Side effects with all 3 compounds occurred in general in the same areas (drowsiness, excessive salivation, rigidity, tremor, etc.). It should be noted that the number of side effects observed during the total trial period differed with each drug and was 32 in patients receiving McN-JR-2498, 24 for patients receiving R-1625 and 20 for patients receiving McN-JR-3345.

This drug trial was originally designed for 15 patients, but during the course of the experimental period 5 patients had to be dropped from the study. Findings presented above therefore are based on the findings with the remaining 10. Of the 5 cases mentioned, 4 were taken off medication while on McN-JR-2498 and 1 while on McN-JR-3345. Furthermore 4 of these 5 patients were taken off because of adverse physical or behavioral effects (depression with suicidal attempt, anxiety spells with marked dystonic and myoclonic seizures, akinetic syndrome with insomnia, incontinence and confusion). In the 5th case, her dramatic improvement resulted in a discharge from the hospital.

It should also be noted that in two McN-JR-2498 cases, marked liver toxicity was revealed (S.G.P.T. 200 and 102, S.G.O.T. 94 and 84 respectively).

Opinion: Order of antipsychotic potency: McN-JR-2498, R-1625 and McN-JR-3345. The same order of toxicity.

(Ban, T.A., Stonehill, E. and Lehmann, H.E. Butyrophenones in Psychiatry. Symposium, L'Annonciation, Quebec. January 10, 1964. In Press.)

V. STUDIES ON THE EFFECT OF COMPOUNDS ON SPECIFIC SYMPTOMS OR TARGET AREAS.

V. (a) Comparative Study of Largactil and Librium in Alcohol Withdrawal.

This study was carried out with 30 newly admitted alcoholic patients over a period of 4 weeks.

Evaluation was based on a battery of tests and examinations: laboratory (Table VIII); physical (Table IX). An observational data sheet on each patient was completed by the physician in charge. The following areas were observed and rated on a 0 to 3 scale: consciousness, orientation, cooperativeness, excitement, restlessness, aggressivity, anxiety, suspiciousness, hostility, perceptual alteration, disturbances of thinking, insomnia, drowsiness, dehydration, tremor, food and fluid intake. These data sheets were compiled daily for the first 7 days and then weekly for 3 weeks. In addition the Verdun Side Effect Check List (Table X) was completed regularly.

Alternate patients were placed on Librium and Largactil to give a total of 15 patients on each. Once an alcoholic patient had been started on either of these compounds, no other psychoactive medication was given. Daily dosages of both medications ranged from 100 mgs. to 400 mgs., the optimal dosage and route of administration (oral or intramuscular) being decided by the physician on the ward.

The ratings were tabulated and analyzed with the following results:

The mean symptomatology levels of both the Librium and Largactil groups dropped significantly over the 4-week trial period. However, there were differences between the two drug groups in the rate and nature of these changes.

Figure XIII gives a general indication of the rates of improvement of the two groups.

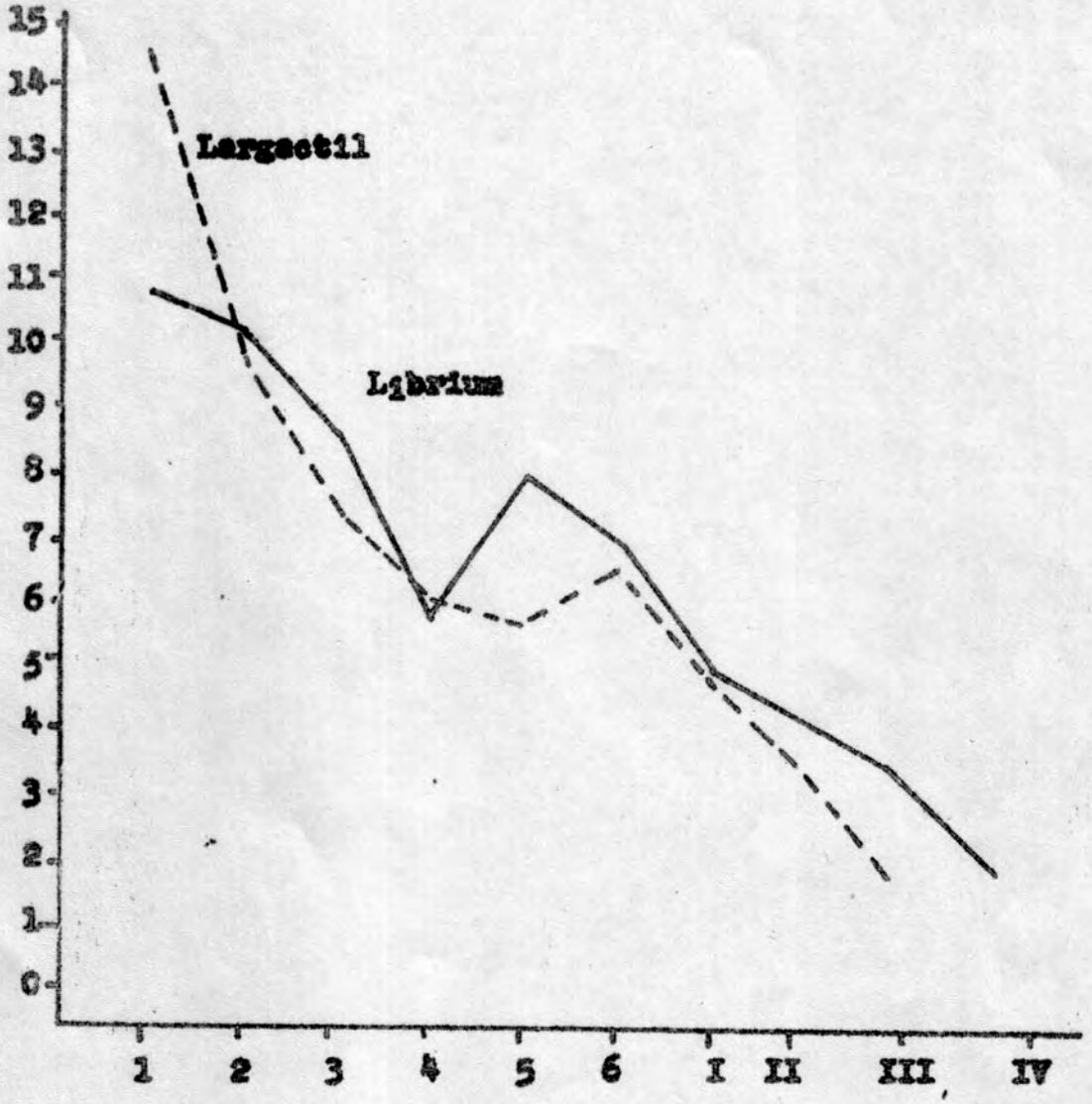

FIGURE XIII.

It will be noticed that the mean symptomatology level of the Largactil-treated patients dropped quickly and steadily for the first 5 days, whereas that of the Librium group dropped at a slower rate, and rose again the 5th and 6th days. From the end of the 1st week to the end of the trial a similar pattern is seen. Although the Largactil group showed more overt disturbance than the Librium group in the pre-trial ratings, from the 1st day after drug administration on the Largactil group showed slightly less total disturbance than the other group and a steadier rate of improvement.

Figure XIV illustrates the findings of Figure XIIIin terms of statistically significant changes (Wilcoxon test).

