Heinz E. Lehmann and Thomas A. Ban

Early Clinical Drug Evaluation Unit

ECDEU

Progress Report

1961-1963

CONTENT

BACKGROUND

Early Clinical Drug Evaluation Units

To help clinical investigators in their research of studying psychotropic drugs, the Psychopharmacology Service Center (PSC) of the US National Institute of Mental Health, was created in 1956. The objectives of the PSC were to support clinical and preclinical research with potentially psychotropic substances, act as an information and communication center for these drugs, and extend technical consultation to people working in psychopharmacology.

According to Dr Jonathan O. Cole, the founding director of PSC, "A great majority of clinical research on new psychotropic drugs has been carried out by investigators at public mental hospitals receiving small amounts of support from the pharmaceutical industry. This work has not been extensive and has resulted in most drugs being released by the United States Food and Drug Administration (FDA) for general clinical use with only a small number of uncontrolled studies with variable quality. The absence of well organized and well supported units carrying out early clinical drug studies may have contributed to the slowness with which new have been developed in recent years."

To facilitate the clinical development of psychotropic drugs, and to improve the quality of clinical investigation funds were provided via the PSC to clinical research units, to be referred to as Early Clinical Drug Evaluation Units (ECDEU), in which drugs with psychotropic potential, on the basis of preclinical findings could be investigated before their approval for general use by the FDA. Thus, the ECDEU program involved government funding of research units around the country primarily to do Phase II and Phase III clinical trials with compounds. The units had essentially two functions: (1) to investigate new, potentially psychoactive drugs and (2) to advance "methodology" by devising more efficient ways of evaluating them. Federal research grants were given on a five-year renewal basis with considerable latitude afforded to the investigator as to the use of his/her funds and as to the compounds he/she wished to investigate.

Within one year of the announcement of the Program in 1960, there were 12 investigational units in operation. By the second annual meeting of the investigational units in January 1962, there were 15 units.

Our Early Clinical Drug Evaluation Unit at the Verdun Protestant Hospital (now Douglas Hospital), a psychiatric inpatient facility in the outskirts of Montreal (Quebec, Canada), was funded in November 1961. Our first Progress Report, submitted in December 1963, provides a detailed account of its operation, including the drugs employed and the assessment instruments used in their evaluation during its first two-years. A copy of the original report can be found in the ACNP-UCLA Archives at the Louise M. Darling Biomedical Library of the University of California, Los Angeles Campus.

December 1963.

COMPREHENSIVE CLINICAL STUDIES WITH PSYCHOACTIVE DRUGS. MH-05202-03.

Two-Year Studies with Psychoactive Drugs - ECDEU Progress Report (1).

by

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(1) This progress report covers the period of November 1961 through November 1963.

(2) From the Verdun Protestant Hospital, Verdun, Quebec, Canada.

LIST OF CONTENTS.

Page

III. EARLY DRUG EVALUATION IN ACUTE PSYCHIATRIC PATIENTS.

IV. COMPARATIVE STUDIES ON THE RELATIVE EFFECTIVENESS OF COMPOUNDS.

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

Page

SUMMARY.

Psychopharmacological drug evaluations were conducted with 61 compounds in 5 different stages.

Human toxicity studies revealed the toxic parasympathicolytic effect of AY-62014 in high dosages and the possible toxic effect of MK-240 on the hemopoietic system; 27937 Ba and 30803 Ba appeared to be free from major toxic effects in our screening.

Early drug evalpations in chronic psychiatric patients revealed the antipsychotic action of Sordinol and Majeptil; the anti-depressant action of MP-809 and MK-240; confirmed the anti-depressant properties of Noxinan; and established the reserpine-like effect of Aldomet.

Drug Evaluations with acute psychiatric patients revealed the ineffectiveness of Valium in schizophrenics; the effectiveness of Taraxan, Largactil, R-1625 in the same group; the anti-depressant action of G-35020; and the anti-manic properties of Majeptil in a manic group of patients. CI-383 was found to be antipsychotic in its action with an undesirable cardiac effect.

In comparative clinical studies R-1625, Largactil and Taraxan were found to have antipsychotic effects in this order of potency, in newly admitted schizophrenics; McN-JR-2498, R-1625 and McN-JR-3345 were found to show antipsychotic action in this order of potency in chronic schizophrenics.

In studies on special symptoms and target areas Largactil was found to be faster-acting on alcohol withdrawal symptoms than Librium; G-29088 seemedto be lacking anti-anxiety properties; Mellaril was demonstrated to produce a reversible quinidine-like effect on the human E.C.G. In our geriatric studies Surmontil proved to be safe and effective as an antidepressant; Valium's hypnotic property appeared to be strong; and Complamin increased psychomotor out put. Desoxyn and Sodium Amytal were beneficial in schizophrenic mutism. Phenergan and Parsitan were found to be potent anti-Parkinsonian drugs; A lidin potentiated the psychotropic properties of phenothiazines as predicted previously on the basis of a physiopathological model. In chronic schizophrenics Mardil and Dexedrine were found to be mildly psychotogenic and Ritalin was judged to be a less disturbing stimulant for chronic psychotics.

INTRODUCTION.

Since the beginning of modern pharmacotherapy there has been a steady increase in the number of chemicals synthesized for which psychotropic properties have been claimed. The primary aim of our research project has been to establish procedures which will 1) enable us to discriminate reliably between active and non-active compounds in the area of clinical psychiatry, and 2) reveal the particular area of therapeutic indications for the substance under investigation as well as its value in comparison with similar drugs. Our special task was to screen a number of chemicals for this purpose and this 2-yearly report gives an account of our evaluative work with 61 drugs (Table I).

Trade Name	Generic Name or Chemical Formula
1. Aldomet	methyldopa
2. Arlidin	perdilatal
3. Artane	trihexyphenidyl
4. AY-62014	10,11-dihydro-N,N,β,trimethyl-5H-dibenzo (a,d) cycloheptan-5-propylamine HCl
5. Caffeine	trimethylxanthine
6. CI-383	(4-(O-(propylthio)phenyl)1-piperazine-pentanol, monohydrochloride
7. CI-515	(3-phenoxypropyl) guanidine sulfate
8. Complamin	3-pyridine carbonic acid xanthine
9. Dexedrine	dextroamphetamine
10. Doriden	glutethimide
11. Desoxyn	methedrine
12. Elavil	amitryptiline
13. Ensidon	opipramol
14. Eutonyl	pargyline
15. G-29088	2-(1-hydroxycyclopentyl)-3-butyn-2-ol
16. G-35020	desmethylimipramine
17. LA XIV	benzodiazepine derivative
18. LA XVII	7-bromo-1,3-dihydro-5-(2 pyridyl)-2H-1,4-benzodiazepine-2-1.
19. Largactil	chlorpromazine
20. Librium	chlordiazepoxide
21. LSD-25	lysergic acid diethylamide
22. Majeptil	thioproperazine
23. MeN-JR-2498	triperidol
24. MeN-JR-3345	floropipamide
25. Mellaril	thioridazine
26. Mequelon	methaqualone hydrochloride
27. Miltown	meprobamate
28. MK-240	protriptyline
29. MO-1255	ethyl-N-benzo-N-cyclopropylcarbonate
30. MP-809	(4-methyl-α methyl tryptamine)
31. MRL-44	2-phenylcyclopentylamine
32. Nardil	phenelzine
33. Niacin	nicotinic acid
34. Nozinan	levomepromazine
35. Ospolot	sulthiame
36. Paneotyl	trimepazine
37. Parsitan	ethopropazine
38. Permitil	fluphenazine
39. Phenergan	promethazine
40. Placidyl	ethchlorvynol

Trade Name	Generic Name or Chemical Formula
41. Quantril	benzquinamide
42. R-1625	haloperidol
43. Ritalin	methyl-phenidate
44. R.P. 8909	3-cyano-10-(3-(4-hydroxypiperidino)-propyl)-phenothiazine
45. Sodium Amytal	amobarbital
46. Sodium Luminal	phenobarbital
47. Somnos	chloral hydrate
48. Soneryl	butyl-ethyl-malonylurea
49. Sordinol	clopenthixol
50. Sparine	promazine
51. Stelazine	trifluoperazine
52. Surmontil	trimepropamine
53. Tarasan	chlorprothixine
54. Tofranil	imipramine
55. UK-738	ethybenzatropin
56. Valium	diazepam
57. Valmid	ethinamate
58. Vesparax I	'formula 1' (atarax (hydroxyzine HCl) 50 mgs. secobarbital sodium 150 mgs. butabarbital sodium 50 mgs.)
59. Vesparax II	'formula 2' (atarax (hydroxyzine HCl) 25 mgs. secobarbital sodium 75 mgs. butabarbital sodium 25 mgs.)
60. 27937 Ba	9-diethylaminomethyl-9,10-dihydro-9,10 ethano-(1,2)-anthracen HCl
61. 30803 Ba	1-methylamino-(2,3) (5,6)-dibenzyl-(2,2,2)-bicyclooctane-HCl

Table I

Drug evaluation was conducted on different levels from early general toxicity studies following adequate animal investigation to highly discriminative studies on the effect of certain compounds in specific diagnostic categories and on specific symptoms.

