings for the high urine group will be briefly summarized.

Psychological Measures

Psychophysiological Data

Skin resistance and reactivity data were read and converted into log conductance units. In each data analysis, the 7-day measure on a subject was used as the covariate in an analysis of covariance of the 28-day data.

Basal skin resistance (in K ohms): As reported previously (4), the basal skin resistance for both drug groups was significantly higher than for the placebo groups (good drug = 372, good placebo = 132, poor drug = 309, poor placebo = 232, F for drug status, 6.00, 1/21 df, p < .05).

Startle bell reaction: Unlike previous data, there were no significant effects for drug, premorbid, or paranoid status.

Reactivity to tension-arousing film: Using the log conductance change from the beginning to

Table 2. Means and ranges for age and Phillips Scale scores, and mean number of prior admissions for patients in second study.

<table>
<thead>
<tr>
<th>Prior admissions</th>
<th>Age</th>
<th>Phillips score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>X</td>
<td>Range</td>
</tr>
<tr>
<td>Good premorbid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paranoid (n=11)</td>
<td>0.58</td>
<td>32.5, 21-45</td>
</tr>
<tr>
<td>Nonparanoid (n=18)</td>
<td>0.83</td>
<td>27.5, 21-44</td>
</tr>
<tr>
<td>Poor premorbid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paranoid (n=6)</td>
<td>0.56</td>
<td>27.3, 21-45</td>
</tr>
<tr>
<td>Nonparanoid (n=19)</td>
<td>1.13</td>
<td>24.2, 19-34</td>
</tr>
</tbody>
</table>
Figure 3. Highest-lowest skin conductance change of low urine patients during interview that followed viewing of a tension-arousing film.

Reactivity to film interview: Using either of two indices of response to the film interview (high-low point during interview and beginning-end of interview) significant interactions were found between premorbidity and drug status of the type previously reported by our group (3). The $F$ was 6.15 for the first index and 4.36 for the second, both significant beyond the .05 level.

As can be seen in figure 3, the pattern for the good premorbid group indicates enhanced skin-resistance responsivity on drug and reduced responsiveness on placebo. The data for the poor premorbid group are the inverse of this. Moreover, the separation between poor drug and poor placebo is greater than between the two good premorbid groups. This replicates our previous finding that responsivity increases markedly when the poor premorbid patient is placed upon a placebo regimen.

A marked correlation can be noted between the data for the first- and second-session film interview reactivity. However, no overall differences in basal skin resistance or initial reactivity were found between good and poor premorbid subjects as total groups—a finding that indicates that these results cannot be explained by initial differences in arousal level. The direction of change in skin-resistance responsivity suggests that both the good drug and poor placebo subjects show marked increases from initial levels, while the good placebo and, to a much larger extent, the poor drug subjects show decreases in responsivity to the film interview.

As found previously, there were no differences in responsivity when the good premorbid sample was subdivided into paranoid and nonparanoid groups.

Contrast with high urine group: The data for basal skin resistance, which were so clear in the low urine group, failed to reveal any differences as a function of drug status and premorbidity; nor were any significant differences in reactivity found among the groups for any of the three stimulus conditions.

Film Comprehension

Analysis of covariance of these data revealed a nearly significant interaction between premorbid and drug status.

Figure 4. Film comprehension ratings of low urine patients at 7 and 28 days following admission.
bidity and drug status ($F = 3.25, p < .10$), paralleling data from our first study. We can see in Figure 4 that the only significant difference was within the poor premorbid group, where drug and placebo groups differed at the .05 level. These data directly parallel our earlier results in which there were no differences between the good premorbid subjects but a significant decrease in comprehension in the poor placebo group.

Examination of the initial 7-day means in film comprehension suggests a difference between goods and poors, but this difference was not statistically significant ($F = 2.00, p < .20$). Previously, only ratings of comprehension were studied, but in the present study four other scales were added: interest, ability to communicate events in the film, involvement, and understanding of the film's logic. Only the last revealed a significant drug effect ($F = 4.53, p < .05$). The only significant difference, however, lay between the poor drug and poor placebo samples.

Contrast with high urine group: Once again, no significant trends were revealed when the high urine group was divided on the premorbidity variable. When the high urine group was further subdivided into good premorbid paranoids and nonparanoids, however, a significant effect was found for communication ($F = 4.76, p < .05$). Group means were as follows: paranoid drug = 3.94, paranoid placebo = 2.97, nonparanoid drug = 4.22, and nonparanoid placebo = 4.12. As these means indicate, paranoids were generally rated as communicating more poorly than nonparanoids, and a significant difference was found between paranoid drug and placebo groups. These differences for the paranoid variable were not found in the low urine subjects.