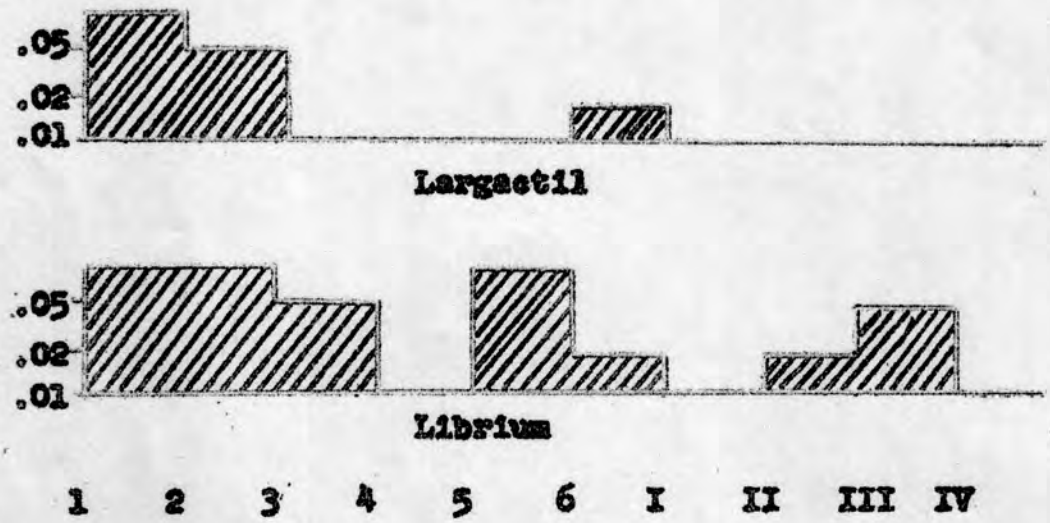

FIGURE XIV.

The bar-graphs at the extreme left represent the pre-trial pathology of the two experimental groups; the numbers 1 to 6 represent the first 6 days, and the Roman numerals I to IV the first 4 weeks of the trial period. Any lessening of the thickness of the bar at the extreme left indicates a statistically significant improvement in the group symptomatology. The more striking the change, the smaller the bar becomes; as indicated on the chart, a slight drop indicates a change of $P > .05$; a drop of over one-half a change of $P > .02$; and a drop to the baseline a change of $P > .01$ or better.

As can be seen from the diagram, the improvement after medication in the Largactil group was faster and much less erratic than in the Librium group, which showed some instability between the 5th and 7th days, and the 2nd and 3rd weeks.

Successive symptom profile changes indicated that Largactil had a faster and more consistent effect on hostility, suspiciousness and aggressivity than Librium; whereas Librium is more effective in reducing tremor and improving food and fluid intake.

Figures XV and XVI represent the successive mean symptomatology levels of the experimental groups divided into subgroups of high and low initial pathology.

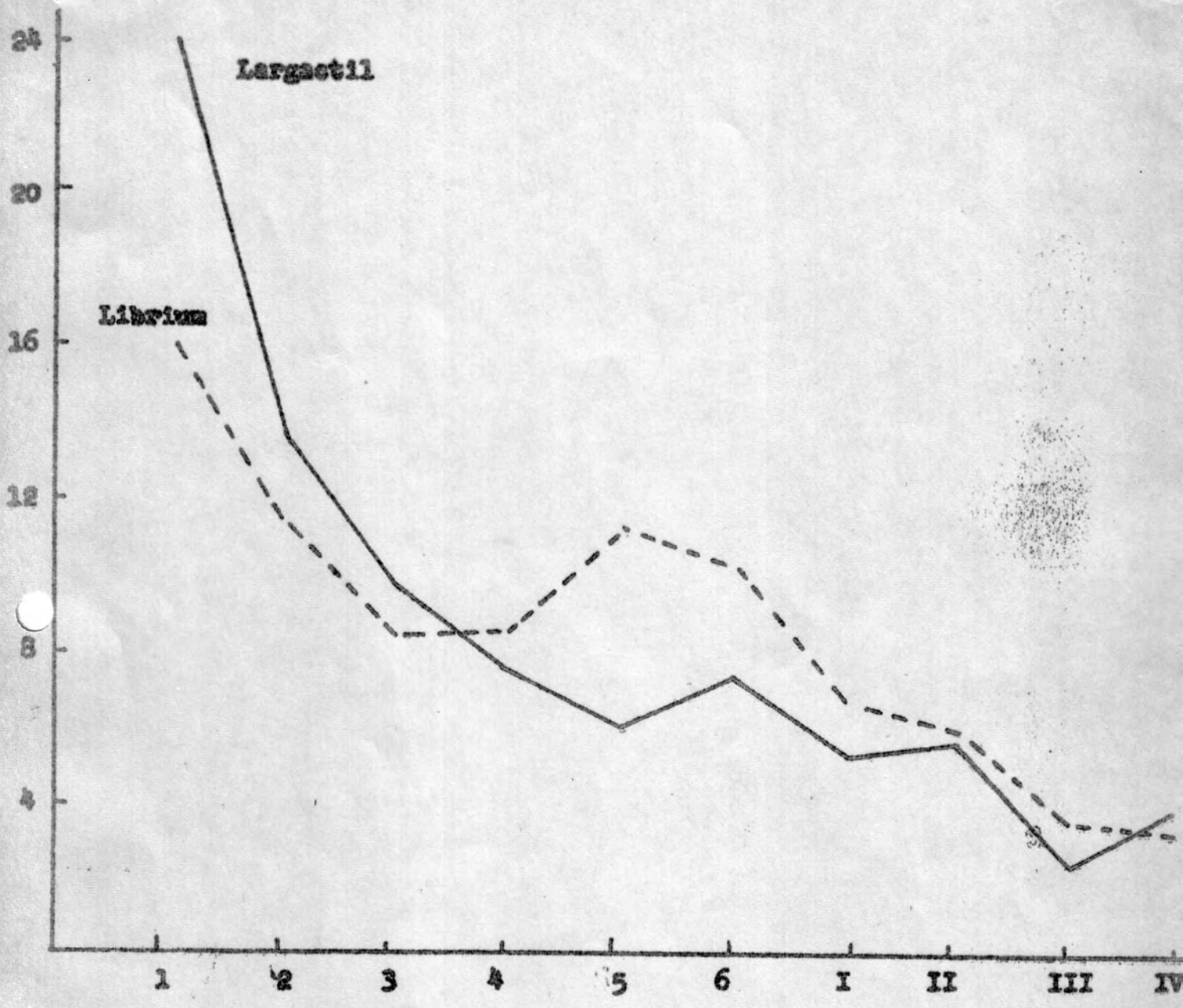

FIGURE XV.