Studies at the different stages were carried out as follows:

I. Human toxicity studies.
II. Early drug evaluation in chronic psychiatric patients.
III. Early drug evaluation in acute psychiatric patients.
IV. Comparative studies on the relative efficacy of compounds.
V. Studies on the effect of compounds on specific symptoms or target areas.
VI. Studies in progress.

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I. Human toxicity studies were carried out with 4 compounds (Table II).

Trade Name	Generic Name or Chemical Formula
1. AY-62014	10,11-dihydro-N,N,β, trimethyl-5H-dibenzo (a,d) cycloheptene-5-propylamine HCl
2. MK-240	protriptyline
3. 27937 Ba	9-diethylaminomethyl-9,10-dihydro-9,10 ethano-(1,2)-anthracen HCl
4. 30803 Ba	1 methylamino-(2,3) (5,6)-dibenzyl-(2,2,2)-bicyclooctane-HCl

Table II

II. Early drug evaluation in chronic psychiatric patients was carried out with 6 compounds (Table III).

Trade Name	Generic Name or Chemical Formula
1. Aldomet	methyldopa
2. Majeptil	thioproperazine
3. MK-240	protriptyline
4. MP-809	(4-methyl-α methyl tryptamine)
5. Nozinan	levomepromazine
6. Sordinol	clopenthixol

Table III

III. Early drug evaluation in acute psychiatric patients was carried out with 8 compounds (Table IV).

Trade Name	Generic Name or Chemical Formula
1. CI-383	(4-(O-(propylthio)phenyl)1-piperazine-pentanol, monohydrochloride.
2. G-35020	desmethylimipramine
3. Largactil	chlorpromazine
4. Majeptil	thioproperasine
5. R-1625	haloperidol
6. Surmontil	trimepropamine
7. Taractan	chlorprothixine
8. Valium	diazepam

Table IV

IV. Comparative work on the relative effectiveness of compounds was carried out with 9 drugs (Table V), in four studies (marked on Table V by the same letter of the alphabet).

Trade Name	Generic Name or Chemical Formula
1. Ensidon (a)	opipramol
2. G-35020 (a)	desmethylimipramine
3. Largactil (c)	chlorpromazine
4. McN-JR-2498 (d)	triperidol
5. McN-JR-3345 (d)	floropipamide
6. Permitil (b)	fluphenazine
7. R-1625 (b,c,d)	haloperidol
8. Taraxan (c)	chlorprothixine
9. Tofranil (a)	imipramine

Table V

V. Studies on the effect of compounds on specific symptoms or target areas were carried out with 32 compounds (Table VI). The effects of certain of these compounds on 10 specific symptoms (a) alcohol withdrawal symptoms, b) anxiety, c) cardiac function, d) geriatrics, e) mutism, f) extra-pyramidal symptoms, g) phenothiazine potentiation, h) psychotogenic property, i) sleep and j) stimulation) are shown on Tables VI (a) to VI (j) inclusive.

Trade Name	Generic Name or Chemical Formula
1. Arlidin	perdilatal
2. Artane	trihexyphenidyl
3. Caffeine	trimethylxanthine
4. Complamin	3-pyridine carbonic acid xanthine
5. Dexedrine	dextroamphetamine
6. Desoxyn	methedrine
7. Doriden	glutethimide
8. G-29088	2-(1-hydroxycyclopentyl)-3-butyn-2-ol
9. Largactil	chlorpromazine
10. Librium	chlordiazepoxide
11. LSD-25	lysergic acid diethylamide
12. Mellaril	thioridazine
13. Mequelon	methaqualone hydrochloride
14. Miltown	meprobamate
15. Nardil	phenelzine
16. Pamelyl	trimepazine
17. Parsitan	ethopropazine
18. Phenergan	promethazine
19. Placidyl	ethchlorvynol
20. Ritalin	methyl-phenidate
21. Sodium Amytal	amobarbital
22. Sodium Luminal	phenobarbital
23. Somnos	chloral hydrate
24. Soneryl	butyl-ethyl-malonylurea
25. Sparine	promazine

Trade Name	Generic Name or Chemical Formula
26. Stelazine	trifluoperazine
27. Surmontil	trimepropamine
28. Terasan	chlorprothixine
29. Valium	diazepam
30. Valmid	ethinamate
31. Vesparax I	'formula 1'
32. Vesparax II	'formula 2'

Table VI

ALCOHOL WITHDRAWAL SYMPTOMS

Trade Name	Generic Name or Chemical Formula
1. Largactil	chlorpromazine
2. Librium	chlordiazepoxide

Table VI (a)

ANXIETY

Trade Name	Generic Name or Chemical Formula
1. G-29088	2-(1-hydroxycyclopentyl)-3-butyn-2-ol
2. Librium	chlordiazepoxide
3. Miltown	meprobamate
4. Sodium Luminal	phenobarbital

Table VI (b)

CARDIAC FUNCTION

Trade Name	Generic Name or Chemical Formula
1. Largactil	chlorpromazine
2. Mellaril	thioridazine
3. Stelazine	trifluoperazine

Table VI (c)

GERIATRICS

Trade Name	Generic Name or Chemical Formula
1. Complamin	3-pyridine carbonic acid xanthine
2. Surmontil	trimepropamine
3. Valium	diazepam

Table VI (d)

MUTISM

Trade Name	Generic Name or Chemical Formula
1. Desoxyn	methedrine
2. LSD-25	lysergic acid diethylamide
3. Sodium Amytal	amobarbital

Table VI (e)

PHENOTHIAZINE-INDUCED EXTRAPYRAMIDAL SYMPTOMS.

Trade Name	Generic Name or Chemical Formula
1. Artane	trihexyphenidyl
2. Mellaril	thioridazine
3. Parsitan	ethopropazine
4. Phenergan	promethazine
5. Sparine	promazine

Table VI (f)

PHENOTHIAZINE POTENTIATION

Trade Name	Generic Name or Chemical Formula
1. Arlidin	perdilatal

Table VI (g)

PSYCHOTOGENIC PROPERTY

Trade Name	Generic Name or Chemical Formula
1. Nardil	phenelzine

Table VI (h)

SLEEP

Trade Name	Generic Name or Chemical Formula
1. Doriden	glutethimide
2. Mequelon	methaqualone hydrochloride
3. Paneetyl	trimepazine
4. Placidyl	ethchlorvynol
5. Somnos	chloral hydrate
6. Soneryl	butyl-ethyl-malonylurea
7. Taractan	chlorprothixine
8. Valmid	ethinamate
9. Vesparax I	'formula 1'
10. Vesparax II	'formula 2'

Table VI (i)

STIMULATION

Trade Name	Generic Name or Chemical Formula
1. Caffeine	trimethylxanthine
2. Dexedrine	dextroamphetamine
3. Ritalin	methyl-phenidate

Table VI (j)

VI. An investigation is now in progress on 18 compounds (Table VII) which includes 6 different types of studies (Tables VII (a) to VII (f) inclusive).

Trade Name	Generic Name or Chemical Formula
1. Aldomet	methyldopa
2. CI-515	(3-phenoxypropyl) guanidine sulfate
3. Elavil	amitryptiline
4. Eutonyl	pargyline
5. Largactil	chlorpromazine
6. LA XIV	benzodiazepine derivative
7. LA XVII	7-bromo-1,3-dihydro-5-(2 pyridyl)-2H-1,4-benzodiazepin-2-1
8. Librium	chlordiazepoxide
9. MO-1255	ethyl-N-benzo-N-cyclopropylcarbonate
10. MRL-44	2-phenylcyclopentylamine
11. Niacin	nicotinic acid
12. Ospolot	sulthiame
13. Parsitan	ethopropazine
14. Quantril	benzquinamide
15. R.P. 8909	3-cyano-10-(3-(4-hydroxypiperidino)-propyl)-phenothiazine
16. UK-738	ethybenzatropin
17. Valium	diazepam
18. 30803 Ba	1 methylamino-(2,3) (5,6)-dibenzyl-(2,2,2)-bicyclooctane-HCl

Table VII

Human Toxicity Studies.

Trade Name.	Generic Name or Chemical Formula
1. MRL-44	2-phenylcyclopentylamine
2. 30803 Ba	1 methylamino-(2,3) (5,6)-dibenzyl-(2,2,2)-bicyclooctane-HCl

Table VII (a)

Early Drug Evaluation in Chronic Psychiatric Patients.