Word Association Data

No significant differences were found for premorbidity, drug status, or their interactions in either the low or high urine groups.

Perceptual Defense Data

These data represent the number of anxiety-linked words used by a subject over a series of 96 guessing trials. The data can be analyzed in terms of the subject's initial approach to the first block of 24 trials and the rate of change (slope) in usage over the remaining three blocks of 24 trials. There were no significant differences for the premorbid variable either in initial approach to the task (block 1) or over the remaining blocks of trials. There was, however, a nearly significant $F (3.98, p < .10)$ for the interaction of paranoid and drug status for block 1 and a statistically significant slope over the total block of trials ($F$, linear slope for paranoid status = 7.46, $p < .01$). In Figure 5, we see that paranoids on placebo showed a marked vigilance for threatening stimuli on block 1, while the other three groups showed no significant trends. Over the subsequent trial blocks, paranoids on placebo reduced their vigilance behavior, while the nonparanoid placebo group became vigilant on the final block; at this same point, nonparanoid drug subjects showed avoidance behavior.

Contrast with high urine group: This is one of the few measures in which consistent results were found for high and low urine groups. As was true for the low urine group, no differences were found for the premorbid variable, but significant results were found when the samples were divided into paranoid/nonparanoid groups. The $F$ for initial approach to the task was 4.19 ($p < .05$) for paranoid status and indicated trends identical to those seen in the low urine data. While marked vigilance for threat can be noted in the paranoid placebo group, the other three groups are not reliably different (see Figure 6). The slope measure reflecting behavior over trials revealed a significant interaction between paranoid and drug status ($p < .01$).

A comparison of data for low and high urine groups reveals both striking similarities and meaningful differences. Paranoid placebo patients in the high urine group remain vigilant for threat throughout the task, as do their low urine counterparts until the last trial when they show very slight avoidance behavior. Like their counterparts in the low urine group, the nonparanoid placebo subjects in the high urine group show an increase in vigilance on the later trials. Data for the high urine group show sharper and more consistent differences across trials than do those for the low urine group.

Clinical Behavior Ratings

The present study included clinical behavior
ratings (omitted from our previous study) in order to indicate how performance on experimental tasks correlates with psychiatric status. In the analysis of NOSIE and IMPS data 7-day ratings were used as covariate for 28-day ratings.

28-Day Behavior Ratings

NOSIE data: The NOSIE revealed significant differences among the premorbid groups at 28 days on three scales—social competence, neatness, and manifest psychosis. In each instance, the significant effect is carried by the poor placebo group, which shows the greatest amount of psychopathology at 28 days (see table 3). These data directly parallel the skin resistance and film comprehension data in which the poor placebo group showed the greatest responsivity and least adequate comprehension.

Although there is a general decrease in psychopathology from 7- to 28-day measures, the least decrease in psychopathology is found in the poor placebo group.
Table 3. Final (28-day) ratings of schizophrenic patients on significant NOSIE scales (compared to 7-day ratings).

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Social competence</th>
<th>Neatness</th>
<th>Manifest psychosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>28-day</td>
<td>7-day</td>
<td>28-day</td>
</tr>
<tr>
<td>Good premorbid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On drug</td>
<td>8</td>
<td>3.66</td>
<td>2.80</td>
</tr>
<tr>
<td>On placebo</td>
<td>7</td>
<td>3.71</td>
<td>3.17</td>
</tr>
<tr>
<td>Poor premorbid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On drug</td>
<td>5</td>
<td>3.55</td>
<td>3.27</td>
</tr>
<tr>
<td>On placebo</td>
<td>6</td>
<td>3.27</td>
<td>3.17</td>
</tr>
</tbody>
</table>

IMPS data: Five of the 10 primary factors on the IMPS—excitement, hostility, perceptual distortion, motor agitation, and conceptual distortion—revealed significant differences between the groups. Means for each are presented in Table 4.

The data for the excitement variable indicate a clear-cut drug effect. Although both poor and good premorbid drug groups have lower ratings in excitement than their paired placebo groups, the greatest contrast can be noted—as in all of our data—within the poor premorbid sample, where the poor placebo patients show the extreme trend of clinical regression from their initial 7-day behavior ratings.

The data for hostility and perceptual distortion indicate trends which parallel the skin-resistance patterns noted earlier. Within the good premorbid group, ratings on these variables are slightly higher among subjects who received drugs. Once again, however, marked drug effects in the opposite direction are found in the poor premorbid group. For each of the IMPS variables, marked drug response can be noted in the poor premorbid group: The drug group shows a marked reduction of behavior pathology and the placebo group shows marked regression. Over

Table 4. Final (28-day) scores of schizophrenic patients on significant IMPS scales (compared to 7-day scores).