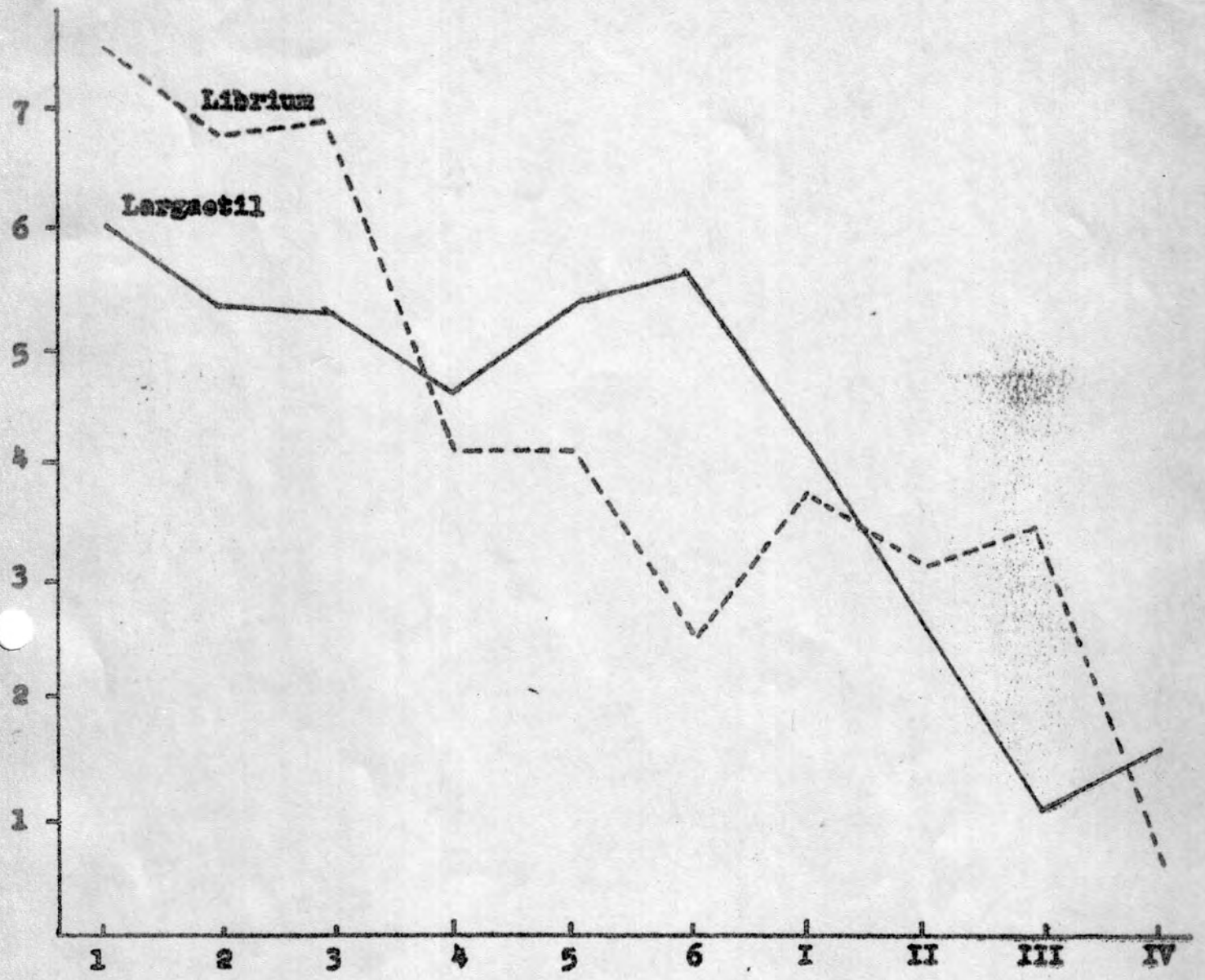

FIGURE XVI.

'High' and 'low' initial pathology was determined on the basis of falling above or below the group median initial rating of 12.

In Figure XV the two high pathology groups are represented. Here it can be seen quite clearly that Largactil acts faster and more consistently, whereas Librium's initial effect slackens between the third and 7th day after administration.

In Figure XVI the two low pathology groups are represented. In these cases Librium appears to have the more immediate effect, but reaches a plateau between the 1st and 3rd weeks during which

patients show little further change, until the 4th week when there is considerable further improvement. Largactil appeared to have almost no effect on these cases until the 6th day, but from then until the end of the trial its effect was steady and rapid.

Opinion: Both drugs effective. Largactil's action prompter and more consistent.

(Ban, T.A., Lehmann, H.E., Matthews, Valerie and Donald, M. Comparative Study of Chlorpromazine and Chlordiazepoxide in the Prevention and Treatment of Alcohol Withdrawal Symptoms. Psychiatry Digest. In Press.)

V. (b) The Comparative Effect of G-29088, Miltown, Librium and Sodium Luminal, on Anxiety.

A double-blind controlled clinical trial, following a latin square design, was carried out over a period of 10 weeks with 15 chronic female patients. The only criterion for selection of the sample for this study was the presence of anxiety in all these cases.

The following tests were conducted: laboratory (except transaminase); physical. The degree of anxiety was rated by one person all through this experiment on a 0 to 4 rating scale of which 0 indicated that the patient was free of anxiety, 1 indicated slight apprehension, 2 anxious tension, 3 moderate anxiety and 4 marked anxiety. As a control of this subjective rating, day-time and sleeping pulses were also obtained during the trial period.

The drugs were administered as follows: Miltown 1200 mgs., Librium 30 mgs., Sodium Luminal 135 mgs., G-29088 900 mgs. daily and an inactive placebo. Patients received no other medication during, and at least two weeks prior to the drug trial; no changes were made in their physical environment. By means of a cross-over design each patient received each medication for a 2-week period. The 15 patients were divided into 5 groups of 3 subjects each.

The results of the experiment indicated that:

1) Anxiety ratings were most markedly reduced by Librium and Luminal and not at all by G-29088.
2) Similarly, day-time pulses were slightly reduced by Librium and Luminal, whereas they were increased by G-29088.
3) Although changes in sleeping pulse rates were very slight, Miltown and Luminal brought about a greater reduction than Librium, and G-29088 had no effect.

4) There was no consistent pattern of change in the placebo group.

Opinion: Luminal, Librium and Miltown have anti-anxiety properties, while G-29088 has not.

(Lehmann, H.E. and Ban, T.A. Notes from the Log-Book of a Psychopharmacological Research Unit I. Canadian Psychiatric Association Journal. In Press.)

V. (c) The Comparative Effectiveness of Mellaril, Largactil and Stelazine on the Electrocardiogram.

This study followed a latin square design and was conducted with 6 psychiatric patients, over a period of 9 weeks. The criteria of selection in this study were a diagnosis of schizophrenia (chronic), and age ranging between 20 and 50 years. Patients had to be free from heart, kidney or liver disease, should not have received medication for a minimal period of 4 weeks before the trial, and they should not have been at any time on drugs with a known effect on the electrocardiogram. An additional criterion for selection was a normal electrocardiogram prior to the trial.

Each drug was administered in increasing dosages for a 16-day period, with a 2-week free interval prior to the commencement of the next medication. Each drug was used in four dosage levels and each increase in dosage took place after 4 days of drug administration. Dosages used in this study were as follows: Mellaril and Largactil 200, 400, 800 and 1200 mgs. daily, and in the case of Stelazine 8, 16, 32 and 64 mgs. daily, each administered in four equally divided dosages.

Prior to the trial, twice during each drug period (6th and 16th day) and before the commencement of the forthcoming medication an ECG was done, potassium and sodium levels of the blood were determined and at the time of interview blood pressure and pulse rate were checked to detect possible adverse reactions to the drug.

Results are presented in Table XXIII

Patient No.	Mellaril			Largactil			Stelazine		
	Days.								
	B	8th	16th	B	8th	16th	B	8th	16th
1	N	A	A	N	N	N	N	N	N
2	B	A	A	N	N	A	N	N	N
3	N	A	A	N	A	A	N	N	N
4	N	A	A	N	N	N	N	A	N
5	N	A	A	N	N	A	N	N	N
6	N	A	A	A	N	N	N	N	N

N-Normal ECG A-Abnormal ECG B-Borderline ECG.