Trade Name	Generic Name or Chemical Formula
1. Eutonyl	pargyline
2. Niacin	nicotinic acid
3. R.P. 8909	3-cyano-10-(3-(4-hydroxypiperidino)-propyl)-phenothiazine

Table VII (b)

Early Drug Evaluation in Acute Psychiatric Patients.

Trade Name	Generic Name or Chemical Formula
1. CI-515	(3-phenoxypropyl) guanidine sulfate
2. HO-1255	ethyl-N-benzo-N-cyclopropylcarbonate
3. R.P. 8909	3-cyano-10-(3-(4-hydroxypiperidino)-propyl)-phenothiazine

Table VII (c)

Comparative Studies on the Relative Efficacy of Compounds.

Trade Name	Generic Name or Chemical Formula
1. Largactil	chlorpromazine
2. LA XIV	benzodiazepine derivative
3. LA XVII	7-bromo-1,3-dihydro-5-(2-pyridyl)-2H-1,4-benzodiazepine-2-1
4. Librium	chlordiazepoxide
5. Quantril	benzquinamide

Table VII (d)

Studies on the Effects of Compounds on Specific Symptoms or Target Areas.

Trade Name	Generic Name or Chemical Formula
1. Aldomet	methyldopa
2. Ospolot	sulthiame
3. Parsitan	ethopropazine
4. UK-738	ethybenzatropin
5. Valium	diazepam

Table VII (e)

Studies on Combined Drug Administration.

Trade Name	Generic Name or Chemical Formula
1. Elavil	amitryptiline
2. Librium	chlordiazepoxide
3. R.P. 8909	3-cyano-10-(3-(4-hydroxypiperidino)-propyl)-phenothiazine

Table VII (f)

I. HUMAN TOXICITY STUDIES.

I. (1) Toxicity Study with AY-62014.

(Animal studies suggested an antidepressant effect of the substance).

This study was carried out over a period of 8 weeks with 5 patients from one of the chronic units of the hospital. Patients were selected on the basis of physical health, the chronicity of their illness, inadequate response to previous therapies, prevailing withdrawal, apathy and/or depressive mood change.

Evaluation was based on a battery of tests and examinations. The laboratory and physical tests are presented in Tables VIII and IX respectively. The Verdun Side Effect Check List (Table X), and the Verdun Psychiatric Target Symptom (Table XI) and Depression Rating Scales (Table XII) provided a further evaluation at regular intervals.

Medication was administered in increasing dosages from 50 mgs. daily in two divided doses in the first week, to 300 mgs. in four divided doses from the 7th week to the end of the trial period. Of the 5 patients only 3 completed the trial period. The other 2 patients had to be taken off medication in the last trial week. One of these latter developed paralytic ileus and bladder paralysis, with confusion and markedly increased diastolic blood pressure (150/120). No specific countermeasures were taken and with conservative treatment the patient recovered fully within a period of 2 weeks. The other patient had increased blood pressure, developed a cloudy state of consciousness, was unsteady on his feet and fell into unconsciousness for periods of 2 to 3 minutes. He fully recovered a week after discontinuation of medication.

There was some temporary decrease in the scores of the Depression Rating Scale in three of the patients, while more constantly in some of the cases agitation was increased.

Opinion: Toxic - parasympatholytic effect - in high dosage.

Verdun Laboratory Tests.

White Blood Cell Count
Hemoglobin Count
Alkaline Phosphatase
Transaminase (S.G.O.T. and S.G.P.T.)
Urinalysis

Table VIII

Verdun Physical Examination.

Blood Pressure
Pulse Rate
Respiration Rate
Temperature
Weight

Table IX

Verdun Side Effect Check List (0-1-2-3).

Week	1	2	3	4	5	6	7	8
1. Headache								
2. Vertigo								
3. Nausea								
4. Fainting								
5. Drowsiness								
6. Insomnia								
7. Conjunctival Inflammation								
8. Pupillary change								
9. Dry mouth								
10. Stuffy nose								
11. Tinnitus								
12. Masked facies								
13. Excessive salivation								
14. Coated tongue								
15. Vomiting								
16. Increase of appetite								
17. Anorexia								
18. Diarrhea								
19. Constipation								
20. Abdominal cramps								
21. Urinary retention								
22. Urinary frequency								
23. Incontinence								
24. Palpitation								
25. Edema								
26. Dyspnea								
27. Hyperactivity								
28. Unsteady gait								
29. Rigidity								
30. Spasticity								
31. Tremor								
32. Akathisia								
33. Dyskinesia								
34. Menstrual abnormality								
35. Seizures								

Week	1	2	3	4	5	6	7	8
36. Itching								
37. Skin rash								
38. Pallor								
39. Jaundice								
40. Other								

Table X

Verdun Target Symptom Rating Scale
(0-1-2-3)

Week	1	2	3	4	5	6	7	8
1. Excitement								
2. Suspiciousness								
3. Hostility								
4. Anxiety								
5. Depression								
6. Impairment in Object Relations								
7. Hallucinations								
8. Disturbance of Thinking								
9. Delusions								
10. Memory Disturbance								
11. Impairment of Consciousness								
12. Impairment of Expected Social Response								

Table XI

Verdun Depression Rating Scale
(0-1-2-3)

Week	1	2	3	4	5	6	7	8
1. Mood								
2. Facies								
3. Retardation								
4. Agitation								
5. Depressive Ideation								
6. Sleep without drugs								
7. Loss of Weight								

Table XII

I. (2) Toxicity Study with MK-240.

(Animal studies suggested an antidepressant effect of this substance.)

This study was carried out over a period of 6 weeks with 5 patients from one of our chronic units. Patients were selected on the basis of physical health, the chronicity of their illness, inadequate response to previous therapies, prevailing withdrawal, apathy and/or depressive mood change.

Evaluation was based on a battery of tests and examinations. In addition to our regular laboratory tests (Table VIII) (except transaminase, S.G.P.T.), thrombocyte count was done. Our usual physical examinations (Table IX) was done. The Verdun Side Effect Check List (Table X) and the Verdun Psychiatric Target Symptom (Table XI) and Depression Rating Scales (Table XII) were completed at regular intervals.

Medication was administered in a fixed dosage of 15 mgs. in three divided doses daily throughout the trial period.

Of the 5 patients selected for this study only 3 completed the total of the 6-week trial period. One schizophrenic patient became increasingly hallucinated, delusional, irritable, excited, unmanageable and physically aggressive. He had to be taken off the medication. Another left the hospital against advice during the 5th week of the trial. With the exception of 1 patient who developed leucopenia (2,750), no organ toxicity was revealed during this period. The only clinical side effects were loss of appetite and coated tongue. Some antidepressant effect was revealed on the Depression Rating Scale while at the same time the drug increased agitation.

Opinion: Leucopenia needs to be confirmed.

I. (3) First Toxicity Study with 27937 Ba.

(Animal studies had suggested an anti-aggression effect of this substance).

This study was carried out over a period of 28 days with 5 patients from a chronic unit of the hospital. Patients for this study were selected on the basis of physical health, chronicity of their illness, inadequate response to previous therapies and prevailing symptoms of aggression.

Evaluation was based on a battery of tests and examinations: laboratory; physical; the Verdun Side Effect Check List; and the Verdun Psychiatric Target Symptom Rating Scale, were regularly completed.

Medication was administered in accordance with a schedule of increasing dosage starting at 50 mgs. a day, reaching the maximum dosage of 300 mgs. a day (divided into three doses) on the 12th day.

This dosage was maintained until the 28th day when the drug trial was terminated.

No kidney, liver or blood toxicity was found in any of the patients during the trial period. Only one patient had to be taken off medication because of alternating arrhythmia and bradycardia. Besides this and some weight loss in 4 of the 5 patients no other physical side effects occurred. The Target Symptom Rating Scale revealed possible favourable effects of the drug in the area of arousal and mental integration.

I. (3) Second Toxicity Study with 27937 Ba.

The second study with this compound was also carried out for 28 days with 5 patients from one of the chronic units, using identical criteria for selection, laboratory and physical testing methods. In this case medication was initiated at 150 mgs. a day, reaching the maximum dose of 600 mgs. a day (divided into three doses) on the 12th day, and it was so maintained until the 28th day and termination of the trial period.

Beside some mild increase in alkaline phosphatase values, transaminase estimates and blood pressure, no other adverse effects occurred. None of the patients had to be taken off medication because of adverse effects. A beneficial result of the drug in the area of affectivity was suggested.

I. (3) Summary of Two Experiments with 27937 Ba.

On the basis of our two experiments, liver toxicity of this compound should be considered and would have to be validated by further experiments in higher dosages and/or longer trial periods. The psychoactive property of the drug in the lower dosage range seems to be in the area of arousal and mental integration while in the higher dosage the parameter of affectivity showed the strongest effects.