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Excitability</th>
<th>Hostility</th>
<th>Perceptual distortion</th>
<th>Motor agitation</th>
<th>Conceptual distortion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>28-day</td>
<td>7-day</td>
<td>28-day</td>
<td>7-day</td>
<td>28-day</td>
</tr>
<tr>
<td>Good premorbid</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On drug</td>
<td>8</td>
<td>1.18</td>
<td>3.67</td>
<td>1.13</td>
<td>0.57</td>
</tr>
<tr>
<td>On placebo</td>
<td>7</td>
<td>1.78</td>
<td>1.70</td>
<td>1.00</td>
<td>1.60</td>
</tr>
<tr>
<td>Poor premorbid</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On drug</td>
<td>5</td>
<td>1.21</td>
<td>1.43</td>
<td>.32</td>
<td>1.04</td>
</tr>
<tr>
<td>On placebo</td>
<td>6</td>
<td>3.75</td>
<td>2.62</td>
<td>1.67</td>
<td>1.60</td>
</tr>
</tbody>
</table>

1F, drug = 13.37, p < .01.
2F, premorbid x drug = 8.18, p < .01.
3F, drug = 2.71, p < .10.
4F, premorbid = 5.12, p < .05; F, drug = 5.68, p < .05.
5F, drug = 4.58, p < .05; F, premorbid x drug = 2.84, p < .10.
the 28-day period, the good premorbid groups show little drug response or placebo regression except on the *excitement* variable.

**Contrast with high urine group:** The 28-day behavior rating data for patients in the high urine group do not show a single significant effect.

### 7-Day Behavior Rating Data

The marked contrast in the results for the high and low urine samples can be explained as the result of two separate drug studies having been imposed upon each other. The low urine group represents an off-on (placebo-drug) design, while the high urine group could reflect an on-off-on (drug-placebo-drug) design in which subtle carryover effects obscured significant drug effects on behavior. If we view the high urine group as one that has been medicated prior to admission, then the best estimate of drug action would be contained in measures obtained on the day of admission; unfortunately, we had not anticipated the need for data of this type. We did, however, analyze the data closest to admission—the behavior ratings carried out after 7 days on the placebo regimen.

Data for the IMPS and NOSIE scales are presented in figures 7 and 8, respectively.

Despite the fact that each patient was tested 7 days after an active medication had last been received, marked differences can be noted between high and low urine groups. On the *excitement* variable, the good premorbiids show a pattern similar to the 28-day data: The high urine (medicated) group received lower excitement ratings than the low urine (no medication) group. On all other IMPS and NOSIE variables, we note sharp differences primarily within the poor premorbid group; here, the previously medicated

![Graph showing comparison of high and low urine groups on significant IMPS scales rated 7 days after admission.](https://academic.oup.com/schizophreniabulletin/article-abstract/1/3/24/1942155)
Figure 8. Comparison of high and low urine groups on significant NOSIE scales rated 7 days after admission.

(high urine) group shows significantly lower ratings of behavior pathology than the previously unmedicated (low urine) group.

Except on the excitement variable, it is evident that two different ways of estimating drug effects—the pre-post data for the low urine groups and pre-only (7-day data) analysis of the high urine groups—support the idea that patients with poor premorbid histories are very dramatic drug responders. They respond equally dramatically to drug withdrawal, displaying marked signs of behavioral disorganization. Although good premorbid patients show marked reduction in excitement when given an active phenothiazine, they show little or no improvement on other variables. In fact, on some variables (e.g., hostility) they show slightly greater disturbance when on drug than on placebo. Also, when on placebo, they clearly do not show signs of marked behavioral regression comparable to those shown by the poor premorbid patients.

It is also interesting to note the marked contrast between the 7-day word association data and the behavior rating data for the two urine groups. The word association data indicate that patients in the high urine group show more evidence of pathological, remote associations than the low urine group. On the basis of these data one could say that the high urine group is “sicker” or more flamboyantly schizophrenic than the low urine group. Yet, the behavior rating data suggest the opposite conclusion in that the high urine group shows less overtly schizophrenic behavior than the low urine group.

Two conclusions are suggested by their inverse relationship. First, that phenothiazines effect a reduction in schizophrenic behavior which is not paralleled by significant alterations in certain primary components of the schizophrenic process, particularly idiosyncratic association—a tendency which is still present when a marked reduction in schizophrenic behavior can be noted. In colloquial terms, it appears that phenothiazines reduce but do not alter the underlying schizophrenic process. What is particularly ironic is that the most dramatic drug responders, the poor premorbid patients, are least likely to effect a satisfactory posthospital adjustment. This implies that behavioral improvement ratings have to be combined with other measures in order to estimate any schizophrenic patient's potential for posthospital adjustment.