Table XXXI

On the basis of these findings we have to assume that phenothiazines may have an effect on the human electrocardiogram and this effect resembles manifestations which are seen in hypokalemia. This particular effect was most pronounced with Mellaril, less so with Largactil and least with Stelazine. It is interesting to note that the same rank order applies to the hypnotic properties of the three compounds.

Opinion: A quinidine-like effect of Mellaril on the ECG was revealed.

V. (d) 1. <u>The Use of Complamin in Geriatric Patients.</u>

A double-blind, placebo-controlled study with 20 senile geriatric patients was conducted for a period of 8 weeks.

Evaluation of this study was based on clinical observations and a battery of tests: laboratory; physical; psychological (Critical Flicker Fusion Frequency, Tapping Speed, Counting Test, Ideational Recall, Digit Span, Paired Associates Learning, Word Association); the Verdun Target Symptom Rating Scale; the Verdun Side Effect Check List.

The experimental group was divided into 2 equal groups, 1 receiving Complamin and the other receiving an active placebo containing the same amount of nicotinic acid as the Complamin tablets. Patients on this study were kept on their former medication to which Complamin or placebo was added. Patients were receiving identical Complamin or placebo tablets in a dosage of 150 mgs. to 450 mgs., 3 times a day.

There was no remarkable change observed in any of the areas measured during the trial period. Only one of the phychophysical tests showed any change during the trial, i.e. Tapping Speed scores rose in the Complamin group but this change merely approached statistical significance ($p \geq .06$).

Opinion: Motor output increased: needs to be confirmed.
No clinical effects different from nicotinic acid.

V. (d) 11. The Effect of Surmontil on Geriatric Psychiatric Patients.

This 6-week study was conducted with 10 patients over 65 years of age, whose prominent symptoms were: inactivity, depression and apathy.

Evaluation was based on clinical observations and rating scales: laboratory; physical; the Verdun Target Symptom, Depression and Sociability Rating Scales.

The patients were continued on whatever previous medication they were receiving to which Surmontil was added in the dosage of 50 mgs. daily in two divided doses.

The data from three psychiatric rating scales were evaluated with two non-parametric tests of significance, the Wilcoxon and Sign tests. The following significant patterns were noted: the total symptomatology as rated on the Verdun Target Symptom Rating Scale tended to improve during the last 5 weeks of the trial period. Changes were slight, but more marked in the following symptoms: hostility lowered ($p \geq .03$), depression slightly alleviated ($p \geq .03$), attention less impaired ($p \geq .03$). From the 3rd week until the end of the trial the total target symptom rating showed a relatively consistent improvement over the pre-trial ratings ($p \geq .048$).

Changes on the Depression Rating Scale were slight and irregular but by the 7th week there had been a drop in the severity of the depressive symptoms, significant at the .02 level of confidence.

The most definite trends in the clinical data were found on those symptoms related to general interest, participation in conversation, and socialization. Improvement in the social behavior of the subjects, as judged by the total scores on the Sociability Rating Scale, began during the 3rd week, and was maintainted throughout the trial ($p \geq .028$).

No organ toxicity was observed in any patient. Among the clinical side effects, transient drowsiness was noted in 4 cases, and dry mouth in 3, accompanied in 1 by coated tongue and stuffed nose. Skin rash, itching and dyspnea occurred in the 1st week of drug administration and they were transient in nature. The dyspnea occurred in a patient with a cardiac condition at the end of the drug trial.

Our findings indicated that Surmontil may be safely used in the treatment of geriatric patients even in combination with other medication. The drug's beneficial effect was seen mainly in the improvement of the affective psychic parameter (depression, hostility, etc.) and in the arousal parameter on the attention function. Note should be made that in spite of the transient clinical side effects, no serious organ toxicity was revealed

and in no case was medication discontinued because of adverse effects.

Opinion: Safe and Effective antidepressant in geriatrics.

(Lehmann, H.E. and Ban, T.A. Notes from the Log-Book of a Psychopharmacological Research Unit II. Canadian Psychiatric Association Journal. In Press.)

V. (d) iii. The Effect of Valium on Geriatric Psychiatric Patients.

This 6-week study was conducted with 10 geriatric patients whose prominent symptoms were inactivity, depression and/or apathy.

Evaluation was based on clinical observations and rating scales: laboratory; physical; the Verdun Target Symptom, Depression and Sociability Rating Scales.

The patients were continued on their previous medication and it was planned to add Valium in the dosage of 2 x 10 mgs. daily.

Due to the clinical side effects which occurred during the 1st week of the drug administration and the increasing severity of these side effects, Valium administration was discontinued in the 2nd week of the trial.

Clinical side effects occurred in 7 of the 10 patients as a syndrome of drowsiness, psychomotor retardation, excessive salivation, stuffy nose, coated tongue, unsteady gait and slurred speech. 2 patients became incontinent and in 9 patients urinary frequency increased. Extrapyramidal symptoms occurred in 3 cases. Other clinical side effects were mild hypotension, constipation, skin rash, puffy face and dyspnea each in 1 patient. No correlation was found between the different medications patients received and the clinical side effects which occurred.

Pre-trial and 1st week data from 4 rating scales were compared, and differences were tested for significance with the non-parametric Wilcoxon and Sign tests. The following patterns were revealed:

1. At the end of 1 week, ratings on the Sociability Rating Scale were significantly lowered ($p \geq .05$). Ratings on the Depression and Target Symptom Rating Scales followed no consistent over-all trend.
2. Of the 23 specific symptoms rated on the above 3 scales, 4 changed significantly, and 2 approached significance:

Object relations impaired	$p = .031$
Retardation increased	$p = .016$
Conversation reduced	$p = .031$
Socialization inhibited	$p = .031$
Social Adaptation impaired	$p = .062$
Expected Social Response impaired	$p = .062$

3. On the Side Effect Check List 2 items were significantly more frequent at the end of 1 week:

Drowsiness.....p=.05
Unsteady gait....p=.05

5 other items, slurred speech, retardation, stuffy nose, incontinence and anorexia changed considerably, but only in certain patients - too few to be tested for significance.

In conclusion, these ratings would suggest that Valium in this dosage with geriatric patients produces a syndrome of increased psychomotor inhibition and loss of contact with the social environment.

Opinion: Valium in this dosage should not be combined with other psychotropic medication in geriatrics.

V. (e) The Comparative Effectiveness of Desoxyn, Sodium Amytal and LSD-25 on Mutism.

This study was designed to explore the possible beneficial effect of 5 therapeutic procedures on psychiatric patients with varying diagnoses, all of whom presented the symptom of mutism. The 5 therapeutic procedures chosen were: 1. intravenous administration of Desoxyn (20 mgs.), 2. intravenous administration of Sodium Amytal (250 mgs.), 3. oral administration of LSD-25 (150 gamma), 4. fever therapy, and 5. one electroconvulsive treatment.

The study was conducted with 10 patients and followed a cross-over single-blind design. 6 of the patients fell within the broad diagnostic category of the schizophrenics, 3 were diagnosed as dementia paralytica and 1 as mentally deficient (imbecile with psychosis who had been able to speak before his illness).

2 patients responded to LSD-25 and 2 to E.C.T., 1 to each of Desoxyn and Sodium Amytal administration. On fever therapy all patients remained mute.

