

COMPARATIVE STUDY OF CHLORPROMAZINE AND INSULIN COMA IN THERAPY OF PSYCHOSIS

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With the advent of "newer" drugs for the treatment of psychiatric illnesses and the concomitant awareness that the effectiveness of insulin coma therapy was limited, a control drug therapy-insulin coma study was undertaken. Preliminary trials with various medicaments available in 1954 demonstrated chlorpromazine to be potent and relatively safe. Concurrent reports had noted its value in schizophrenic illnesses, and it was therefore selected as the experimental agent.

The study was designed to assess the therapeutic efficacy and indications for intensive chlorpromazine therapy, compared to classic insulin coma therapy, in an open-ward, voluntarily hospitalized psychiatric population.

Subjects and Method

All patients referred for insulin coma therapy during the period Sept. 1, 1955, to Dec. 31, 1956, were observed. Supervising psychiatrists made the recommendation for insulin coma therapy independent of the research group. Their criteria for referral were those implicitly held by the hospital administration and were not altered for this study. Randomly selected patients were placed on chlorpromazine therapy instead of insulin coma therapy. This selection was made by the psychiatrist in charge of the insulin therapy unit without prior notice of the referring therapist or the supervising psychiatrist. Sixty patients were referred for insulin coma therapy during the study period, and half of these received chlorpromazine.

Insulin Coma.—The standard technique of Sakel for insulin coma was used. All patients received 50 comas, each of a duration of at least one hour, at the physiological level of Babinski reflex, absent lid reflex, or deeper. Recovery was induced by gavage and occasionally by intravenous administration of glucose. Treatments were given five times weekly for a period of three to four months.

Chlorpromazine.—To establish an equivalent group, chlorpromazine was given for at least three months. Dosages were determined by the research team and were rapidly increased until well-defined physiological effects were observed. These included rigidity, drooling and fixed facies, seizures, or severe dermatitis. In most instances this was achieved below 1,400 mg. daily, although dosages were increased to 3,600 mg. in one patient. In each instance, the drug dosage was slowly reduced until

The effectiveness of chlorpromazine was compared with that of insulin coma in 60 patients referred for insulin coma therapy. One-half the group, selected on a random basis, received chlorpromazine by mouth for at least three months in doses adjusted so as to fall just short of toxicity in the individual patient; this dosage varied from 300 mg. to 2,000 mg. daily, with a median of 800 mg. The insulin coma was induced by a standard technique 50 times in each patient. Although many minor differences were noted in comparing the effects of these two methods of treatment, the ultimate results at the time of discharge were essentially the same for the two groups of patients. Neither treatment affected the basic schizophrenic process, but chlorpromazine had the advantage of being safer, easier to administer, and better suited to long-term management.

a maintenance dose, just under that producing toxicity, was obtained. This varied from 300 mg. to 2,000 mg. daily with a median of 800 mg.

To determine the comparability of the subjects in the random sampling procedures used in this study, the groups were compared as to their psychiatric diagnoses and ages. Table 1 shows a comparison of the groups as to diagnoses and demonstrates an equal distribution of subjects in each category. In the analysis of the age distribution, the median age for patients subjected to insulin coma was 24 years, with a range of 17 to 38; the median age for patients receiving chlorpromazine was 28, with a range of 19 to 42. Here, too, the distribution shows no significant difference.

For both treatment groups, behavioral observations were made by the research staff at weekly intervals. After completion of the treatment period, reports of the patients' behavior were obtained from the therapist and supervising psychiatrist. The "improvement" rating was determined by the medical director at the patient's discharge conference and was based on the fourfold scale of recovered, much improved, improved, and unimproved. Neither the authors nor the supervisor of the insulin therapy unit participated in these evaluations.

Observations

Clinical Observations.—The following clinical effects were noted in patients who received chlorpromazine and in those subjected to insulin coma therapy.

Chlorpromazine: Chlorpromazine induced motor retardation in all subjects. Overactive, destructive behavior rapidly disappeared, and patients became more tractable, less negativistic, and less violent. The nurses' and therapists' records noted patients as "less easily excited and frightened," "cooperating

TABLE 1.—*Psychiatric Diagnoses*

	Insulin Coma	Chlorpromazine
Psychoneurosis	1	2
Schizophrenia, paranoid	10	10
Schizophrenia, catatonic	7	7
Schizophrenia, mixed	8	6
Schizophrenia, hebephrenic	3	2
Manic-depressive psychosis	1	3

better in ward activities," and "less restless and less panic-ridden." One-third of the patients were more sociable and less seclusive and were noted to care for themselves in a more presentable fashion. In instances where severe motor symptoms supervened, however, the patients were less able to care for themselves; they became sloppy and failed to dress themselves. Such periods were usually short and could be significantly modified either by a reduction in drug dosage or by anti-Parkinsonism drugs.

Affective changes during chlorpromazine treatment were varied. Four patients became increasingly agitated, tense, and tremulous and either refused to continue on the drug regimen or were induced to do so only with difficulty. Such an affective "storm" appeared early in the treatment and persisted. In four other patients, depressive symptoms were relieved with an increase in affective lability and responsivity. Depressive ideation increased, associated with complaints of insomnia and anorexia in two patients. The medication was continued, however, with an eventual alleviation. In most patients, mood changes were small.

Ideation was dramatically altered during the period of chlorpromazine therapy in 12 patients. Eight had a loss or a significant diminution of their psychotic ideation. In five, hallucinatory and referential experiences were no longer reported even on inquiry, and, in three others, delusional ideas were less prominent. In one patient, phobias were relieved and the patient could once again participate in ward activities. In another, hypochondriasis was sufficiently modified to permit a more meaningful relationship between therapist and patient. In one patient, paranoid ideation became more prominent. This was associated with increasing anxiety and panic during drug administration and resulted in discontinuation of the drug regimen.

Insulin Coma: The clinical observations in this group were similar to those reported by others.¹ Alteration in behavior was prominent in all patients once repeated comas were induced. Overactive, hostile behavior rapidly diminished and was replaced by alternating periods of somnolence, irritability, and withdrawal. In most patients, nausea, abdominal distress, belching, sweating, and lassitude were common sequelae each afternoon and assumed prominence in the recorded reports. These symptoms often interfered with the patients' ability to care for themselves, and they became unkempt in their dress.

Changes in ideation appeared slowly during the course of therapy. In eight patients, paranoid and delusional thoughts became less prominent, disappearing in these on direct inquiry. Suicidal and outwardly directed destructive thoughts were modified in three patients, only to recur in each at the end of the treatment period.

Mood changes were small. Increasing agitation, tension, and panic were reported in three patients, leading in two to a refusal of further therapy. In one depressed patient, relief of depressive symptoms was noted early in the treatment and was sustained.

In the usual practice of the treatment unit, concurrent electroconvulsive therapy was instituted when behavioral control by insulin coma alone was limited. In six patients, such combined treatment was instituted primarily because of a continuation of overactive or delusional ideation. There was, in four instances, a well defined alteration in behavior, but this was unsustainable. None of these patients was rated as improved on discharge.

Discharge Evaluation.—All patients were discharged from the hospital within four months of the end of treatment. Table 2 lists the hospital discharge evaluations for patients treated with chlorpromazine and insulin coma.

TABLE 2.—*Discharge Ratings in Patients Treated with Chlorpromazine and Insulin Coma*

	Treatment	
	Chlorpromazine	Insulin Coma
Recovered, no.	2	0
Much improved, no.	4	5
Improved, no.	17	15
Unimproved, no.	7	10

Included in the group of patients treated with chlorpromazine who were rated as unimproved were four who received inadequate course of therapy (less than one month) because of complications of the therapy. Of the 10 patients treated with insulin coma who were rated as unimproved, four had inadequate courses of therapy, two because of complications (seizures and prolonged coma), one because she became more disturbed, and one because of administrative transfer to another facility.