Opinion: Liver toxicity needs to be confirmed.

I. (4) First Toxicity Study with 30803 Ba.

(Animal studies had suggested an anti-aggression effect of the substance.)

This study was carried out over a period of 28 days with 5 chronic patients of the hospital. They were selected on the basis of physical health, chronicity of their illness, inadequate response to previous therapies and prevailing symptoms of aggression.

Evaluation was based on a battery of tests and examinations: physical; laboratory; the Verdun Side Effect Check List; and the Verdun Psychiatric Target Symptom Rating Scale, were regularly completed.

Medication was administered in accordance with a schedule of increasing dosage, starting at 10 mgs. a day and reaching the maximum dosage of 90 mgs. a day, divided into three doses, on the 19th day. This dosage was maintained until the 28th day and termination.

Some toxic effect on the hemopoietic system was indicated in 4 of the 5 cases. There was a tendency toward decrease of white blood cell count and hemoglobin values, but neither fell outside normal limits. During the trial period one patient died. No permission for autopsy could be obtained but the evidence did not suggest that the death was due to toxic effects of the drug. No psychotropic properties of the drug were observed.

I. (4) Second Toxicity Study with 30803 Ba.

This second study with the compound was carried out over the same 28-day period with five chronic cases. Selection and testing were as stated under I (4). A variant was the medication level which began at 30 mgs. a day, reaching a maximum of 120 mgs. a day (divided into three doses) on the 13th day and being there maintained until the 28th day and termination.

With the exception of a mild hypotensive effect, no other side effects occurred in this dosage range and again no psychoactive properties of the compound were revealed.

I. (4) Summary of Two Experiments with 30803 Ba.

Neither toxic effect nor psychoactive properties appeared in the dosage ranges used. (Additional information: in a single dose study conducted on 15 patients after the reporting period, 150 mgs. of the drug produced marked drowsiness.)

Opinion: No toxicity revealed.

II. EARLY DRUG EVALUATION IN CHRONIC PSYCHIATRIC PATIENTS.

II. (1) Early Drug Evaluation with Aldomet in Chronic Psychiatric Patients.

(Preclinical and early clinical studies suggested depressant properties of the compound.)

An uncontrolled clinical trial was carried out over a period of 4 weeks with 15 chronic hospitalized psychiatric patients, subdivided into the following 3 equal categories: A) hypertensive chronic schizophrenics; B) normotensive chronic schizophrenics; C) chronic depressions compensated with imipramine for several months before the trial. The schizophrenics received no other medication, but the depressed patients continued to receive their antidepressive medication during the 4-week trial.

Evaluation was based on clinical observations and a battery of tests and examinations: laboratory (Table VIII); physical (Table IX); the Verdun Psychiatric Target Symptom (Table XI) and Depression Rating Scales (Table XII).

Medication was administered in the amount of 1000 mgs. daily divided into 4 equal doses.

Results are presented in Figures I to III. Laboratory and physical examinations revealed no significant changes during the trial period. Weekly blood pressure readings indicated a significant drop ($p \geq .03$) in systolic blood pressure in all patients during the first 2 weeks (Figure I).

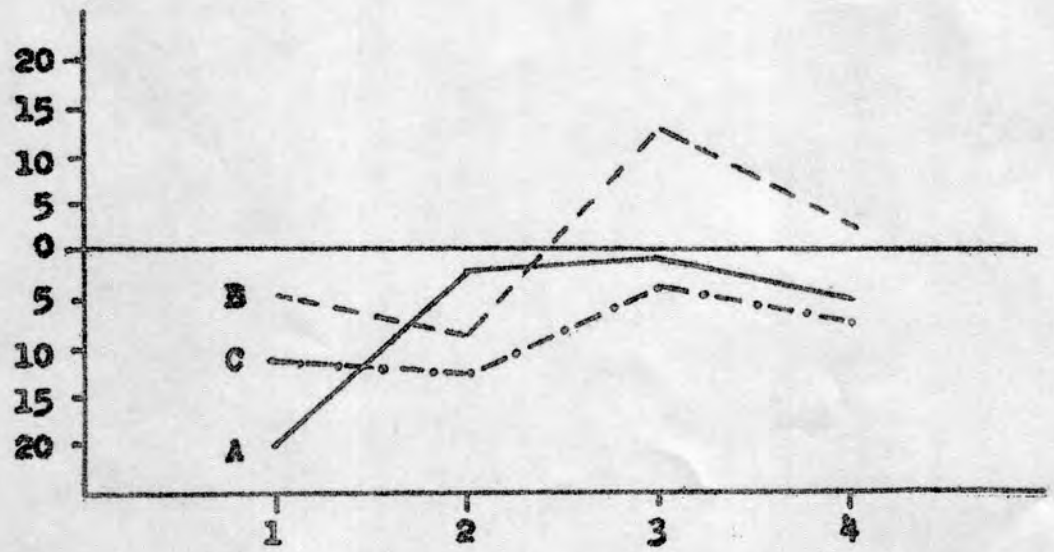


FIGURE I.

In groups A and C systolic pressure gradually regained its pre-trial level in the 3rd and 4th weeks, but 4 of the patients in group B showed a considerable rise in blood pressure (beyond the pre-trial level) during the 3rd week, before dropping approximately to the pre-trial level, indicating a possible paradoxical vaso-pressor effect. Diastolic pressure followed the same patterns as shown in Figure II.

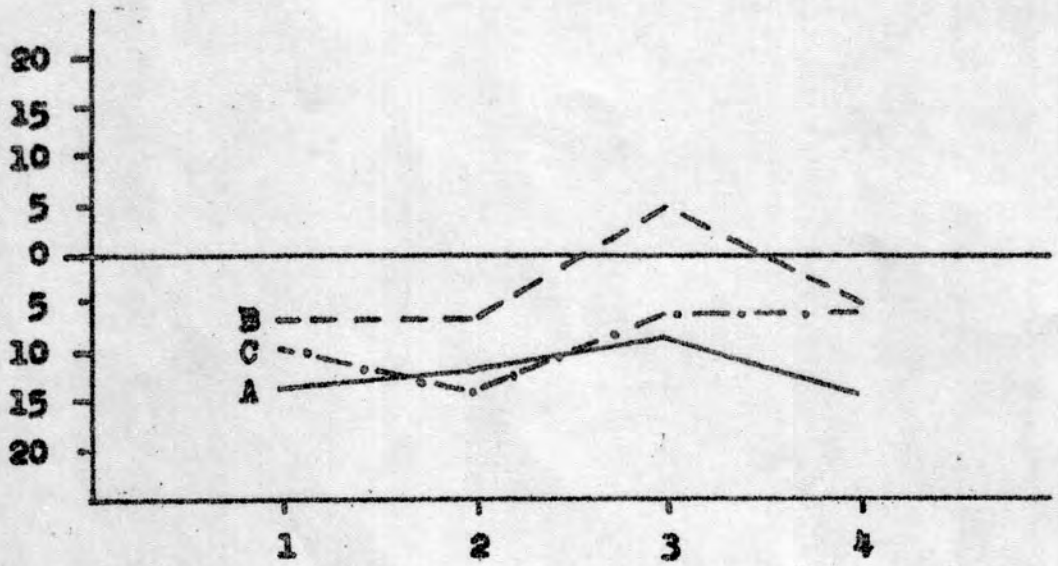


FIGURE II.

The symptomatology of the population as measured by the Verdun Target Symptom Rating Scale and the Verdun Depression Rating Scale showed the following trends: the level of general psycho-pathology of the population was lowered (Figure III) at the same time as depression became marked; an effect similar to that of Reserpine.