All patients responding to Desoxyn, Sodium Amytal or E.C.T. were schizophrenics, and 1 of the 2 patients who responded to E.C.T. also responded to the disinhibitory dose of Sodium Amytal. Only 1 of the 10 patients responded to more than 1 therapeutic procedure. While 3 of the 6 chronic mute schizophrenics began to speak temporarily in response to these procedures, none of them responded with speech to the administration of LSD-25. The 2 patients whose mutism was temporarily interrupted by LSD-25 were diagnosed as suffering from dementia paralytica.

Opinion: Mute schizophrenics may respond to Desoxyn, Sodium Amytal or E.C.T., while mute G.P.I.'s may respond to LSD-25.

(Lehmann, H.E. and Ban, T.A. Notes from the Log-Book of a Psychopharmacological Research Unit. Canadian Psychiatric Association Journal. In Press.)

V. (f) 1. The Comparative Effectiveness of Phenergan, Paraitan and Artane on Extrapyramidal Symptoms.

In a placebo-controlled comparative study Artane, Phenergan and Paraitan was administered to 30 male patients of varying diagnoses. The criterion for selection of patients for the experimental observations was formerly present extrapyramidal symptomatology controlled by Artane administration.

Evaluation was based on clinical observations and examinations: laboratory; physical. A psychiatric rating scale was completed including the items of general appearance, excitement, anxiety, depressive mood change, apathy, hallucinations, thought disturbance and delusions, in addition to a rating scale on extrapyramidal symptomatology (head, neck and extremities).

For at least one month prior to the drug trial all subjects received Artane as routine antiparkinsonian medication. Then the population was subdivided into 3 sub-groups each receiving 1 month trials of Phenergan (3 x 10 mgs. to 3 x 25 mgs.), Paraitan (3 x 25 mgs. to 3 x 50 mgs.) and an inactive placebo according to a Latin square design.

All medication used before and during the trial was more effective than placebo ($p = .005$, Wilcoxon test), in controlling extrapyramidal symptomatology of the population. It was under Phenergan that the ratings of the population were at their lowest, followed by Paraitan and Artane in this order. These differences, however, did not reach statistical significance.

Opinion: The order of potency of antiparkinsonian effect was Phenergan, Paraitan, Artane.

V. (f) 11. The Effects of Mellaril versus Sparine on Phenothiazine-Induced Behavioral Toxicity, in Particular on Depressive Mood, Psychotic Mannerisms and Extrapyramidal Symptoms.

A 4-week comparative cross-over study was conducted with 20 chronic schizophrenics.

The following tests were conducted: laboratory; physical. The effect of the compound was tested on 3 specific target symptoms: extrapyramidal symptoms, mannerisms and depression.

The drugs were administered consecutively; at first Mellaril in doses of 75 to 400 mgs. followed by Sparine in doses of 150 to 800 mgs. daily, each for a period of 2 weeks.

Of the 20 patients in this study, 85% had received a different phenothiazine medication immediately prior to the start of the trial and of these, 52% also required additional antiparkinsonian drugs. All the patients had presenteddepressive mood, psychotic mannerisms, or both, and in addition a high proportion showed extrapyramidal symptoms.

Of the 9 depressed patients, 6 became less depressed while on Mellaril. This improvement was not maintained on Sparine. Of the 13 patients presenting psychotic mannerisms, six improved while on Mellaril and a further 3 while on Sparine. 20% of the sample required antiparkinsonian medication while on Mellaril and 11% while on Sparine.

On the basis of our results it was concluded that Mellaril appears to be superior to Sparine in controlling phenothiazine-induced depression in schizophrenic patients. Both drugs appeared to be effective in controlling, i.e. preventing or reducing the incidence of psychotic mannerisms and extrapyramidal symptoms.

Opinion: Mellaril superior to Sparine in controlling phenothiazine-induced depression.

(Lehmann, H.E. and Ban, T.A. Notes from the Log-Book of a Psychopharmacological Research Unit I. Canadian Psychiatric Association Journal. In Press.)

V. (g) <u>The Phenothiazine Potentiating Effect of Arlidin.</u>

This 12-week study was carried out with 30 chronic psychiatric patients. The only criteria for selection was that the patients had to be on phenothiazine medication for a minimum of 6 months prior to the drug trial.

Evaluation was based on a battery of tests and examinations: laboratory; physical; Word Association, Conformity Index, Reaction Time, Tapping Speed; the Verdun Target Symptom and Depression Rating Scales.

Patients were divided into 2 groups and Arlidin in the dosage of 3 x 6 mgs. (1 tablet) to 3 x 18 mgs. (3 tablets) or an identical placebo was added to their medication.

In the active compound group, mood, appearance and thought disorder improved significantly at the .001 level of confidence. There was no consistent change in the inactive group.

No adverse effect of the combination of Arlidin with phenothiazines was revealed. (Additional information: it was demonstrated that Arlidin pretreatment potentiates the dextran-induced edema inhibiting properties of Hexinan, Tarasan and R-1625. A hypothetical correlation is assumed between the effect on dextran-induced edema of these drugs and their antipsychotic properties. Our study confirmed this correlation.)

Opinion: Arlidin potentiates the psychotropic effect of phenothiazine drugs.

(Lehmann, H.E., Ban, T.A., Kato, G., Gozzy, E. and Kato, L. Potentiation of the Pharmacological and Therapeutic Action of Phenothiazines by Hylidrin (Arlidin). Journal of Comprehensive Psychiatry. In Press.)

V. (h) First Study on the Psychotogenic Properties of Nardil in Schizophrenic Patients.

A clinical trial with 10 psychiatric patients was conducted over a period of 4 weeks. All patients selected for this study were schizophrenics belonging to different schizophrenic sub-categories and all but 1 were prior to and during the trial period on maintenance phenothiazine medication.

Evaluation was based on the following tests: laboratory; physical; the Verdun Target Symptom and Depression Rating Scales.

Nardil was administered 30 mgs. daily in 2 divided doses.

Of the 10 cases only 2 showed change in the areas included in the Verdun Target Symptom Rating Scale. (None on the Verdun Depression Rating Scale.)

Nardil had no beneficial effect, but 2 of the patients showed increasing psychiatric symptoms and the 1 who was not on phenothiazine drugs became so excited and hallucinated that the withdrawal of the drug was necessary.

V. (h) Second Study on the Psychotogenic Properties of Nardil in Schizophrenic Patients.

Nardil was administered to 10 hospitalized chronic schizophrenic patients for a period of 4 weeks.

Evaluation was based on the following tests: laboratory; physical; the Verdun Target Symptom and Depression Rating Scales.

Nardil was administered in a dosage of 30 mgs. daily, in 2 divided doses.

Assessment of the results distinguished between 4 groups of patients on the basis of [illegible] response to the drug. 5 patients showed no change, 2 patients showed no change in the test results but reported subjective pleasant experiences although in an irrational manner, 2 patients showed evidence of a rise in psychotic symptoms, becoming increasingly excitable and withdrawn simultaneously with increasing thought disorder and 1 patient showed decreasing depression without any other change.

Summary of Two Experiments with Nardil.

Increase of psychotic manifestations was revealed in both studies.

Opinion: The psychotogenic effect of Nardil is mild and is partly counteracted by antipsychotic medication.

V. (1) 1. Study on the Effect of Placidyl and Doriden.

The trial was carried out as a placebo-controlled, double-blind 6-day experiment with a cross-over design. The criteria used for selecting the sample group were willingness to cooperate in the experiment and the fact that they had not been receiving other medication.