It is apparent that there is no difference in the clinical evaluation at the time of discharge between the group receiving insulin coma and that receiving chlorpromazine. To determine whether this sample was biased because of its small number, we compared these discharge ratings with a similar group treated in this hospital in 1950 and previously reported.² In table 3, the discharge ratings for both

TABLE 3.—Discharge Ratings Compared for 1950 and 1956

	Present Group (30 Subjects)	1950 Group (48 Subjects)
Recovered, %	0	14
Much improved, %	17	19
Improved, %	50	42
Unimproved, %	33	25

years are compared. The percentage improvement rates for each category are not significantly different.

Toxicity and Complications.—Patients receiving chlorpromazine and those subjected to insulin coma therapy were compared as to toxic reactions and complications, with the following effects noted.

Chlorpromazine: Inherent in the design of this study were high doses of chlorpromazine, pushed to a level producing symptoms of toxicity. In this context, all patients developed significant drug effects. Rigidity of extremities, accompanied by a decrease in facial expression, drooling, and festination, was frequently observed. In three instances, rigidity appeared as drug dosage was reduced. Most patients became drowsy, retarded, and less active in ward activities. In four patients increased tension, agitation, restlessness, and excitement supervened, leading to a discontinuation of the drug regimen in two.

Seizures occurred spontaneously in three patients. Pretreatment electroencephalograms had manifested no dysrhythmia, and no history of seizures had been elicited. In each, the drug medication was reduced, and seizures did not develop at the lower dosages.

Dermatitis was a frequent complication. All patients developed a transient erythema to mild solar radiation. Severe intractable skin reactions occurred in three patients, with resultant discontinuation of drug therapy in two. In the third, promazine hydrochloride therapy was substituted for chlorpromazine, with a relief of the dermatitis. The behavioral effect of the promazine was indistinguishable in this patient from that noted in patients receiving chlorpromazine.

In this group, no patient developed clinical jaundice. This complication has been variously reported as occurring in less than 0.5% of subjects treated. In the preliminary studies at Hillside Hospital, 3 patients of a group of 20 developed transient clinical jaundice.

Electroencephalograms were obtained in 20 of the patients who received chlorpromazine. With increasing doses, the modulation of the record became more irregular in each. A moderate amount of low-voltage 4-7 cps delta and theta activity was induced, and this activity was exaggerated by hyperventilation. There was a suggestive relationship between the degree of the induced slow-wave activity and the drug dosage.

Insulin Coma: The complications of insulin coma therapy in this series were not unusual. Insulin resistance was noted only once and was eventually overcome by the method of alternating dosages. Prolonged reactions occurred in three patients. In each, neurological examination and electroencephalography demonstrated signs of persistent central nervous system dysfunction for at least 10 days. Aphasia, hemiparesis, and paresthesias were frequent in five patients and transient in eight others. Seizures occurred in five patients and were recurrent in three. Frequent secondary reactions, nausea, vomiting, abdominal distress, sweating, pallor, lassitude, and generalized weakness occurred in all patients with varying frequencies.

The complications of both forms of treatment are listed in table 4. Certain effects, such as dermatitis and hypotension, secondary reactions, and prolonged coma are individual for each therapy, and seizures, agitation, and refusal of therapy were noted with both regimens. The frequencies of these are not significantly different.

Effects on Psychotherapeutic Relationship.—Patients were referred for insulin coma therapy after a period of verbal relationship therapy. Such referral implies a failure of interpersonal communication.

TABLE 4.—Complications of Treatment with Chlorpromazine and Insulin Coma

	Treatment	
	Chlorpromazine	Insulin Coma
Agitation and panic	4	3
Dermatitis, severe	3	...
Seizures	3	5
Refusal of further therapy	2	2
Hypotension	2	...
Secondary reaction, frequent	5
Prolonged coma (>6 hr.)	3
Insulin resistance	1

Chlorpromazine: During the period of effective drug action, 15 of the patients treated with chlorpromazine were described by the therapist in response to an inquiry as "more accessible," "speaking more freely," and "more amenable to psychotherapy." The behavioral changes could be classified in two groups: subjects in whom tension and preoccupation with somatic symptoms became much less, and those in whom hallucinatory or delusional preoccupations ended. Such changes in

relationship were frequently described as an increase in "contact." In 13 subjects, psychotherapy either was still "not feasible" or had become less feasible because of increasing uncontrolled tension, anxiety, or preoccupation with the side-effects of the drug regimen.

Insulin Coma: Similar observations were made in the patients treated with insulin. Of the 30 patients, 7 were noted to be less tense and less anxious during therapeutic sessions. The therapists noted that the patient "verbalized more freely" and "was more aware of his environment." Four patients were specifically treated with a "modified anaclitic" approach. In each instance, this relationship was unsustained during treatment and the therapists resorted to more conventional tactics. In the remaining patients (19), while supportive, educational, and environmental manipulating techniques were applied, the therapists were no more successful than prior to insulin therapy. In 11 patients, the physiological effects of the treatments (secondary reactions, sweating, nausea, vomiting, and weight gain) were reported as interfering with psychotherapeutic attempts.

Comment

Clinical Considerations.—In these patients, neither chlorpromazine in high therapeutic doses nor insulin coma specifically modified the psychotic process. Since 88% of these patients had a diagnosis of schizophrenic illnesses, we concluded that neither treatment has a specificity in altering the schizophrenic process. When given in adequate dosage, however, both treatments are potent methods for the alteration of behavior. In the discharge evaluations, the treatments are similar. In only 20% of the patients were induced behavioral patterns persistent, with the rating "much improved" or "recovered." For the others, the induced behavioral changes were transient or minimal.

Since these therapies fail to induce a recovery from the psychotic process, consideration should be given to their ameliorative, palliative, and supportive aspects. Symptomatic relief was frequent but generally limited to the treatment period. Patients were made uncomfortable by both therapies, however, and the complications and toxic effects have already been noted.

In assessing the role of concomitant psychotherapy, there is little advantage in either therapy. Both methods were said to enhance relationship therapy, although the therapists' evaluations favored chlorpromazine therapy. Excluding those who developed increased agitation, patients were more comfortable, more alert, and physically better able to discuss their feelings and experiences while on chlorpromazine treatment. It is clear that "interpretive" psychotherapy is not enhanced; rather,

supportive, educative, reorienting, and directive types of therapy are. When there is a modification of agitated, hallucinatory, depressed, manic, or aggressive behavior, both the therapist and the patient are more comfortable and better able to discuss the reality aspects of the life situation.

Therefore, in this context, the ease of administration and the possibility of continued maintenance of chlorpromazine in an outpatient setting assume decisive significance. To maintain such therapy after discharge and continue thereby the relationship established in the hospital setting may be an important element in sustaining the behavioral changes induced by hospitalization.

Other Studies.—While many reports of the treatment of psychosis by chlorpromazine have appeared, we are aware of only one similar comparative study. Boardman, Lomas, and Markowe,³ after a review of the problem, reported a study of 100 patients randomly divided into two groups of 50 and treated with either insulin coma or chlorpromazine. The chlorpromazine dosage was lower than that used in the present series (average 300 mg.), but the drug period (three months) was the same. Their observations are directly comparable to this study. They reported no difference either in discharge evaluations or in symptom assessments for either treatment group.

The patients treated with chlorpromazine, however, remained in the hospital an average of 6.2 weeks less than the subjects treated with insulin. This was a significant difference between the groups. They concluded, "There is inconclusive evidence that chlorpromazine has advantages over insulin in the treatment of schizophrenia [but] insulin has disadvantages in the form of greater danger and more unpleasantness for the patients and greater strain on the nurses. Chlorpromazine is the first treatment of choice in schizophrenia, but this conclusion is based on the immediate results of treatment and has not yet been confirmed by an adequate follow-up study."