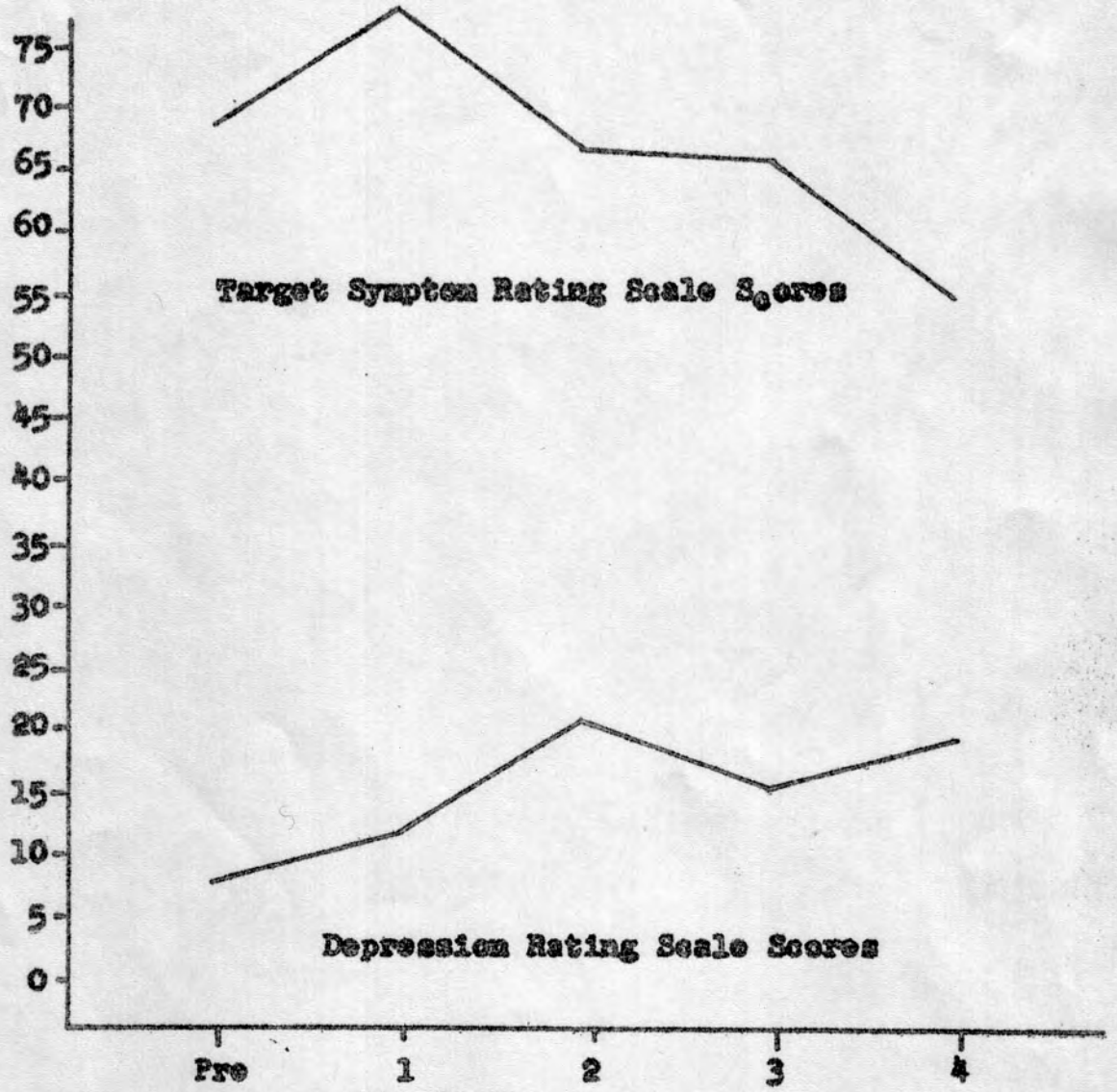


FIGURE III.

Opinion: Antipsychotic, may be anti-manic.

(St. Jean, A., Donald, M.W., and Ban, T.A. Les Effets Psycho-physiologiques de la Méthyldopa. L'Union Médicale. In Press.)

II. (2) Early Drug Evaluation with Majeptil in Chronic Psychiatric Patients.

(Pre-clinical and early clinical studies suggested psychotropic properties of this compound, not limited to any specific area).

An uncontrolled clinical trial was carried out over a period of 10 weeks with 45 male, chronic hospitalized psychiatric patients. They were selected on the basis of the chronicity of their illness, inadequate response to previous therapies and prevailing symptoms in the area of mental integration.

Evaluation was based on clinical observations and a battery of tests and examinations: physical; laboratory; the Verdun Side Effect Check List; and Target Symptom Rating Scale, were regularly completed.

Treatment customarily began with a dosage schedule of 3 mgs. daily, administered orally and divided into 3 doses, which was usually increased daily by 3 mgs. at first to 30 mgs., thereafter, depending on the individual's tolerance to higher doses ranging from 39 to 45 mgs. In a high proportion of patients (40%) it was found necessary to combine Majeptil therapy with anti-Parkinsonian drugs to counteract extrapyramidal symptoms. Medication was discontinued in only 1 case due to side effects.

Results were evaluated in percentage changes of the individual's score. As baseline, the pretrial score of the patient was used which had been obtained before commencement of therapy. A 75 to 100% reduction was considered equivalent to a remission, and classified as an 'excellent' result; a 50 to 75% reduction was rated a good improvement, and classified as 'good'; and a 25 to 50% reduction was considered equivalent to a partial or temporary improvement and classified as 'fair'. A reduction of the score below 25% was adjudged a 'failure' of the therapy.

The results obtained according to the Target Symptom Rating Scale are presented in Table XIII.

	No. of Patients	Excellent	Good	Fair	Failure
Schizophrenia, simple	6		2	1	3
Schizophrenia, hebephrenic	4			1	3
Schizophrenia, catatonic	11	1	1	3	6
Schizophrenia, paranoid	11		3	6	2
Schizophrenia, undifferentiated	4		2	2	
Miscellaneous	9		1	4	4
Total	45	1 (2.2%)	9 (20%)	17 (37.7%)	18 (40%)

Table XIII

Among the clinical side effects, extrapyramidal symptoms occurred in a high percentage of the cases, while one patient had a cerebral seizure and another vomited repeatedly during the trial period. Considering this and our findings it would appear that Majeptil has a value comparable to that of other phenothiazines in the treatment of this group of schizophrenics. (Additional information: our psychophysical studies with a single dose (10 mgs.) of Majeptil revealed that the drug dampens sensory input and motor output; these results being comparable to the effect of the other phenothiazine drugs.)

Opinion: Therapeutic in chronic schizophrenics.

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

II. (3) Early Drug Evaluation with MK-240 in Chronic Psychiatric Patients.

(Pre-clinical and early clinical studies suggested an antidepressant effect of this substance.)

This 6-week study was carried out with 15 of our chronic mental patients, selected on the basis of the chronicity of their illness, inadequate response to previous therapies, prevailing withdrawal, apathy, and/or depressive mood change.

Our procedure was based on clinical observations and a battery of tests and examinations: laboratory (except transaminase); physical; the Verdun Side Effect Check List; the Verdun Target Symptom and Depression Rating Scales were regularly completed.

Medication was administered in 15 mgs. daily in 3 divided doses.

The general impression gained by the ward staff during this trial was that patients on the drug appeared to be more active, less withdrawn, less depressed, but some were rather euphoric. The ward personnel was pleased with the effects of the drug in about 50% of the cases and enquired about the possibility of keeping these improved patients on the medication after termination of the trial. These changes were also expressed on the rating scales of the total group, with 8 presenting decreased scores on the Depression and Target Symptom Rating Scales. The remaining 7 were unchanged on the Depression Rating Scale while on the Target Symptom Scale, 5 remained unchanged and 2 became aggravated. The improvement was manifested on the two scales in the following areas: mood, facial expression, retardation, expected social response. The aggravation was due to an increase in excitement and anxiety.

5 of the 15 cases had to be taken off medication because of adverse effects. The first patient was taken off the drug trial shortly after the beginning of administration because of behavioral toxicity

(excitement, anxiety), the second after 22 days because of orthostatic hypotension, the third on the 30th day because of bradycardia, the fourth on the 32nd day because of behavioral toxicity (excitement, anxiety) and the fifth on the 35th day because of the occurrence of haemorrhagic urticaria.

Because of the occurrence of haemorrhagic urticaria, platelet counts were determined at the end of the 5th week on 10 of these patients. Only 1 showed a definitely normal value (280,000), 2 were borderline (191,000 and 189,000), and the 7 others were below 175,000, 1 of them having a value of 61,000. Platelet count determinations were completed again in 14 cases one week later which revealed one case in the normal range (250,000) 1 borderline (175,000), all the others below 175,000 and 3 below 100,000. (Additional information: human toxicity study conducted later with 5 patients did not confirm the thrombocytopenic effect.)

Opinion: Therapeutic in chronic depressions. Thrombocytopenia needs to be confirmed.

II. (4) Early Drug Evaluation with MP-809 in Chronic Psychiatric Patients.

(Pre-clinical and early clinical studies suggested antidepressant properties of this compound.)

An uncontrolled clinical trial was carried out over a period of 6 weeks with 15 patients selected from different chronic units of the hospital. Patients for this study were selected on the basis of the chronicity of their illness, depressive mood change, inadequate response to previous therapies, prevailing withdrawal and/or apathy.

In addition to our clinical observations, the following tests were conducted: laboratory; physical; and the usual testing by the Verdum Target Symptom and Depression Rating Scales.

Medication was administered from 15 to 60 mgs. daily in gradually increasing doses.

On the Depression Rating Scale improvement was seen in 4 of the 7 items in the following order: mood, facial expression, retardation and depressive ideation. The sum of the total score of the Depression Rating scale decreased in this experiment (mean: 4.93 to 3.64).