The subjects were moved into two bedrooms, a large one containing 18 beds, and an adjacent room containing two beds. Patients were not permitted in the bedrooms or allowed to sleep during the day. Breakfast time was rearranged to allow them to sleep as long as they desired. In the evening they were asked to go to bed at 8:45 p.m. at which time the emotional tension level of each patient was recorded. A rating scale was devised for this purpose, ranging from 1 indicating no apparent tension to 4 indicating that the patient was highly agitated. At 9 p.m. medication was given without comment and thereafter a check was made every 15 minutes to ascertain if the patient was asleep. A patient was judged to be asleep if he did not turn or move when a flashlight was focused on him. Time elapsed from administration of medication until the patient fell asleep was measured, as was the frequency of getting up during the night. The time of each patient's awakening in the morning was recorded, and his activities during the subsequent morning hours noted and rated on a 4-point scale.

All three compounds, Placidyl (500 mgs.), Doriden (500 mgs.) and placebo were administered twice during the trial. In order to effect a cross-over design the patients were subdivided into two groups for drug administration.

Results are presented in Table XXIV

	Doriden	Placidyl	Placebo
Onset	3	1	2
Duration	2	1	3
Disturbance	2	3	1
After-effects	1	3	2

Table XXIV

Drug effects on sleep in ranking order and based on the means for the patients tested. 1: most effective. 5: least effective.

The results were subjected to statistical analysis (t-test). The differences between Doriden and placebo proved to be statistically non-significant. When Placidyl and Doriden were compared in regard to the onset of sleep, the results at the $p \geq .001$ level proved significant. This was also the case in the comparison of Placidyl and placebo, which showed significant results at the $.05 \geq p \geq .02$ level. None of the other findings reached statistical significance.

The main results as revealed in the table suggest that of the drugs tested, Placidyl, in the dosage chosen, was the more effective hypnotic. Subjects on this drug fell asleep faster and stayed asleep for a longer time than those on Doriden. There were no meaningful differences in the level of pre-sleep tension, frequency of waking at night or post-sleep activity in patients from either group. Placebo administration resulted in a distinctly inferior effect when compared with Placidyl. No after effects were observed with either of the active medications Owing to their lengthy hospitalization, it was suspected that these patients, in the event of subjective discomfort would frequently fail to communicate this or complain to the attendant staff. Thus in order to avoid possible concealment of side effects, a special 3-day study was conducted, similar to the original design, but this time patients were specifically questioned regarding side effects. The results of this study were negative, no side effects being found.

Opinion: Placidyl is a superior hypnotic to Doriden.

V. (1) 11. Study on the Effect of Somnos, Noqualon and Vesparax I and Vesparax II.

This trial was carried out with 24 patients over a period of 8 weeks.

The patients selected for this study were those who were found by the night-nurse to be still awake, half-an-hour after the time of going to bed, during the period of the drug trial. These patients received compulsory PRN medication with these drugs according to a predetermined administration schedule. The nurse then made a record of 1. time medication was given; 2. time the patient fell asleep; 3. approximate duration of sleep (in minutes); 4. the number of times he was up during the night.

The day nurse interviewed the patients who had received medication the following morning and rated them for 1. drowsiness; 2. slurring of speech; 3. impairment of activity level; 4. depression of mood. She also questioned each patient on 1. howlong it took to go to sleep; 2. how long he slept; and made notes of these self-evaluations of sleep.

The following dosages of the drugs were administered: Somnos 500 mgs., Noqualon 150 mgs., Vesparax I (hydroxyzine 50 mgs., secobarbital 150 mgs., butobarbital 50 mgs.), and Vesparax II (hydroxyzine 25 mgs., secobarbital 75 mgs., butobarbital 25 mgs.), placebo.

Results are presented in Table XXV.

	Somnos	Noctalon	Vesparax I	Vesparax II	Placebo
Onset	1	3.5	2	3.5	5
Duration	3	3	1	5	3
Disturbance	3	5	1	2	4
After-effects	3	1	5	2	4

Table XIV.

In Table XIV above drug effects on sleep are expressed in ranking order, and based on the means of the values in the 24 patients, i.e., 1: most effective. 5: least effective.

Vesparax I proved superior to the other drugs with regard to duration of sleep and number of times up during the night. It also produced the greatest number of after-effects. It came second to Somnos in speeding onset of sleep. Noctalon and Vesparax II were the slowest of the preparations to produce sleep. The patients on the latter two drugs were found to have fewer unpleasant after-effects than the other groups, and some of them remarked on a positive feeling of well-being the morning after medication. Onset of sleep was later with the placebo than with any of the active preparations; but duration of sleep was equal to that of the two groups of Somnos and Noctalon and longer than that of patients on Vesparax I.

These results indicate that Somnos in the dosages used was the most effective drug regarding onset of sleep, but was not so effective as a sleep-sustainer. Vesparax I was effective as a sleep-inducer and as a sleep-sustainer. In the dosages used inthis study, neither Noctalon nor Vesparax II were effective as sleep-inducers or sleep-sustainers, but both were followed, in a number of patients, by a feeling of well-being and relaxation the next morning.

Opinion: Somnos and Vesparax I are more potent hypnotics than Noctalon and Vesparax II.

V. (1) iii. Study on the Effect of Panectyl, Valnid, Doriden, Somnyl and Tarasan.

The experimental group consisted of 30 normal volunteers who had reported disturbances of their sleep habits. This trial was carried out for a period of 20 days and followed a single-blind, cross-over Latin square design.

Daily, following each h.s. drug administration, the subjects rated the following aspects of their sleep behavior in a 3-point scale:

Speed on onset of sleep (short to long).
Length of sleep (short to long).
Morning activity level (slight to marked hypoactivity).
Drowsiness in morning (slight to marked drowsiness).
Morning speech (slight to marked inhibition).
Morning mood (slight to marked depression).

Medication was administered in the following dosages: Panectyl 10 mgs., Valmid 500 mgs., Doriden 500 mgs., Somnyl 100 mgs. and Tarasan 50 mgs. Each of the 5 compounds was administered twice to each subject, at 10 day intervals.

Results are presented in Table XVI .

	Panectyl	Valmid	Doriden	Somnyl	Tarasan
Onset	4	2	5	1	3
Duration	2	5	3	4	1
After-effects	4	1	3	2	5

Table XXVI .

Table XXVII above shows drug effects on sleep expressed in ranking order and based on means of the values in the 30 volunteers: 1: most effective; 5: least effective.

It can be seen from the table that Valmid and Somnyl induced sleep most rapidly and sustained it for the shortest period of time, with the minimum of after-effects of the 5 drugs tested. Panectyl and Doriden were considerably slower to induce sleep but sustained it longer, with slightly greater after-effects than Valmid or Somnyl. Tarasan induced sleep faster than these two and sustained it longer; but produced worse pronounced after-effects than any of the other compounds.

These results indicate two drugs to be most effective as rapid sleep-inducers (Valmid and Somnyl) and one to be the best sleep-sustainer (Tarasan). Doriden and Panectyl are also sleep-sustainers but their action is more moderate, and they are also slower to induce sleep than Tarasan. All three sleep-sustainers produced greater after-effects than the sleep-inducers. It is interesting to note that the two drugs on the study that are not known to cause addiction, i.e. Panectyl and Tarasan, have the greatest after-effects.

Opinion: Valmid and Somnyl are potent sleep-inducers while Tarasan is a potent sleep-sustainer.