Boardman and his co-workers emphasize the problem of evaluating the therapeutic efficacy of insulin coma. They note a number of reports that raise doubts as to the efficacy of insulin coma therapy in schizophrenia. Bourne,⁴ in an extensive review of the merits of insulin therapy in schizophrenia, concluded, "There is no proof of any specific therapeutic effect, and the long term prognosis is in no way influenced."

The recent observations of insulin treatment of schizophrenia by Ackner, Harris, and Oldham⁵ are relevant. In a carefully controlled study, young schizophrenic patients were randomly treated either by insulin or by barbiturate coma in the same ward and under similar conditions. Evaluations of results were made by psychiatrists without knowl-

edge of which treatment the patients received. The authors noted a similar outcome, whether the loss of consciousness was induced by a barbiturate or by insulin, and concluded that insulin was not a specific therapeutic agent in the outcome.

In the follow-up studies done in this hospital,² the therapeutic results of insulin coma therapy were disappointing. Patients referred for insulin coma had the longest period of hospitalization (6.5 months, as against 6.04 with psychotherapy and 4.95 with electroshock), the poorest discharge rating (33% recovered and much improved as against 63% with psychotherapy and 67% with electroshock), and, within four years, a 50% rehospitalization rate (compared to 33% with psychotherapy and 29% with electroshock). While these observations reflect the idea that the more severely ill patients are referred for insulin coma, they also support the belief that insulin coma is not a specific treatment for the patients referred.

From these reports we would conclude that, despite considerable study and the passage of many years, insulin coma therapy has not been shown to induce persistent behavioral changes more frequently than other nonspecific, less dangerous, and less expensive therapies. To the list of alternate therapies of limited value in the management of psychosis we may now add chlorpromazine, noting, however, its advantage of lesser risk and ease of administration.

Dosage of Chlorpromazine.—For the purpose of assuring an adequate level of chlorpromazine dosage for evaluation, the amount of medicament given was increased in all subjects to toxic levels. This level was too high for its behavioral effects, as evidenced by the reduction in all responsive cases to maintenance levels of 300 to 2,000 mg.

It is our impression that chlorpromazine affects the function of the central nervous system (as evidenced by changes in modulation and per cent time delta in the electroencephalogram and the systemic phenomena of rigidity and lassitude) and results in a nonspecific alteration in behavior.^{6A} Such behavioral change is varied and is dependent on a variety of factors, of which the personality organization and the expectancy of the milieu are significant. In this context, the induction of a state of altered cerebral function is a necessary prerequisite to behavioral change. The only assurance of achieving a therapeutic level, therefore, is the appearance of toxicity and a lowering of dosage from that level to a maintenance dose. The effects of rigidity, drowsiness, and lassitude, therefore, are necessary concomitants of the therapy and should be induced in all patients in whom a therapeutic effect is desired. In instances where an affective "storm" supervenes, continuation of therapy at

higher levels, with concomitant administration of trihexyphenidyl hydrochloride (Artane) and bethtropine (Cogentin) methanesulfonate should be considered. Such an attitude in therapy is comparable to the application of digitalis in cardiology and to the present concept of the mode of action of electroshock therapy.⁶

Summary

In a study of patients referred for insulin coma therapy in an open-ward, voluntary psychiatric hospital, patients received randomly either insulin coma therapy or intensive chlorpromazine therapy. Chlorpromazine was found to be as effective in modifying psychotic behavior as insulin coma therapy. There was no difference in the improvement rating on discharge, incidence of complications, or effects on the psychotherapeutic relationship for either therapy.

In comparison to insulin coma, chlorpromazine is safer, easier to administer, and lends itself to long-term management. Patients receiving chlorpromazine therapy are more comfortable than those receiving insulin coma. No evidence has been educed that either therapy has altered the basic schizophrenic process, nor is there any evidence that there is greater specificity of either form of therapy for schizophrenic illnesses.

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The chlorpromazine used in this study was supplied as Thorazine by Smith, Kline & French Laboratories, Philadelphia.

The promazine hydrochloride used in this study was supplied as Sparine by Wyeth, Inc., Philadelphia.

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Comparative Study of Chlorpromazine and Insulin

Coma in the Therapy of Psychosis

With the advent of "newer" drugs for the treatment of psychiatric illnesses, and the concomitant awareness that the effectiveness of insulin coma therapy was limited, a control drug therapy-insulin coma study was undertaken. Preliminary trials with various medications available in 1954 demonstrated chlorpromazine to be potent and relatively safe. Concurrent reports had noted its value in schizophrenic illnesses, and it was therefore selected as the experimental agent.

The study was designed to assess the therapeutic efficacy and indications for intensive chlorpromazine therapy compared to classical insulin coma therapy in an open-ward, voluntary hospitalized psychiatric population.

Subjects and Method

All patients referred for insulin coma therapy during the period September 1, 1955 to December 31, 1956 were observed. Supervising psychiatrists made the recommendation for insulin coma therapy independent of the research group. Their criteria for referral were those implicitly held by the hospital administration, and were not altered for this study. Randomly selected patients were placed on chlorpromazine therapy instead of insulin coma. This selection was made by the psychiatrist in charge of the insulin therapy unit, without prior notice of the referring therapist or the supervising psychiatrist. Sixty patients were referred for insulin coma therapy during the study period, and half received chlorpromazine.

a) Insulin Coma: The standard technique of Sakel was used. All patients received 50 comas, each of a duration of at least one hour at the physiologic level of Babinski reflex, absent lid reflex, or deeper. Recovery was induced by gavage and occasionally by intravenous glucose. Treatments were given five times weekly, for a period of 3-4 months.

b) Chlorpromazine: To establish an equivalent group, chlorpromazine* was given for at least three months. Dosages were determined by the research team and were rapidly increased until well defined physiologic effects were observed. These included rigidity, drooling and fixed facies, seizures or severe dermatitis. In most instances this was achieved below 1400 mgm daily although dosages were increased to 3600 mgm in one patient. In each instance, the drug dosage was slowly reduced until a maintenance dose, just under toxicity, was obtained. This varied from 300 mgm to 2000 mgm daily with a median of 800 mgm.

To determine the comparability of the subjects resulting from the random sampling procedures used in this study, the groups were compared as to their psychiatric diagnoses and ages. Table I compares both groups as to diagnoses, and demonstrates an equal distribution of subjects in each category.

* Chlorpromazine supplied as "Thorazine" through courtesy of Smith, Kline & French, Inc.

TABLE I
PSYCHIATRIC DIAGNOSES

	<u>Insulin Coma</u>	<u>Chlorpromazine</u>
Psychoneurosis	1	2
Schizophrenia, Paranoid	10	10
Schizophrenia, Catatonic	7	7
Schizophrenia, Mixed	8	6
Schizophrenia, Hebephrenic	3	2
Manic-Depressive Psychosis	1	3

In the analysis of the age distribution, the median age for the insulin patients was 24 with a range of 17 to 38; while the chlorpromazine patients had a median age of 28 and a range of 19-42. Here, too, the distribution shows no significant difference.

For both treatment groups, behavioral observations were made by the research staff at weekly intervals. Following completion of the treatment period, reports of the patients' behavior were obtained from the therapist and supervising psychiatrist. The "improvement" rating was determined by the Medical Director at the patient's Discharge Conference and was based on the four-fold scale of recovered, much improved, improved and unimproved. None of the authors, nor the supervisor of the insulin therapy unit, participated in these evaluations.