In analysis of the individual cases, of 15 patients, 10 (66.6%) improved, 1 showed no change and 4 became worse. Behavioral toxicity of the drug was mild and was manifested in these 4 cases in the increased scores on the Target Symptom Rating Scale, in symptoms of increased excitement and suspiciousness.

None of the 15 patients was taken off medication because of clinical side effects. No physical toxicity was observed. In 4 of the patients the antidepressant effect of the drug was thought by the ward personnel to be superior to previously applied treatment.

Opinion: Therapeutic in chronic depressions.

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

II. (5) Early Drug Evaluation with Nozinan in Chronic Psychiatric Patients.

(Pre-clinical and early clinical trials suggested anti-psychotic and antidepressant properties of this compound.)

An uncontrolled clinical trial was carried out over a period of 10 weeks with 20 patients from a chronic unit of the hospital. Patients were selected on the basis of chronicity of illness and having a depressive syndrome as their prominent clinical feature. The group was subdivided into the following categories: schizo-affective disorder 6; manic-depressive psychosis 4; involutional melancholia 5; neurotic depressive reaction 5.

Evaluation was based on clinical observations and a battery of tests and examinations: laboratory (except transaminase); physical; the Verdun Side Effect Check List and Depression Rating Scale were administered.

Treatment usually began with an oral dosage schedule of 15 mgs. daily in three divided doses, usually increased after a few days, at first to 30 mgs. daily and thereafter to higher doses ranging from 75 to 150 mgs.

As the baseline, the total score was taken of the Depression Rating Scale obtained before commencement of therapy. A 75 to 100% reduction of this score was considered equivalent to a remission, and classified as 'excellent'; a 50 to 75% reduction was rated a good improvement, and classified as 'good'; and a 25 to 50% reduction equivalent to a partial or temporary improvement, and classified as 'fair'. A reduction of the score of less than 25% was considered as 'failure' of therapy.

The results obtained according to the rating scale are seen in Table XIV.

	Excellent	Good	Fair	Failure	Total
Schizoaffective	1	4	1	0	6
Manic-Depressive	0	2	1	1	4
Involutional Melancholia	1	3	1	0	5
Neurotic Depressive Reaction	0	1	1	3	5
Total	2	10	4	4	20

Table XIV

Reduction of the score was observable in clinical assessment within 2 weeks of commencement of the therapy. The greatest improvement in our sample occurred between the 4th and 8th weeks. At the end of the 8th week, rating score was approximately the same as at the end of the drug trial.

A further breakdown according to diagnostic categories shows that the best results were observed in patients diagnosed as having schizoaffective disorders and involutional melancholia. There was no failure of therapy in these groups. Patients with a diagnosis of neurotic-depressive reaction responded less favorably and four-fifth of this group did not improve. (Additional information: our psychophysical studies with single doses (25 mgs.) of Mozinan revealed that the drug dampens sensory input and motor output, as is the case with other phenothiazine drugs.)

Opinion: Therapeutic in chronic depressions.

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

II. (6) Early Drug Evaluation with Sordinol in Chronic Psychiatric Patients.

(Pre-clinical and early clinical studies suggested antipsychotic effect of this substance.)

An uncontrolled clinical trial was carried out over 10 weeks with 20 chronic patients. They were selected on the basis of chronicity of their illness, inadequate response to previous therapies and prevailing symptoms in the area of mental integration.

Evaluation was based on clinical observations and on a battery of tests and examinations: laboratory (except transaminase); physical; psychological: Word Association Time (Table XV) and

Conformity Index (Table XVI) from the Verdun Projective Battery, and the Verdun Side Effect Check List and Symptomatological Check List (Table XVII) completed at regular intervals.

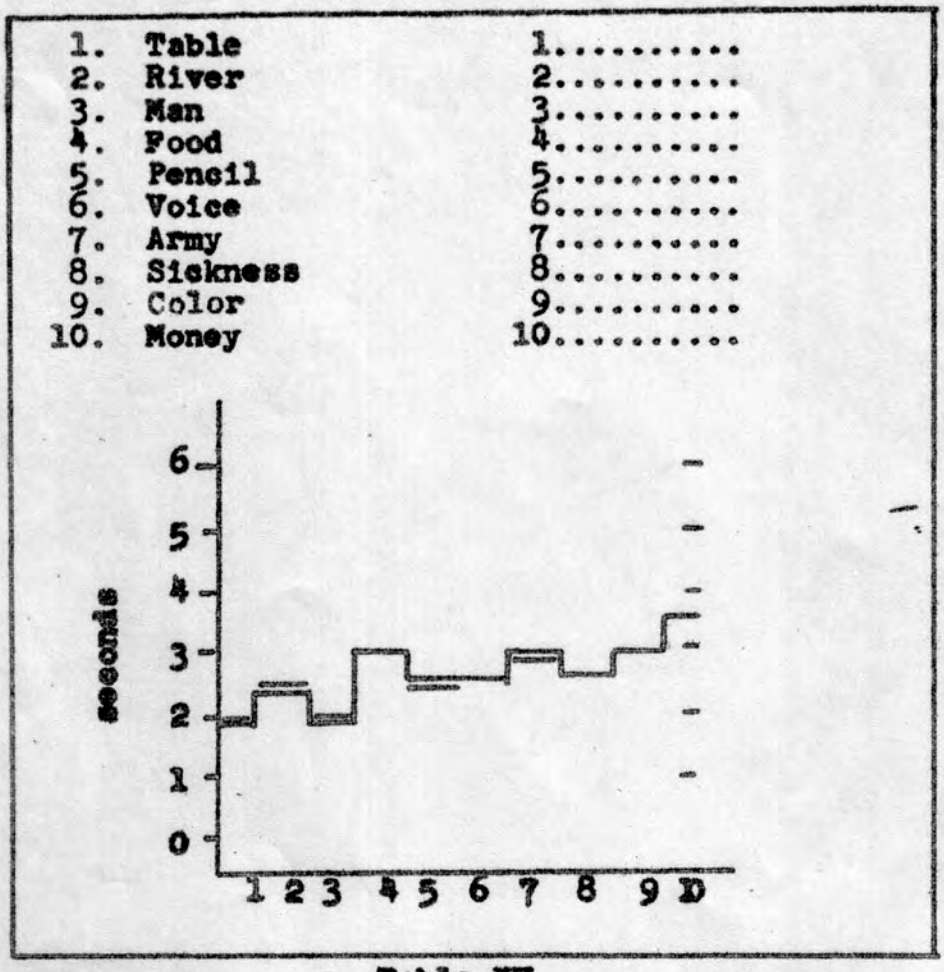


Table XV.

Association times below the single-line cut-off fall within the 80 percentile of the normal, below the double-line within the 90 percentile.

Man	(Woman)
Cabbage	(Vegetable)
Hard	(Soft)
Eagle	(Bird)
Ocean	(Sea)
Lamp	(Light)
Long	(Short)
Tobacco	(Smoke)
Scissors	(Cut)
Blossom	(Flower)

Table XVI

80% of normal controls give at least four of the "common" responses (in brackets) taken from the Kent-Rosanoff list.

SENSATION: hyperesthesia	hypoesthesia	anesthesia	paresthesia
PERCEPTION: illusions	pseudo hallucinations	hallucinations	body image disturbances
ASSOCIATION: homophonic	increased association time	decreased association time	
THINKING: blocking	decreased stream	increased stream	
concrete	symbolical	perseverative	obsessive
overvalued ideas	non systematized delusions	systematized delusions	megalo or micromanic delusions
persecutory delusions	autistic	dissociated	confused
JUDGEMENT: impaired personal	impaired non-personal		
INSIGHT:		partial	absent
EMOTIONAL: richness or poverty	ambivalence	incontinence	inappropriateness
suspiciousness	fear	anxiety	phobias
SENSITIVITY: loss of moral feelings	loss of esthetic feelings	loss of vital feelings	
MOOD: euphoric	apathetic	dysphoric	
AFFECT: fatigue	tension	aggressiveness	pathological impulse
INSTINCT: refusal of food	decreased food or fluid intake	increased food or fluid intake	specific deviation of appetite
impotency	increased libido	homosexuality	other sex deviations
self mutilation	suicidal tendencies		
MOTOR ACITIVITY: hypoactivity	hyperactivity	agitation	motor incoherence
amimia	hypomimia	hypermimia	gesticulation and grimacing
autistic excitement	stupor	negativism	flexibilitas cerea
stereotypy	mannerisms	loss of automatic coordination	loss of spontaneous activity
SPEECH: decreased speech	increased speech	logorrhea	incoherence
mutism	echolalia	alliteration	verbigeration
aphasia	paraphasia	neologism	confabulation
CONSCIOUSNESS: clouded	somnolence	sopor	coma
delirium	twilight	oneiroid	
ORIENTATION: completely disoriented	disoriented to time	disoriented to place	disoriented to person

ATTENTION:			
VIGILANCE: hypervigil	hypovigil		
TENACITY: hypertenax	hypotenax		
CONCENTRATION:		poor	absent
PERSONALITY: depersonali-sation	ego split		
INTELLIGENCE:	above average		below average
MEMORY: hypermnesia	paramnesia	amnesic syndrome	
total amnesia	partial amnesia	retrograd or anter-ograd amnesia	
impairmed memory for immediate past	for recent past	for remote past	
SLEEP: hypersomnia	hyposomnia	insomnia	somnus vigilans
somnoloquism	somnambulism	nightmares	enuresis
OTHERS:			

Table XVII

During the trial period 30 to 90 mgs. of Sordinol were administered daily in three equally divided doses.