Summary of Three Hypnotic Studies.

Of the 9 compounds examined, Placidyl stands out as being very effective both as a sleep-inducer and a sleep-sustainer. As sleep-inducers Valmid, Somnyl and Somnos were very effective at the dosages used. As sleep-sustainers, Tarasan and Vesperax I

were most potent. In general, after-effects were more pronounced with the sleep-sustainers, than with the sleep-inducers.

(Lehmann, H.E., Ban, T.A., Matthews, Valerie, Donald, N.W. A Comparative Study of Thirteen (13) Hypnotic Drugs. Submitted for publication to the Canadian Medical Association Journal.)

V. (j) The Comparative Stimulating Effectiveness of Caffeine, Dexedrine and Ritalin.

A comparative 4-week clinical study was conducted on 45 chronic hospitalized schizophrenic patients.

Evaluation was based on the following tests: laboratory (except transaminase); physical; the Verdun Target Symptom Rating Scale; Verdun Side Effect Check List.

The dosage schedule of drug administration was from 400 to 1200 mgs. of Caffeine daily, from 10 to 30 mgs. daily for both Dexedrine and Ritalin, for the 4-week period.

We observed that all 3 drugs had a euphorizing effect. This effect was combined with an increase in motor activity, work performance and social behavior in the Ritalin group and with some improvement in social behavior in the Caffeine group. On the other hand, the euphoria and increased motor activity in the Dexedrine group were associated with an increase in thought disturbance, delusions, regressed social behavior, seclusiveness and an inclination to aggression.

Subjectively the patients experienced Caffeine and Ritalin effects as pleasant and Dexedrine as unpleasant when drugs were given for several weeks.

On the basis of these findings it would appear that while all three compounds had stimulating properties, therapeutically valuable psychological stimulation was effected both by Ritalin and Caffeine. Dexedrine appeared to produce more of a psychotogenic action.

Opinion: Ritalin and Caffeine are safe as stimulants in chronic psychotics.

(Lehmann, H.E. and Ban, T.A. Notes from the Log-Book of a Psychopharmacological Research Unit II. Canadian Psychiatric Association Journal. In Press.)

DISCUSSION.

In order to carry out a program such as the one described, a large number of psychiatric patients and trained personnel is required. The Verdun Protestant Hospital, where the greater part of this work was conducted, is a 1550-bed mental hospital with all the modern treatment facilities for acutely ill and chronically hospitalized patients. However, in the second year of our study we felt that our task could be better fulfilled if a larger selection of patients was available for the different projects. At that time we expanded our facilities to include a French-speaking hospital in the Province, having a population of 800 patients, an acute and chronic treatment center, and an out-patient department. This expansion in facilities and a larger population, greatly improved our research capacity.

In the course of this two-year period we adopted a scheme of drug evaluation that consisted of the five stages described in our progress report. On the basis of prior experience these stages were developed through the discovery that the division of patients on the basis of either the chronicity of their illness or their diagnostic category was inadequate only for the purposes of drug screening and drug evaluation. During the two-year experience as herein reported, we once again modified our scheme. In our new scheme we distinguish between methods and procedures used in drug screening as opposed to drug evaluation, and those used in drug evaluation and screening on chronic as opposed to acute psychiatric patients. Finally, we used a still different method and procedure in studying the effects of different drugs on specific target areas.

The number of patients varied in each of the different types of studies except for the human toxicity studies where the number of patients was standardized at five. On the basis of this two-year experience we are now using small groups, 15 to 20 patients, and large groups, 30 to 35 patients, in different studies. In the small group studies we follow a design in which intensive clinical observations are of the utmost importance and in which our Symptom Check List appears to be the most important tool. The large group studies follow a design in which rating scales are of particular importance and parametric (t-test, discriminant function, etc.) and non-parametric statistics are employed in evaluation.

Our small group studies are often uncontrolled while those with large groups are usually controlled.

In drug screening, patients are carefully selected from different diagnostic categories while in drug evaluation, emphasis is laid on diagnostic homogeneity.

Our studies with chronic patients follow a simultaneous design which means that all the patients included in these studies start and terminate their drug trial at the same time, while our studies with acute patients follow a successive design, meaning that patients are admitted to the project as they become available through admission to the hospital.

During the past two years several changes were made in our test procedures. While our physical testing procedures remained unchanged, our clinical laboratory testing procedure was extended to include transaminase (S.G.O.T. and S.G.P.T.) determinations.

The most frequently used rating scales of the past two years were the Verdun Target Symptom and Depression Rating Scales (neither of them standardized). We developed a brief Sociability Rating Scale, a Symptom Check List and extended the Target Symptom Rating Scale by 4 items (1. impairment in expected social response; 2. impairment of consciousness; 3. memory disturbance; 4. impairment in object relations). As our rating scales are not standardized, particular emphasis was laid on establishing inter-rater reliability among our raters. The findings of our special inter-rater reliability studies are presently being evaluated.

A 15-item psychological test battery was established which differentiates among schizophrenic, organic and normal profiles. In our later work we employed this battery in abbreviated form to measure drug-induced changes.

In our toxicity studies we were able to prove the toxic (parasympathicolytic effect) of one compound (AY-b2014) in high dosages, to screen out two non-toxic compounds (27937 Ba and 30803 Ba) and to reveal the possible toxic effect of MK-240 on the hemopoietic system.

In our early drug evaluations in chronic psychiatric patients we revealed the antipsychotic action of Serdinol and Majeptil, and the antidepressant action of MF-809 and MK-240. We were able to confirm the antidepressant properties of Nozinan and to establish the reserpine-like effect of Aldomet.

Our early drug evaluations with acute psychiatric patients revealed the ineffectiveness of Valium in newly admitted schizophrenics and the effectiveness of Taraxan, Largactil and R-1625 in the same group. We found G-35020 to be an antidepressant and Majeptil an anti-manic agent. Although we found definite antipsychotic properties in CI-383, we felt that its cardiac effect would have to be eliminated before further studies are conducted with it.

In our comparative studies we found R-1625, Largactil and Taraxan to be antipsychotic, in this order of potency, in newly admitted schizophrenics. Similarly McN-JR-2498, R-1625 and McN-JR-3345 were found to be antipsychotics, in this order of potency, in chronic hospitalised schizophrenics. The antidepressant properties on chronic schizophrenics of Tofranil, G-35020 and Ensidon, in that order of potency, were established.

In our special symptoms and target areas studies we found Largactil to be faster acting on alcohol withdrawal symptoms than Librium; G-29088 to be lacking anti-anxiety properties, while Miltown, Librium and sodium luminal had these properties;

Mellaril to have a reversible quinidine-like effect on the human electrocardiogram, Largactil to have the same property to a definitely lower degree, while Stelazine showed the lowest occurrence of this characteristic.

In our geriatric studies Surmontil proved to be safe and effective as an antidepressant; Valium's tonic (hypnotic) property appeared to be too strong; and Complamin appeared to be ineffective with the exception of increasing psychomotor output. In mutism we revealed that Desoxyn and sodium amytal but not LSD-25 may be beneficial if the mutism is associated with a schizophrenic process. Phenergan and Parsitan were found to be potent anti-Parkinsonian drugs and Arlidin was shown to potentiate the psychotropic properties of phenothiazines. In chronic schizophrenics Nardil and Dexedrine were found to be mildly psychotogenic.