Observations

1. Clinical Observations

a) Chlorpromazine: Chlorpromazine induced motor retardation in all subjects. Overactive, destructive behavior rapidly disappeared, and patients became more tractable, less negativistic and less violent. The nurses' and therapists' records note patients as "less easily excited and frightened," "cooperates better in ward activities," and "less restless and less panic ridden." One-third of the patients were more sociable and less seclusive, and were noted to care for themselves in a more presentable fashion. In instances where severe motor symptoms supervened, however, the patients were less able to care for themselves; became sloppy and failed to dress. Such periods were usually short, and could be significantly modified either by a reduction in drug dosage or by anti-Parkinson drugs.

Affective changes during chlorpromazine were varied. Four patients became increasingly agitated, tense and tremulous and either refused to continue on the drug regimen or were induced only with difficulty. Such an affective "storm" appeared early in the treatment and persisted. In four other patients, depressive symptoms were relieved, with an increase in affective lability and responsivity. Depressive ideation increased, associated with complaints of insomnia and anorexia, in two patients. The medication was continued, however, with an eventual alleviation. In most patients, mood changes were small.

Ideation was dramatically altered during the period of chlorpromazine therapy in twelve patients. Eight had a loss or a significant diminution of their psychotic ideation. In five, hallucinatory and referential experiences

were no longer reported even on inquiry and in three others, delusional ideas were less prominent. In one patient, phobias were relieved and the patient could once again participate in ward activities. In another, hypochondriasis was sufficiently modified to permit a more meaningful relatedness of therapist and patient. In one patient, paranoid ideation became more prominent. This was associated with increasing anxiety and panic during drug administration, and resulted in discontinuation of the drug regimen.

b) Insulin Coma: The clinical observations in this group were similar to those reported by others (1). Alteration in behavior was prominent in all patients once repeated comas were induced. Overactive, hostile behavior rapidly diminished, and was replaced by alternating periods of somnolence, irritability and withdrawal. In most patients, nausea, abdominal distress, belching, sweating and lassitude were common sequellae each afternoon, and assumed prominence in the recorded reports. These symptoms often interfered with the patient's ability to care for themselves, and they became unkempt in their dress.

Changes in ideation appeared slowly during the course of therapy. In eight patients, paranoid and delusional thoughts became less prominent, disappearing in these on direct inquiry. Suicidal and outwardly directed destructive thoughts were modified in three patients, only to recur in each at the end of the treatment period.

Mood changes were small. Increasing agitation, tension and panic were reported in three patients, leading in two to a refusal of further therapy. In one depressed patient, relief of depressive symptoms were noted early in

the treatment, and was sustained.

In the usual practice of the treatment unit, concurrent electroconvulsive therapy was instituted when behavioral control by insulin coma alone was limited. In six patients, such combined treatment was instituted primarily because of a continuation of overactive or delusional ideation. There was, in four instances, a well defined alteration in behavior, but this was unsustained. None of these patients was rated as improved on discharge.

2. Discharge Evaluation

All patients were discharged from the hospital within four months of the end of treatment. Table II lists the hospital discharge evaluations for both the chlorpromazine and insulin coma treated patients.

TABLE II
DISCHARGE RATINGS

	<u>Chlorpromazine</u>	<u>Insulin Coma</u>
1. Recovered	2	0
2. Much Improved	4	5
3. Improved	17	15
4. Unimproved	7	10

Included in the unimproved group of chlorpromazine patients are four who received inadequate course of therapy (less than one month) because of complications of the therapy. Of the ten unimproved insulin coma patients, four had inadequate courses of therapy - two because of complications (seizures, prolonged coma), one because she became more disturbed, and the fourth by administrative transfer to another facility.

It is apparent that there is no difference in the clinical evaluation at the time of discharge between the insulin coma and the chlorpromazine treated groups. To determine whether this sample was biased because of its small number, we compared these discharge ratings with a similar group treated in this hospital in 1950 and previously reported (2). In Table III, the discharge ratings for both years are compared.

TABLE III

	<u>Present Group</u> (30 subjects)	<u>1950 Group</u> (48 subjects)
Recovered	0	14%
Much Improved	17%	19%
Improved	50%	42%
Unimproved	33%	25%

The percent improvement rates for each category are not significantly different.

3. Toxicity and Complications

a) Chlorpromazine: Inherent in the design of this study were high doses of chlorpromazine, pushed to symptoms of toxicity. In this context, all patients developed significant drug effects. Rigidity of extremities, accompanied by a decrease in facial expression, drooling and festination was frequently observed. In three instances, rigidity appeared as drug dosage was reduced. Most patients became drowsy, retarded, and less active in ward activities. In four patients increased tension, agitation, restlessness and excitement supervened, leading to a discontinuation of the drug regimen in two.

Seizures occurred spontaneously in three patients. Pre-treatment electroencephalograms had manifested no dysrhythmia and no history of seizures had been elicited. In each, the drug medication was reduced, and seizures did not develop at the lower dosages.

Dermatitis was a frequent complication. All patients developed a transient erythema to mild solar radiation. Severe intractable skin reactions occurred in three patients, with resultant discontinuation of drug therapy in two. In the third, promazine* therapy was substituted for chlorpromazine, with a relief of the dermatitis. The behavioral effects of the promazine was indistinguishable in this patient from that noted for the chlorpromazine group.

In this group, no patient developed clinical jaundice. This complication has been variously reported as occurring in less than $\frac{1}{5}\%$ of subjects treated **.

Electroencephalograms were obtained in twenty of the chlorpromazine patients. With increasing doses, the modulation of the record became more irregular in each. A moderate amount of low voltage 4-7 cps delta and theta activity was induced, and this activity was exaggerated by hyperventilation. There was a suggestive relationship between the degree of the induced slow wave activity and the drug dosage.

b) Insulin Coma: The complications of insulin coma therapy in this series were not unusual. Insulin resistance was noted only once, and was eventually overcome by the method of alternating dosages. Prolonged reactions

* Supplied as "Sparine" through courtesy of Wyeth & Co.

** In the preliminary studies at Hillside Hospital, three patients of a group of twenty developed transient clinical jaundice.

occurred in three patients. In each, neurologic examination and electroencephalography demonstrated signs of persistent central nervous system dysfunction for at least ten days. Transient aphasia, hemiparesis, and paresthesias were frequent in five patients, and transient in eight others. Seizures occurred in five patients, and were recurrent in three. Frequent secondary reactions, nausea, vomiting, abdominal distress, sweating, pallor, lassitude and generalized weakness occurred in all patients in varying frequencies.

The complications of both forms of treatment are listed in Table IV. Certain effects, as dermatitis and hypotension, secondary reactions and prolonged coma are individual for each therapy, and seizures, agitation and refusal of therapy were noted in both regimens. The frequencies of these are not significantly different.

TABLE IV
COMPLICATIONS

	<u>Chlorpromazine</u>	<u>Insulin Coma</u>
Agitation and Panic	4	3
Dermatitis, severe	3	-
Seizures	3	5
Refusal of further therapy	2	2
Hypotension	2	-
Secondary reaction, frequent	-	5
Prolonged Coma (+ 6 hours)	-	3
Insulin Resistance	-	1

4. Effects on the Psychotherapeutic Relationship

In this setting, patients are referred for insulin coma therapy after a period of verbal relationship therapy. Such referral implies a failure of interpersonal communication.

During the period of effective drug action, fifteen of the chlorpromazine-treated patients were described by the therapist in response to an inquiry as "more accessible," "spoke more freely" and were "more amenable to psychotherapy." The behavioral changes could be classified into two groups: subjects in whom tension and preoccupation with somatic symptoms became much less, and those in whom hallucinatory or delusional preoccupations ended. Such changes in relationship were frequently described as an increase in "contact." In thirteen subjects, psychotherapy was either still "not feasible" or had become less feasible because of increasing, uncontrolled tension, anxiety or preoccupation with the side effects of the drug regimen.