Secondly, it appears that patients who arrive at a State hospital in a medicated state are not a random sample of patients who just happen to get “caught” in one of the community's treatment networks. They are the patients with severe thought disturbances who are more likely to be judged as so disturbed or disruptive that they require some treatment before assignment to a State hospital. After a proper period of drug withdrawal, these patients may look very similar behaviorally to other groups who do not appear to require medication, and the investigator may be inclined to combine them within a single schizophrenic sample. If he does so, he will be losing sight of meaningful individual differences in the potential for schizopathology which will ultimately cloud and confuse his experimental or clinical findings. The solution to this problem is obviously to carry out research in a primary treatment center, if such exists, in which patients arrive essentially untreated by phenothiazines.
this is not possible, then the investigator should be aware of the methodological issues raised by the inverse relationship between association deviance and behavioral ratings of pathology.

Course in the Hospital

Most of the previous findings are based upon a discrete period in the patient's hospitalization. Many patients remained in the hospital after completion of this 28-day period and were then assigned to active medication. Upon each patient's discharge, analyses were carried out on (1) number of days the patient stayed in the hospital and (2) recommendations for posthospital treatment made by physician and social worker. The data on number of days spent in the hospital related significantly to the patient's premorbid adjustment ($F = 5.45, p < .05$). The goods stayed in the hospital an average of 63 days while the poors averaged 100 days. There were no significant effects for the patient's drug status during the 28-day period.

These data were further subdivided according to the patient's initial urine level (see table 5 below). In the low urine sample, both groups of good premorbid subjects had shorter hospital stays than both poor premorbid groups. Within the low urine, good premorbid group, the placebo patients had a shorter hospital stay than the drug patients. The interaction for premorbidity and drug status in the low urine sample is only of borderline significance, however ($F = 2.94, p < .10$). In the good premorbid group, the expected difference between drug and placebo groups is seen only in the high urine patients.

<table>
<thead>
<tr>
<th>Admission urine reading</th>
<th>Good premorbid on drug</th>
<th>Good premorbid on placebo</th>
<th>Poor premorbid on drug</th>
<th>Poor premorbid on placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>73 (n=8)</td>
<td>41 (n=7)</td>
<td>83 (n=5)</td>
<td>88 (n=6)</td>
</tr>
<tr>
<td>High</td>
<td>58 (n=6)</td>
<td>81 (n=7)</td>
<td>110 (n=6)</td>
<td>119 (n=6)</td>
</tr>
</tbody>
</table>

Table 5. Length of hospital stay (in days) of schizophrenic patients with low and high levels of phenothiazine in urine on admission.

Within the poor premorbid group, both groups of low urine samples (drug or placebo) stay in the hospital for a shorter period than their comparable high urine group. This finding, which is true for three of the four low vs. high urine contrasts, supports our earlier hypothesis that the high urine group, despite its initially superior behavior ratings, is in some way a "sicker" group of patients.

The second analysis involved discharge-planning data available in the patient's file. These plans were formulated without any explicit knowledge of the patient's premorbid status. Most interesting to us was a formal recommendation concerning the advisability of keeping the patient on active medication following his discharge. These recommendations were analyzed with a dichotomy of yes vs. no. Their frequencies are presented above in table 6. We can see that these recommendations relate significantly to the patient's premorbid status. Good premorbid patients are rarely seen in need of further medication while poors almost always are. It should be noted that the recommendations do not refer to initial urine level, which we know relates to length of hospital stay, but to premorbidity exclusively.

<table>
<thead>
<tr>
<th>Premorbid status</th>
<th>Medication prescribed</th>
<th>Medication not prescribed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td>Poor</td>
<td>14</td>
<td>2</td>
</tr>
</tbody>
</table>

$X^2 = 13.91, df = 1, p < .001$

Table 6. Posthospital medications recommended by hospital staff for good and poor premorbid schizophrenics. Data coded only on those cases in which clear-cut treatment planning information was available in patient's folder.

Analysis of NOSIE Data at Time of Discharge

In an effort to understand the basis for these differential decisions related to premorbid status, the NOSIE ratings at 7 days and on the day of discharge were compared. Only one scale, social competence, related to the premorbid variable. No differences between goods and poors were
found for the 7-day data, but on the day of discharge goods were rated as significantly higher in social competence than the poors ($F = 4.45, p < .05$). Thus, the differences in medication recommended relate to the rated social competence of the schizophrenic patient which, in turn, relates to his preillness psychosocial adequacy. Whatever phenothiazines do for schizophrenic patients, they cannot make up for preillness deficits in social competence and adequacy.