Based on the daily notes and check lists the drug's principal effects were seen in the following areas: integration of mental activity, affectivity, arousal, behavior and social contact. In 9 patients improvement was manifested in mental integration as a reduction of disorders of thought and perception together with positive behavioral changes. There was better social contact. On the other hand, the activity (arousal parameter) of 3 patients decreased and 4 became depressed (affectivity parameter). Simultaneously a general improvement was noted in Word Association Time while the Conformity Index did not show any conclusive changes.

The following side effects occurred: paroxysmal tachycardia (1), dry mouth, skin and scalp (3), facial flushing (4), extrapyramidal symptoms (10), depressive mood change (4), transient drowsiness (14). Medication had to be discontinued in 1 case because of side effects (paroxysmal tachycardia). The majority of the extrapyramidal symptoms occurred in the 3rd week and were controlled with anti-Parkinsonian medication. Drowsiness was prominent at the beginning of the trial but diminished during the course of treatment, while dryness of skin and scalp increased as time passed.

Of the 20 cases, 9 showed clinical improvement (3 marked and 6 moderately), one became less controlled, 4 became more depressed and another 6 remained unchanged. Global impressions collected from the ward staff were in agreement with these findings.

The observation that this drug was therapeutically effective in certain chronic schizophrenic patients where previous treatments had failed suggests that Sordinol may deserve a place among the clinically used antipsychotic compounds.

Opinion: Therapeutic in chronic schizophrenics.

(Ban, T.A., Ferguson, K. Lehmann, H.E. The Effect of Clopenthixol on Chronic Psychiatric Patients.
American Journal of Psychiatry, 119:984-985, April 1963)

III. EARLY DRUG EVALUATION IN ACUTE PSYCHIATRIC PATIENTS.

III. (1) Early Drug Evaluation with CI-383 in Acute Psychiatric Patients.

(Pre-clinical and clinical studies with chronic psychiatric patients suggested antipsychotic properties of the drug.)

A clinical trial was carried out with CI-383 over a 10-week period with 16 newly-admitted schizophrenic patients.

The following baseline tests were conducted biweekly: laboratory (Table VIII); physical (Table IX); and the Verdun Target Symptom Rating Scale (Table XI) completed at weekly intervals.

Medication was administered in 100 to 300 mgs. dosage daily, divided in four doses.

In 5 of the 16 cases medication had to be discontinued during this period due to insufficient clinical improvement (2 were discontinued in the 5th week, 1 in the 6th, 1 in the 7th and 1 in the 8th week); in 4 cases medication was discontinued because of side effects, namely, repeated palpitations and tachycardia that started approximately 20 to 60 minutes after the drug was given and subsided spontaneously within 2 hours.

On the basis of findings on the Verdun Target Symptom Rating Scale the compound appeared to be most effective in controlling excitement and hallucinations and counteracting hostility. It is also effective but somewhat slower in ameliorating suspiciousness and anxiety. Its effect on disturbance of thinking increases with the increase in dosage and length of administration. In regard to depression, there was some amelioration of mood in patients with depressive features but it should be noted that depressive mood changes occurred also in a patient as a side effect (1 patient). A slight reduction in weight was noticed in patients after 4 weeks, this trend being maintained throughout the trial.

Opinion: Therapeutic in newly admitted schizophrenics; toxicity (cardiac) needs to be confirmed.

III. (2) Early Drug Evaluation with G-35020 in Acute Psychiatric Patients.

(Pre-clinical and clinical studies with chronic psychiatric patients suggested antidepressant properties of the compound.)

A clinical trial was carried out with G-35020, over a period of 10 weeks, with 25 newly admitted patients who presented a depressive syndrome as the principal or at least as a prominent clinical feature.

The following tests were conducted: laboratory; physical;. In addition the Verdun Depression Rating Scale was completed at daily intervals in the first week, three times in the second, two times in the third and weekly thereafter.

Treatment usually began at 75 mgs. daily in 3 equally divided doses. This was increased to 150 mgs. and if required to 225 mgs. Patients were kept on the least effective dosage until the end of the 10-week clinical trial. There were only 2 cases in whom medication had to be discontinued because of side effects.

Results were evaluated in percentage changes of the individual patient's score. The total score obtained before commencement of therapy was taken as a baseline. A 75 to 100% reduction of the score was classified as an 'excellent' result, a 50 to 75% reduction as 'good' and a 25 to 50% reduction as a 'fair' result of the therapy. Below a 25% reduction of the score, patients were considered as 'failures'. It was found that the evaluation by rating scale corresponded very closely with the clinical impression collected from the ward staff after termination of the trial.

The results obtained according to the rating scales and their distribution among the diagnostic categories are shown in Table XVIII.

	Excellent	Good	Fair	Failure
Manic-depressive	8	2	1	2
Involutional melancholia	3	2	1	1
Schizophrenia	1	1	1	1
Neurotic depressive reaction	1	0	0	0
Total	13	5	3	4

Table XVIII

A variety of side effects was encountered in about one-third of the patients. Insomnia was seen in four, hypomania occurred in 2 cases and dryness of mouth, sweating and mydriasis in 1 case each. 1 patient developed definite extrapyramidal symptoms. Our findings also revealed that it required 2 to 3 days for a response to show on the rating scale; that the peak effect was observed between the 2nd and 3rd week and that older and agitated patients required longer periods to respond than others; that within an 8-week period 75% of the patients treated with the drug recovered or were much improved. (Additional information: in a single dose (50 mgs.) psychophysical study, the drug evoked a slight reduction of psychomotor functioning.)

Opinion: Therapeutic in newly admitted depressed patients.

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

III. (3) Early Drug Evaluation with Largactil in Acute Psychiatric Patients.

(Pre-clinical and clinical studies with chronic psychiatric patients suggested antipsychotic properties of the compound).

A clinical trial was carried out with Largactil over a period of 6 weeks with 10 newly admitted schizophrenic patients.

The following tests were conducted: laboratory; physical. The patients were interviewed and assessed on three rating scales (Verdun Target Symptom, Depression and Sociability (Table XIX) Rating Scales).

	1	2	3	4	5	6	7	8
1. Interest in television or radio								
2. Interest in reading								
3. Participation in conversation								
4. Socialisation								
5. Social adaptation (at work or other)								

Table XIX.
(0-1-2-3)

Immediately after arrival and before receiving medication a short battery of psychophysical tests selected from the Verdun Psychophysical Battery (Table XX) (Reaction Time, Tapping Speed, Cancellation Time and Stroop Test) were administered.

1. Tapping Speed
2. Reaction Time
3. Stroop Test
4. Critical Flicker Fusion Frequency
5. Spiral After-Image
6. Trecktracer Time and Error
7. Time Production
8. Time Reproduction
9. Body Sway
10. After-Image Disappearance
11. Wechsler Memory Scale: Storytelling
12. Digits Forward and Backward
13. Paired Associates Learning
14. Word Association Test
15. Cancellation Test

Table XX

The physical measurements and ratings were done weekly during the 6-week trial period and laboratory and psychophysical tests were repeated after 3 weeks and again after 6 weeks.

In all cases Largactil was used freely in the dosage from 900 to 4000 mgs. daily.

The results of the weekly psychiatric ratings are shown in Figures IV and V. Figure IV presents the weekly mean ratings for each of the three rating scales employed.