Similar observations were made in the insulin treated patients. Of the thirty patients, seven were noted to be less tense and less anxious during therapeutic sessions. The therapists noted that the patient "verbalized more freely" and "was more aware of his environment." Four patients were specifically treated with a "modified anaclitic" approach. In each instance, this relationship was unsustainable during treatment and the therapists resorted to more conventional tactics. In the remaining patients (19), while supportive, educational and environmental manipulating techniques were applied, the therapists were no more successful than prior to insulin therapy. In eleven patients, the physiologic effects of the treatments (secondary reactions, sweating, nausea, vomiting and weight gain) were reported as interfering with psychotherapeutic attempts.

Discussion

1. Clinical Considerations

In these patients neither chlorpromazine in high therapeutic doses nor insulin coma specifically modified the psychotic process. Since 88% of these patients were diagnosed as suffering from schizophrenic illnesses, we concluded that neither treatment has a specificity in altering the schizophrenic process. When given in adequate dosage, however, both treatments are potent methods for the alteration of behavior. In the discharge evaluations, the treatments are similar. In only 20% of the patients were induced behavioral patterns persistent and rated as much improved or recovered. For the others, the induced behavioral changes were transient or minimal.

Since these therapies fail to induce a recovery from the psychotic process, then consideration should be given to their ameliorative, palliative and supportive aspects. Symptomatic relief was frequent, but generally limited to the treatment period. Patients were made uncomfortable by both therapies, however, and the complications and toxic effects have already been noted.

In assessing the role of concomitant psychotherapy, there is little advantage of either therapy. Both methods were said to enhance relationship therapy although the therapists' evaluations favored chlorpromazine therapy. Excluding those who developed increased agitation, patients were more comfortable, more alert and physically better able to discuss their feelings and experiences while on chlorpromazine, than on insulin coma. It is clear that "interpretive" psychotherapy is not enhanced, but rather supportive, educative, re-orienting and directive types of therapy. When there is a modification of agitated, hallucinatory, depressed, manic or aggressive behavior, then both the therapist and the patient are more comfortable and able to discuss

the reality aspects of the life situation.

Therefore, in this context, the ease of administration and the possibility of continued maintenance of chlorpromazine in an outpatient setting assumes decisive significance. To maintain such therapy after discharge and continue thereby the relationship established in the hospital setting may be an important element in sustaining the behavioral changes induced by hospitalization.

2. Other Studies

While many reports of the treatment of psychosis by chlorpromazine have appeared, we are aware of only one similar comparative study. Boardman, Lomas and Markowe (3), after a review of the problem, report their study of one hundred patients randomly divided into two groups of 50 and treated either by insulin coma or chlorpromazine. The chlorpromazine dosage was lower than that in this series (average 300 mgm) but the drug period (3 months) was the same. Their observations are directly comparable to this study. They reported no difference in the discharge evaluations, nor in symptom assessments for either treatment group.

The chlorpromazine treated patients, however, remained in the hospital an average of 6.2 weeks less than the insulin treated subjects. This was a significant difference between the groups. They concluded that: "There is inconclusive evidence that chlorpromazine has advantages over insulin in the treatment of schizophrenia," but "that insulin has disadvantages in the form of greater danger and more unpleasantness for the patients and greater strain on the nurses. Chlorpromazine is the first treatment of choice in schizophrenia, but this conclusion is based on the immediate results of treatment and has not yet been confirmed by an adequate follow-up study."

Boardman and his co-workers emphasize the problem of evaluating the therapeutic efficacy of insulin coma. They note a number of reports that raise doubts as to the efficacy of insulin coma therapy in schizophrenia. Bourne (4), in an extensive review of the merits of insulin therapy in schizophrenia concluded that "there is no proof of any specific therapeutic effect, and the long term prognosis is in no way influenced."

The recent observations of insulin treatment of schizophrenia by Ackner, Harris and Oldham (5) are relevant. In a carefully controlled study, young schizophrenic patients were randomly treated either by insulin or by barbiturate coma in the same ward and under similar conditions. Evaluations of results were made by psychiatrists without knowledge of which medication the patients received. The authors noted a similar outcome whether the loss of consciousness was induced by a barbiturate or by insulin, and concluded that insulin was not a specific therapeutic agent in the outcome.

In the follow-up studies in this hospital (2), the therapeutic results for insulin coma therapy were disappointing. In that report, patients referred for insulin coma had the longest period of hospitalization (6.50 months vs 6.04 for psychotherapy and 4.95 for electroshock), poorest discharge rating (33% recovered and much improved, vs 63% for psychotherapy and 67% for electroshock), and within four years, a 50% re-hospitalization rate (compared to 33% for psychotherapy and 29% for electroshock). While these observations reflect the observation that the more severely ill patients are referred for insulin coma, it also supports the belief that insulin coma is not a specific treatment for the patients referred.

From these reports we would conclude that, despite considerable study and the passage of many years, insulin coma therapy has not been shown to

induce persistent behavioral changes more frequently than other non-specific, less dangerous and less expensive therapies. To the list of alternate therapies of limited value in the management of psychosis we may now add chlorpromazine, noting, however, its advantage of lesser risk and ease of administration.

3. Dosage of Chlorpromazine

For the purpose of assuring an adequate level of chlorpromazine for evaluation, the medication was increased in all subjects to toxic levels. This level was too high for its behavioral effects, as evidenced by the reduction in all responsive cases to maintenance levels of 300 to 2000 mgm.

It is our impression that chlorpromazine affects the function of the central nervous system (as evidenced by changes in modulation and percent time delta in the electroencephalogram and systemic phenomena of rigidity and lassitude) and results in a non-specific alteration in behavior. Such behavioral change is varied and is dependent upon a variety of factors, of which the personality organization and the expectancy of the milieu are significant. In this context, the induction of a state of altered cerebral function is a necessary prerequisite to behavioral change. The only assurance of achieving a therapeutic level, therefore, is the appearance of toxicity, and a lowering of dosage from that level to a maintenance dose. The effects of rigidity, drowsiness and lassitude, therefore, are necessary concomitants of the therapy and should be induced in all patients in whom a therapeutic effect is desired. In instances where an affective "storm" supervenes, continuation of the drug at higher levels, with concomitant artane and cogentin, should be considered. Such an attitude in therapy is comparable to the application of digitalis in cardiology, and to the present concept of the mode of action of electroshock therapy (6).

Conclusions

1. In a study of patients referred for insulin coma therapy in an open ward, voluntary psychiatric hospital, patients randomly received either insulin coma therapy or intensive chlorpromazine therapy.

2. Chlorpromazine was as effective in modifying psychotic behavior as insulin coma therapy. There was no difference in the improvement rating on discharge, incidence of complications or effects on the psychotherapeutic relationship for either therapy.

3. In comparison to insulin coma, chlorpromazine is safer, easier to administer, and lends itself to long term management. Patients receiving chlorpromazine therapy are more comfortable than those receiving insulin coma.

4. No evidence has been educed that either therapy has altered the basic schizophrenic process; nor is there any evidence that there is greater specificity of either form of therapy for schizophrenic illnesses.

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January 31, 1957

Subject: Chlorpromazine - Insulin Control Study: Interim Report
From: Drs. Max Fink, Robert Shaw, George Gross and Fred Coleman
To: Dr. Joseph S. A. Miller, Dr. Simon Kwalwasser and the
Research Committee of Medical Board

Following is a summary of the observations in the control chlorpromazine-insulin coma study, instituted September 1, 1955 and completed January 1, 1957. During this period, 59 patients were referred for insulin coma therapy. Half of the group was placed, by random sampling, on chlorpromazine * therapy instead of insulin coma. Four patients received both insulin and chlorpromazine therapy. Of the patients who received chlorpromazine, seven received courses of therapy of less than one month. Of the 29 insulin patients, three had an inadequate course of therapy.