On the basis of our and other investigator's experience, we have decided to extend the duration of our studies in the third year from 8 to 12 weeks.

List of Publications.

1. Ban, T.A., Ferguson, K., Lehmann, H.E.
The Effect of Clopenthixol on Chronic Psychiatric Patients.
American Journal of Psychiatry, 119:984-185, April 1963.

2. Ban, T.A. and Lehmann, H.E.
Clinical Trial with Demethylimipramine (G-35020), A New Antidepressive Compound.
C.M.A.J., 86:1031-1032, June 2, 1962.

3. Ban, T.A., Lehmann, H.E., Matthews, Valerie, and Donald, M.
Comparative Study of Chlorpromazine and Chlordiazepoxide in the Prevention and Treatment of Alcohol Withdrawal Symptoms.
Psychiatry Digest. In Press.

4. Ban, T.A., Papathomopoulos, E. and Schwarz, L.
Clinical Studies with Thioproperazine (Majeptil).
Comprehensive Psychiatry, 3:284-291, October 1962.

5. Ban, T.A. and Schwarz, L.
Systematic Studies with Levomepromazine (Nozinan).
Journal of Neuropsychiatry. In Press.

6. Lehmann, H.E. and Ban, T.A.
Notes from the Log-Book of a Psychopharmacological Research Unit I.
Canadian Psychiatric Association Journal. In Press.

7. Lehmann, H.E. and Ban, T.A.
Notes from the Log-Book of a Psychopharmacological Research Unit II.
Canadian Psychiatric Association Journal. In Press.

8. Lehmann, H.E., Ban, T.A., Kato, G., Gâsky, B. and Kato, L.
Potentiation of the Pharmacological and Therapeutic Action of Phenothiazine by Nylidrin (Arlidin).
Comprehensive Psychiatry. In Press.

9. Lehmann, H.E., Ban, T.A., Matthews, Valerie, Donald, M.W.
A Comparative Study of Thirteen (13) Hypnotic Drugs.
Submitted for publication to the Canadian Medical Association Journal.

10. St. Jean, A., Donald, M.W. and Ban, T.A.
Les Effets Psychophysiologiques de la Méthyldopa.
L'Union Médicale. In Press.

QPRA SYMPOSIA AND PUBLICATIONS

Activities in our Early Clinical Drug Evaluation Unit program stimulated interest in clinical research with psychoactive drugs in the Province of Quebec, Canada, and were instrumental to the founding of the Quebec Psychopharmacological Research Association (QPRA).

The chain of events that led to the founding of the QPRA began in the summer of 1963, when about 20 people, involved in research in psychopharmacology in the Province met in the Medical Library of the Verdun Protestant Hospital (VPH), to discuss possible collaboration in clinical investigations. It was in the course of this meeting that Ban proposed the founding of an association that was to become the Quebec Psychopharmacological Research Association (QPRA). Three month later, in October the same year, the same group met again at the same place, and founded the QPRA: Heinz Lehmann, at the time clinical director of VPH, was elected president, and Ban, at the time chief of the clinical research service at VPH, executive secretary. The primary objective of the Association was to improve standards in clinical psychopharmacological research by facilitating discussion and communication of research findings through symposia and colloquia (Ban, 2004).

The Butyrophenones in Psychiatry

The first QPRA symposium was held on January 10, 1964, at Hôpital des Laurentides, a psychiatric inpatient facility, in L'Annonciation, Quebec with nearly 100 participants. It was the first North American symposium dedicated to the butyrophenones, with special reference to haloperidol, a substance which in the early 1960s was already extensively used in the treatment of schizophrenia in Europe, but was still little known in North America. Five of the 12 presentations in the symposium were based on findings in our ECDEU program (Ban, 1964; Ban and Stonehill, 1964; Lehmann, Ban, Matthews and Garcia-Rill, 1964; St. Jean, Lidsky, Ban and Lehmann, 1964; Warnes, Lee and Ban, 1964). The proceedings of the symposium were published in 1964 with the title The Butyrophenones in Psychiatry (Lehmann and Ban, 1964).

Publication was supported by McNeil Pharmaceuticals, the Company that was to become haloperidol's Canadian distributor.

Trimipramine, a New Antidepressant

The second QPRA event was held on May 28, 1964 at Hôpital Sant-Jean-de-Dieu (now Hôpital-H Louis Lafontaine), a psychiatric inpatient Facility in Montreal. It was the first North American colloquium on trimipramine, a tricyclic dibenzazepine, in which imipramine's 5-[3-(dimethylamino) propyl]-10, 11-dihydro-5H-dibenz [b,f] azepine side chain was replaced by a 1-(3-dimethylamino-2-methylpropyl)-10,11-dihydro-5H-dibenz [b,f] azepine side chain. The drug was different also pharmacologically from the parent substance. At the time of our symposium, trimepramine was already in use in France for depression, but the information discussed at the colloquium was based on the first studies with the drug in North America. Four of the 13 presentations in the colloquium were based on findings in our ECDEU program (Ban, 1964; St.Jean, Ban and Noe, 1964; Erutku, Ban and Lehmann, 1964; Lehmann, Kral, Ban, Ast, Barriga and Lidsky, 1964). The proceedings of the colloquium were published by QPRA with the title Trimipramine a New Anti-Depressant (Lehmann, Berthiaume and Ban, 1964). Publication was supported by Rhône-Poulenc, the company that was to become trimipramine's Canadian distributor.

Toxicity and Adverse Reaction Studies

The next three meetings of the QPRA were dedicated to toxicity studies and adverse reactions with psychotropic drugs. The first of these meetings was held on March 25, 1965, at the Allan Memorial Institute of Psychiatry, the primary teaching facility of McGill. It was devoted to the toxicity studies required for the registration of psychoactive drugs in Canada. The second meeting was held on April 3, 1965 at the Douglas Hospital (formerly VPH). It dealt with skin pigmentation with chlorpromazine, encountered in Canada, primarily in the Provincial Mental Hospital in Essondale (British Columbia) and in our hospital (Ban and Lehmann, 1965). The third meeting was held on June 4, 1965, at Hôpital des Laurentides. It was the first meeting at which electrocardiographic changes with psychoactive drugs were reviewed and cardiac conductance changes induced by thioridazine were discussed (Ban and St.Jean, 1965). The proceedings of these three meetings were published in one volume by QPRA with the title

Toxicity and Adverse Reaction Studies with Neuroleptics and Antidepressants (Lehmann and Ban, 1965).

The Thioxanthenes

A fourth meeting of the QPRA, the proceedings of which was published, was held on June 21, 1967 at the Douglas Hospital. It was the first North American symposium on the thioxanthenes at which findings with chlorprothixene and clopenthixol, substances developed in Europe, and thiothixene a substance developed in North America, were presented and discussed. In addition to investigators from the Province, investigators from several Early Clinical Drug Evaluation Units, including Max Fink, Barbara Fish, Don Gallant, Burt Goldstein, Sid Merlis, Burt Schiele, George Simpson and Art Sugerman, participated in the meeting. We reviewed our findings in a series of studies with chlorprothixene, clopenthixol and thiothixene, in one paper (Lehmann and Ban, 1969b). It included also findings from studies with thiothixene, which were conducted later than the period covered in our 1961-1963 Progress Report (Lehmann and Ban, 1969a). The proceedings of the symposium were published by S. Karger AG Basel (Switzerland) in 1969 in their series, Modern Problems of Pharmacopsychiatry (Lehmann and Ban, 1969a).

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