**Conclusions**

These data suggest that reactions to phenothiazines relate consistently to premorbid adjustment and, to a lesser extent, to paranoid status. In our data and that of others, these subgroups, if unseparated, yield data which cancel each other out, leaving the investigator with "noise." It seems more profitable to investigate reactions to phenothiazines in the context of the patient’s life history of social adaptation.

The high responsivity of minimally coping (poor premorbid) patients to phenothiazines may reflect a preference for physical treatment, a special passivity, or even critical biochemical or physiological variations. Likelihood of clinical deterioration was well documented in the pre-drug era and can be seen very clearly in the present poor premorbid placebo groups. Phenothiazines appear to forestall the poor premorbid patient’s behavioral disorganization, but the discharge-planning and final NOSIE data indicate that they fail to leave him in a highly competent state at the time of discharge.

In the group with some evidence of psychosocial adequacy (the good premorbid group), very small drug effects can be noted. Phenothiazines appear to reduce excitement, but on other variables, less psychopathology is evident in the placebo than the drug group. The positive behavioral changes in this group appear to result from the effects of the general hospital milieu. In one group, the low urine good premorbid, a shorter hospital stay was found for placebo than for drug groups.

The breakdown of the good premorbid into paranoid and nonparanoid subsamples indicates marked effects of phenothiazine medication on cognitive (film comprehension) and perceptual (perceptual defense) processes. In the paranoid group, less adequate cognitive functioning and greater perception of threat in the environment were noted in the placebo groups. This would suggest recrudescence of basic features of the paranoid mechanisms when active phenothiazine medication is either withdrawn or not initially administered. These findings, while they have not been paralleled by clinical behavior ratings, suggest that it is the nonparanoid patient with a good premorbid history who is least likely to respond dramatically to phenothiazines. In fact, our data indicate these patients may do better without medication.

However, one important caveat is in order. All of our data have involved a single phenothiazine, thioridazine. The findings for the other phenothiazines may not support these trends; clearly, these drugs warrant closer investigation.

In summary, it appears that the impact of a particular phenothiazine interacts with a schizophrenic patient’s lifelong pattern of stress and his effectiveness in coping with it. On the basis of the present data we cannot agree too strongly with a point previously emphasized by Donald Klein:

> ...[T]he end point the patient will reach after treatment cannot be predicted simply from initial clinical status, but requires knowledge of his entire development. During the psychotic exacerbation excited patients with lifelong histories of social withdrawal, eccentricity, ineptness and fearful adaptive responses, such as the "process" schizophrenics, may be cross-sectionally similar to schizoaffective patients with good developmental histories. However, following remission these patients will end at quite different positions on behavioral scales. ... Attempts to predict drug effect might well be improved by incorporating developmental history into the predictions (6).

**Summary**

The present paper relates premorbid adjustment and paranoid/nonparanoid status to response to a single fixed dosage (100 mg. Q.I.D.) of thioridazine or placebo over a 21-day period in a sample of 54 newly admitted male schizophrenic patients. The following results are reported:

1. Premorbid adjustment and paranoid/nonparanoid status are not independent dimensions.
Patients with good premorbid histories are equally often paranoid or nonparanoid, but poor premorbid schizophrenics are typically diagnosed nonparanoid.

2. When behavioral and psychophysiological measures are used, good and poor premorbid schizophrenics vary in their response to 21-day drug or placebo regimens. Poor premorbid patients respond to drug or placebo treatment according to clinical expectation, but good premorbid patients show a reverse pattern of response.

3. When the good premorbid patients are divided into paranoid and nonparanoid subsamples, only measures of cognitive processes and perceptual vigilance for threat differentiate them. Paranoids on placebo show decreased cognitive adequacy and greater vigilance for threat in the environment (behavior which is far less apparent in paranoids on active medication). Good premorbid / nonparanoid schizophrenics show no deterioration on placebo and little positive drug response, suggesting that this group may actually be adversely affected by phenothiazine treatment.

4. Readings of phenothiazine presence in urine samples taken at hospital admission reveal significant differences among newly admitted patients. Division of the sample into high and low urine groups was necessary to see many of the findings summarized above. Also, there are indications that these two groups vary on the "schizophrenopathology" continuum.

5. These findings suggest that the impact of a particular phenothiazine interacts with a schizophrenic patient's lifelong pattern of, and effectiveness in, coping with stress.

References


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