I. PROBLEM: During the period 1954-1955, preliminary trials of chlorpromazine resulted in the awareness that the drug was both potent and safe. In view of the unusually poor showing of the insulin coma population in the 1950 Follow-up Study (1), and the appearance of numerous articles in the psychiatric literature recommending chlorpromazine as a therapy for schizophrenia, a comparative study of chlorpromazine - insulin coma was undertaken. The following questions were postulated:

- a) What is the clinical effect of adequate doses of chlorpromazine?
- b) What is its therapeutic efficacy when compared to insulin coma therapy?
- c) What are the indications (and contraindications) for the use of chlorpromazine and/or insulin coma?

* Chlorpromazine supplied as "Thorazine" through the courtesy of Smith, Kline and French Co., Philadelphia.

(1) Rachlin, H.L., Goldman, G.S., Gurvitz, M., Lurie, A., and Rachlin, L.: Follow-up Study of 317 Patients Discharged from Hillside Hospital in 1950, J. Hillside Hosp., 5: 17-40, 1956.

II. SUBJECTS: All patients referred for insulin coma therapy during the period September 1, 1955 and December 31, 1956 were observed.

Supervising psychiatrists made the recommendation for insulin coma therapy independent of the research group. Their criteria were those implicitly held by the hospital administration, and were not altered for this study. Selected patients were placed on chlorpromazine therapy. The selection was random and made by the supervising psychiatrist of the physical therapy unit, without prior notice of the referring therapist.

III. METHOD: a.) Insulin Coma: The standard technic of Sakel was used.

All patients received 50 comas, each of a duration of one hour or longer at the physiologic level of Babinski reflex or absent lid reflex or deeper. Recovery was induced by gavage and occasionally by intravenous glucose. Treatments were given five times weekly, for a period of 3-4 months.

b.) Chlorpromazine: To establish a complementary therapeutic group, chlorpromazine was given for at least three months.

Dosages were determined by the research team and were rapidly increased until clear-cut physiologic effects were observed. These included clinically manifest rigidity, drooling, and fixed facies; or toxicity, as seizures or severe dermatitis. In each instance, the drug dosage was slowly reduced until a maintenance dose, just under toxicity, was obtained. This was maintained for the duration of the observation period.

Laboratory tests were carried out at irregular intervals and included blood counts, liver function tests, glucose tolerance tests and electroencephalograms.

In both experimental groups, behavioral observations were made at weekly intervals. Following completion of the treatment period, reports of the ther-

apist and supervising psychiatrist were obtained. The rating of "improvement" was that established by the Medical Director at the patient's Discharge Conference.

IV: RESULTS:

A. Chlorpromazine

1. Dosage of chlorpromazine: The dosage of chlorpromazine was increased rapidly until signs of rigidity appeared. In most instances this was achieved in daily dosages below 1400 mgm. although dosages were increased to 3600 mgm. in one patient. The maintenance dose varied from 300 mgm. to 2000 mgm. daily.

2. Clinical effects of chlorpromazine: Chlorpromazine induced a motor retardation in all subjects. Overactive, destructive behavior rapidly disappeared, and the patients were more tractable, less negativistic and less violent. The nurses' and therapists' records relate that patients are "less easily excited and frightened," "cooperates better in ward activities," and "less restless and less panic-ridden." One-third of the patients were more sociable and less seclusive, and were noted to care for themselves in a more presentable fashion. In the instances where severe parkinsonism supervened, however, the patients were less able to care for themselves; became sloppy and failed to dress. Such periods were short or could be significantly modified by anti-parkinson drugs.

Affective changes during chlorpromazine were varied. In four instances, the patients became increasingly agitated, tense, tremulous and either refused to continue on the drug regimen or were induced only with difficulty. Such an affective "storm" appeared early in the therapy and persisted.

In four other instances, depressive symptoms were significantly relieved, with an increase in affective lability and responsivity. In two patients, de-

pressive ideation increased and was associated with complaints of insomnia. The medication was continued, however, with an eventual alleviation. In most patients, mood changes were small.

Ideation was dramatically altered during the period of chlorpromazine therapy in twelve of the patients. Eight patients had a loss or a significant diminution of psychotic ideation. In five, the hallucinatory and referential experiences were no longer reported even on inquiry; and in three others, delusional ideation was less prominent. In one patient, phobias were relieved to a degree that the patient could participate in ward activities. In another, hypochondriasis was sufficiently modified to permit of a more meaningful relatedness of therapist and patient.

In one patient, paranoid ideation became more prominent. This was associated with increasing anxiety and panic during drug administration, with resultant discontinuation of the drug regimen.

3. Effects on the psychotherapeutic relationship: Patients are referred for insulin coma therapy after a period of verbal relationship therapy. Such referral implies a failure of interpersonal communication.

During the period of effective drug activity, ten of the patients were described by the therapist in response to an enquiry as "more accessible," "spoke more freely" and were "more amenable to psychotherapy." The responses could be classified into two groups: the subjects whose tension and preoccupation with somatic symptoms became much less and those in whom hallucinatory or delusional preoccupations ended. In each instance, the therapist described the change in relationship as an increase in "contact". In twelve subjects, psychotherapy was either still "not feasible" or "less so because of increasing, uncontrolled tension."

In no instance did the problem of drug addiction or drug dependence play a role, nor was there an appreciation that drug therapy altered the therapeutic relationship adversely.

4. Ratings of "improvement": Of the thirty patients in this series, twenty four have left the hospital. Table I lists the number of patients evaluated by the Discharge Conference, according to the four-fold classification in use in the hospital. For comparison, the discharge ratings of the insulin coma therapy patients, following the same criteria, have been included.

TABLE I
DISCHARGE RATINGS

	<u>Chlorpromazine</u>	<u>Insulin Coma</u>
1. Recovered	1	0
2. Much Improved	3	1
3. Improved	15	10
4. Unimproved	5	8

Included in the unimproved group of chlorpromazine patients are four who received inadequate courses of therapy (less than one month) because of complications of the therapy. Of the eight unimproved insulin coma patients, four had inadequate courses of therapy - two because of complications (seizures, prolonged coma), one because she was a severe management problem; and the fourth by administrative transfer to the V. A.

5. Toxicity of chlorpromazine: Inherent in the design of this study were the high doses of chlorpromazine, pushed to symptoms of toxicity. In this context, all patients developed significant drug effects. In all, rigidity of extremities appeared; frequently accompanied by a decrease in facial expression, drooling and festination. In a number of patients the parkinson-

ian features appeared as the drug dosage was reduced. In each patient the symptoms were relieved when the drug was discontinued. Almost all patients became drowsy, retarded, and less active in ward activities. In four patients, increased tension, agitation, restlessness and excitement supervened, to a degree that led to a discontinuation of the drug regimen.

Seizures occurred in three patients. In each, the drug medication was reduced, and seizures did not develop at the lower dosages.

Dermatitis was a frequent complication. Severe, intractable skin reaction occurred in three patients, with resultant discontinuation of drug therapy in two. In the third, promazine * therapy was substituted for chlorpromazine, with a relief of the dermatitis. The behavioral effect of the promazine was indistinguishable in this patient from the chlorpromazine group. All patients developed a skin photosensitivity so that on exposure to sun, transient erythema developed.

Refusal of further medication because of drug effects occurred in two patients. Both developed severe tension and agitation. In two other instances, agitation resulted in the therapist insisting upon a change in treatment regimen.

Table II lists the complications of both treatments. Certain effects are individual to the type of therapy, as dermatitis for chlorpromazine; and prolonged coma, severe secondary reactions and nausea and vomiting in insulin coma. Others, as seizures, fainting spells, and increased states of agitation are seen in both.

* Supplied as "Sparine" by the courtesy of Wyeth and Co.

TABLE II
COMPLICATIONS

	<u>Chlorpromazine</u>	<u>Insulin Coma</u>
Agitation and Panic	4	2
Dermatitis, severe	3	-
Seizures	3	3
Refusal of further therapy	2	2
Hypotension	2	-
Secondary reaction, frequent	-	5
Prolonged Coma (+ 6 hours)	-	3
Insulin Resistance	-	1

In this chlorpromazine series, no patients developed clinical jaundice. This complication has been variously reported as occurring in less than $\frac{1}{2}\%$ of the subjects treated.* Liver function and blood element studies were done in this group of patients. Changes were small, and at the recommendation of the medical consultant, the studies were discontinued.

Electroencephalograms were obtained in fifteen of the chlorpromazine patients. On adequate doses, a moderate amount of low voltage 4-7 cps. delta and theta activity was induced. This activity was exaggerated by hyperventilation. There was a suggestive relationship between the degree of the induced slow wave activity and the drug dosage.

6. Adjuvants to Chlorpromazine: With the development of rigidity, festination, and drooling, patients received cogentin or artane medication. Both drugs relieved the symptoms, and in a few instances, to a significant

* In the initial studies at Hillside Hospital, three patients of a group of twenty developed transient clinical jaundice.

degree. Concomitant with the relief of the rigidity a feeling of euphoria and well-being was occasionally noted. In one of the patients who developed an affective "storm" the administration of artane had a salutary effect.

In patients who developed seizures during insulin coma therapy, anti-convulsant medication (dilantin, phenobarbital) has been routinely employed. Such agents were not used with chlorpromazine as the seizures did not recur on lowered dosages.

B. Insulin Coma Therapy

The clinical effects, complications, the treatment results of insulin coma therapy have been exhaustively reported. In this series, twenty-nine patients began insulin coma therapy. Of these, nineteen have completed their period of hospitalization and ten are either completing their treatment period or are awaiting discharge.

The over-all ratings of "improvement" are listed in Table I. When compared with the Hillside Hospital Follow-up Study of 1955, the percent improvement in each category is not significantly different, although the trend is to rate the present series somewhat less optimistically than the 1950 group. In Table III the percentages are listed for each evaluation category of this group compared to the 1950 population.

TABLE III

INSULIN COMA THERAPY

	<u>Present Group</u>	<u>1950</u>
1. Recovered	0%	14%
2. Much Improved	4%	19%
3. Improved	52%	42%
4. Unimproved	44%	25%

Such a difference in trend, if sustained, may reflect a variety of factors, including changes in criteria of "improvement;" prior administration

of the newer tranquillizing agents exerting a selectivity on the population admitted to the hospital; and changes in staff criteria for referral for insulin coma therapy.

The complication rate in this insulin group is comparable to published studies. No unusual complications, and no deaths were observed.

The role of psychotherapy in patients undergoing insulin coma therapy is complex. In this group, four patients were treated with a "modified analytic" approach and an effort at establishing a working psychotherapeutic relationship was made. In the remaining patients, no unusual efforts at psychotherapy were made, with the consensus that a supportive, educative, environmental-manipulative, reassuring type of therapy was achieved, to varying degrees. Therapists reported (in 7 instances) that patients were less tense and less anxious during sessions while in coma therapy. In eight patients the physiologic effects of the treatment (secondary reactions, sweating, nausea, vomiting, weight gain) interfered with relationship therapy to a significant degree.

C. Therapeutic Results in Relation to Final Diagnosis

Table IV lists the final diagnostic categories for the patients in each group. All diagnoses were represented in each series with an equivalent distribution.

TABLE IV

PSYCHIATRIC DIAGNOSES

	<u>Insulin Coma</u>	<u>Chlorpromazine</u>
Psychoneurosis	1	2
Schizophrenia, Paranoid	6	9
Schizophrenia, Catatonic	5	6
Schizophrenia, Mixed	5	5
Schizophrenia, Hebephrenic	3	2
Manic Depressive Psychosis	1	2

No diagnostic group had a significantly better treatment response than any other with either form of therapy.

V. DISCUSSION:

A. Comparison of Chlorpromazine and Insulin Coma Therapies:

Neither chlorpromazine in high therapeutic doses, nor insulin coma, are specific treatments for schizophrenia. The discharge evaluations for both treatments are not significantly different. There is, however, a definite tendency for more patients in the chlorpromazine group to be rated in the better classifications than in the insulin coma group. The trend assumes significance when both the type of sampling and the qualitative aspects of the treatments are taken into account. The random sampling is exemplified by the resultant matching of diagnoses.

Since these treatments have not resulted in a recovery from the psychotic process, then their ameliorative, palliative and supportive aspects must be considered. The insulin coma patients are usually uncomfortable throughout their treatment period. Nausea, vomiting, secondary reactions, and drowsiness are common. Prolonged coma is a realistic threat; as well as the threat to loss of life.

The chlorpromazine patients also suffered considerable disagreeable side effects. Parkinsonism, drowsiness, and skin reactions are significant, and must be considered as concomitant management problems. Seizures and jaundice are the most severe reactions, and to date, have not been permanent. It is possible to modify the significance of these side effects to a considerable extent by anti-parkinson and anti-convulsant medication.

There is no question, furthermore, as to the ease with which chlorpromazine can be administered, in contrast to insulin coma.

A significant element in the use of these agents in the therapy of schiz-

ophrenia is concomitant psychotherapy. Such relationship therapy was enhanced by both therapies. It was apparent in the therapist's evaluations, however, that the chlorpromazine regimen was more conducive to concomitant verbal therapy. Patients, excluding those who developed increased agitation, were more comfortable, alert and physically able to discuss their feelings and experiences while on chlorpromazine, than insulin coma.

In another respect, the ease of administration of chlorpromazine is of advantage. Patients who respond to drug therapy can be maintained on such therapy for as long as needed, even on an outpatient basis, while the "course" of insulin coma is limited.

Are these treatments equivalent? Can one be substituted for the other? While these questions cannot be answered by the data in a positive assertion, the negative can be denied. The results of these treatments in equivalent groups are not different with regard to the discharge evaluation. The changes in behavior noted and the symptoms alleviated are not significantly different. In this series, three patients had adequate courses of both regimens. Two have been discharged "improved," and the third is still in the hospital. There has been no significant differences in their response to either form of therapy.

B. Comparison With Other Studies:

While many studies of chlorpromazine in schizophrenia have appeared, only one report of a controlled study is available. Boardman, et al (2) after an excellent review of the problem, report their results in one hundred patients, randomly divided into two groups of 50 and treated either by insulin coma or chlorpromazine. Their chlorpromazine dosage was lower than in this series (average 300 mgm) but the drug period (3 months) was the same. Their observations are directly comparable to this series. They noted that the over-

(2) Boardman, R.H. et al: Insulin and Chlorpromazine in Schizophrenia - A Comparative Study of Previously Untreated Cases, Lancet 2: 487-491, (September) 1956.

all clinical results were slightly more favorable in the chlorpromazine group than in the insulin group judging both by interview status and by a rating scale of symptom change. The difference was not of high statistical significance. They did state, however, that the chlorpromazine patients remained in the hospital an average of 6.2 weeks less; and that this difference was statistically significant. They concluded that: "There is inconclusive evidence that chlorpromazine has advantages over insulin in the treatment of schizophrenia," but "that insulin has disadvantages in the form of greater danger and more unpleasantness for the patients and greater strain on the nurses. Chlorpromazine is the first treatment of choice in schizophrenia, but this conclusion is based on the immediate results of treatment and has not yet been confirmed by an adequate follow-up study."

In Boardman's review, due cognizance is given to the problem of the therapeutic efficacy of insulin coma. He notes the number of dissident reports that raise doubts as to the role of insulin coma therapy in schizophrenia. In this regard, it is important to note the results of the Hillside Follow-up for insulin coma, in which patients referred for such therapy had the longest period of hospitalization, poorest discharge ratings, and a 50% rehospitalization rate (compared to 33% for psychotherapy and 29% for the electroshock therapy groups).

Two other control studies of chlorpromazine in psychoses are relevant to this report. Feldman et al, (5) reporting the observations in a controlled, "blind" study at Topeka State Hospital noted a significant degree of improvement for chlorpromazine. They concluded that "thorazine was found to be useful in converting acutely disturbed psychotics into tractable, accessible patients who could then participate more actively in the hospital rehabili-

(5) Feldman, P.E. et al: A Controlled, Blind Study of Effects of Thorazine on Psychotic Behavior, Bull. Men. Clinic, 20: 25-47, 1956.

tation program." Tenenblatt and Spagno (6), describing the St. Elizabeth's Hospital experience, in another control study, noted significant behavioral effects in psychotic illnesses other than involuntional psychoses.

D. Effect of Study on Staff:

An inherent factor in a control study of any therapeutic modality is the effect that the knowledge of random selection of patients or the use of placebos has on the therapist in his choice of therapy. Knowledge that insulin coma referrals were to be given either chlorpromazine or insulin coma created a feeling of insecurity and impotence in the therapist. Their control of the therapeutic situation was felt as severely constricted. This resulted in a decrease in the number of referrals, an exaggeration of the physiologic drug effects, and in the patients expressing doubts as to the therapeutic efficacy of the drug despite significant changes in ward behavior. On numerous occasions, therapists called to enquire which therapy their patient, whose referral for ICT had not yet been made, would get. Prior prejudice about the suitability of either therapy resulted in the therapist's expressing disappointment at the modality used. In two instances, such prejudices led to early discontinuation of chlorpromazine therapy, when the patient experienced early signs of drug effects.

E. Dosage of Chlorpromazine:

For the purposes of assuring an adequate level of chlorpromazine for evaluation, the medication was "pushed" in all subjects to toxicity. This level was too high for its behavioral effects, as evidenced by the reduction in all responsive cases to maintenance levels of 400-1000 mgm. The effects of parkinsonism, drowsiness and lassitude are probably necessary concomitants

(6) Tenenblatt, S.S. and Spagno, A.: A Controlled Study of Chlorpromazine Therapy in Chronic Psychotic Patients, *Quart. Rev. Psych. & Neurol.*, 17: 81-92, 1956.

of the therapy; and should be induced in all patients in whom a therapeutic effect is desired. In instances where an affective "storm" supervenes, continuation of the drug at higher levels, with concomitant artane or cogentin, should be considered.

VI. CONCLUSIONS:

In a control study of patients referred for insulin coma therapy, chlorpromazine therapy was found to be as effective in modifying psychotic behavior patterns as insulin coma therapy. There is a tendency for the discharge ratings to be better for the chlorpromazine group than for the insulin coma group.

In comparison to insulin coma therapy, chlorpromazine is safer, easier to administer, more controllable in its effects, and has fewer side effects.

No evidence has been educed that either therapy has altered the basic schizophrenic process; nor is there any evidence that there is greater specificity for either form of therapy for schizophrenic illnesses.

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1. Fink, M.: Individual Differences in EEG Responsivity. Read at Metropolitan EEG Society, New York, February 1957.
2. Fink, M.: Criteria in Evaluation of Clinical Behavioral Change: Neuro-physiologic Aspects. Presented at A.P.A., Round Table, Chicago, May 1957.
3. Fink, M., Kahn, R.L. and Green, M.A.: Experimental Studies of the Electroshock Process. Read at the Society of Biological Psychiatry, Atlantic City, June 1957.
4. Fink, M. and Kahn, R.L.: Therapy of Schizophrenia: Role of Alteration in Brain Function in Behavior. Presented at Int. Congress of Psychiatry, Zurich, Sept. 1957.
5. Fink, M., Kahn, R.L. and Korin, H.: Effects of Diffuse Altered Brain Function on Perception. Presented at the XV Int. Congress of Psychology, Brussels, August 1957.
6. Fink, M. and Kahn, R.L.: Behavioral Patterns in Induced States of Altered Brain Function. Read at the New York Divisional Meeting, A.P.A. Nov. 1957.
7. Fink, M.: Significance of EEG Frequency Shift for Psychiatry. Read at Metropolitan EEG Society, N.Y. Nov. 1957.
8. Fink, M.: Effects of Diethazine on EEG and Significance for Theory of Process of Convulsive Therapy. Read at Eastern Association of Electroencephalographers, New York, Dec. 1957.
9. Jaffe, J.: Criteria in Evaluation of Clinical Behavioral Change: Psycholinguistic Aspects. Presented at A.P.A., Round Table, Chicago, May 1957.
10. Jaffe, J.: An Objective Study of Communication in Psychiatric Interviews. Read at the New York Divisional Meeting, A.P.A. Nov. 1957.
11. Kahn, R.L. and Fink, M.: Personality Factors in Behavioral Response to Electroshock Therapy. Presented at Electroshock Research Association, Chicago, May 1957.
12. Kahn, R.L. and Fink, M.: Perception of Embedded Figures After Induced Altered Brain Function. Read at Amer. Psychol. Assoc., New York, August 1957.
13. Korin, H. (with Tarachow, S. and Friedman, S.): Perception Experiments in a Study of Ambivalence. Read at Section on Neurology & Psychiatry of N.Y. Academy of Medicine and N.Y. Neurol. Society, N.Y. Jan. 1957.

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14. Korin, H. (with Tarachow, S. and Friedman, S.): The Relation of Ambivalence to Aggression and Authority in Psychoneurotic Patients. Read at Amer. Psychol. Assoc. Sept. 1957. (New York).
15. Korin, H. (with Tarachow and Friedman, S.): Studies in Ambivalence. Presented before Schilder Society, New York, Oct. 1957.
16. Pollack, M. (with Goldfarb, W. and Dorsen, M.): Pain Reactions in Schizophrenic Children. Presented at Amer. Orthopsychiatric Assoc. Chicago, March 1957.
17. Pollack, M. (with Krieger, H.P.): Oculomotor and Postural Patterns in Schizophrenic Children. Presented at Amer. Academy of Neurology, Boston, April 1957.
18. Pollack, M. (with Battersby, W.S. and Bender, M.B.): Figure-ground Perception in Patients with Cerebral Tumor. Read at Eastern Psychol. Assoc., New York April 1957.
19. Pollack, M. (with Battersby, W.S. and Bender, M.B.): Defects in Visual Perception in Brain Tumor Patients. Presented before Int. Congress of Psychol., July 1957, (Brussels).
20. Pollack, M. (with Battersby, W.S. and Bender, M.B.): Visual Deficit After Brain Damage in Man as Measured with Rapidly-Exposed Chromatic Stimuli. Presented at Amer. Psychol. Assoc., New York, Sept. 1957.
21. Pollack, M. (with Goldfarb, A.): Cultural and Environmental Factors Affecting Complex Perception in the Institutionalized Aged. Presented at the Gerontological Society, Cleveland, Oct. 1957.
22. Pollack, M.: Brain Damage, Mental Retardation and Childhood Schizophrenia. Presented at New York Divisional Meeting, A.P.A. Nov. 1957.