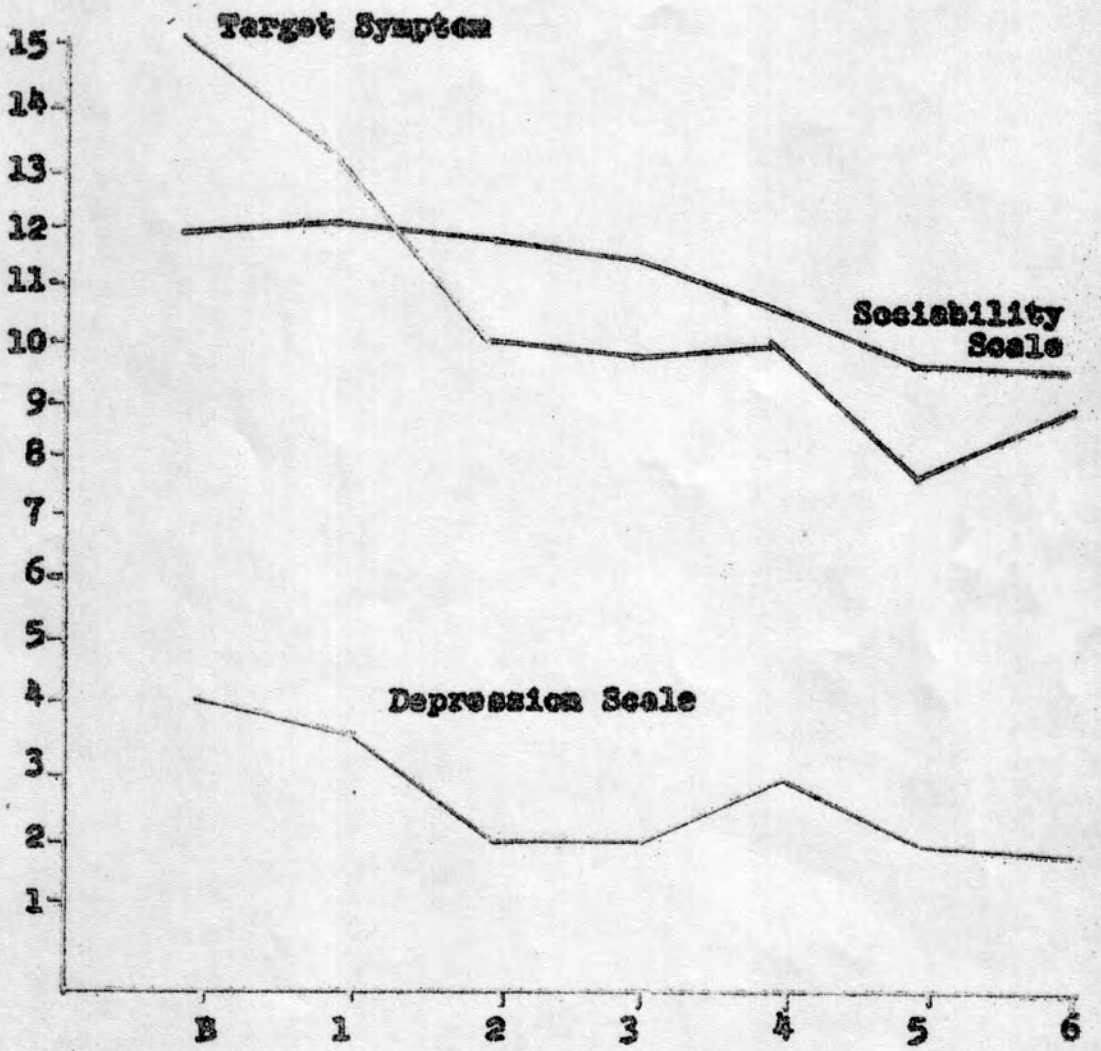


FIGURE IV.

Figure V presents the significance of these weekly changes (Wilcoxon and Sign tests).

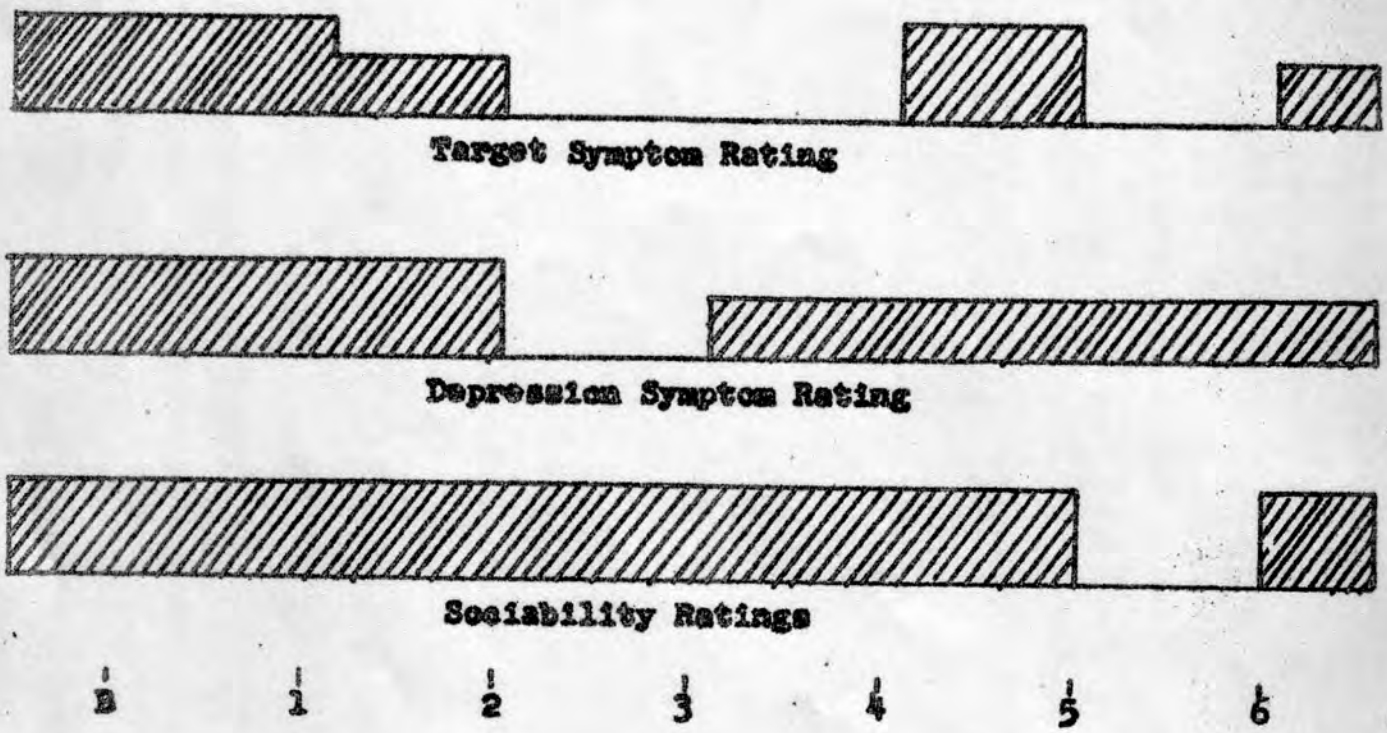


FIGURE V.

From Figure V it can be seen that all symptomatology was lowered during the six-week trial period. There was a significant drop ($p \geq .05$) in the score of the Target Symptom Rating Scale after the 1st week and this remained at a decreased level for the remainder of the trial with exception of the 5th week during which 3 patients had a brief relapse. Depression symptoms became significantly lowered ($p \geq .01$) by the second week and remained at the lower level ($p \geq .05$) until the end of the trial. In the 4th week 2 patients became considerably more depressed than they had been for most of the trial however 1 recovered completely and the other showed some improvement before the end of the trial. Sociability ratings showed few changes, but 6 patients showed some gradual improvement in this area so that the over-all drop became statistically significant ($p \geq .01$) in the 5th week.

Our findings further indicated that at the end of 2 weeks the symptom areas which had decreased the most were anxiety, depression, object relations, and expected social response; whereas those which had dropped the least were memory disturbance, hallucinations, thought disorder and delusions.

At the end of the 6-week period the most ameliorated symptoms were anxiety, object relations, suspiciousness, expected social response and excitement. The least were hallucinations, delusions, memory disturbance and impairment of consciousness.

7 of the 10 patients refused psychophysical testing in the pre-trial period; however all patients were cooperative after the 3rd and most after the 6th week. Because of these gaps in the pre-trial testing most of the statements that follow are based on a comparison of the 2nd and 3rd testings. From a population of 9 patients who were tested at least twice, the following trends were noted: the only consistent findings were a drop in reaction time which occurred in 7 of the 9 patients. Both of those whose reaction time slowed manifested a corresponding increase in total target symptomatology. Neither the Tracktracer, the Cancellation Test, nor the Stroop Test showed any consistent pattern, but it should be noted that 2 patients who did not improve clinically manifested this also in lengthened Cancellation and Tracktracer Times as well as in slower Reaction Time.

Drowsiness was the commonest side effect and occurred in 8 patients at some time during the trial. Vertigo was the next most frequent and occurred in 7 patients. Constipation was reported in 5 patients, headache in 4, dry mouth in 3, coated tongue in 3, tremors in 2, and unsteady gait in 2. In 1 case only there occurred itching of the skin, cerebral seizures, fainting attacks, nausea, vomiting, abdominal cramps, rigidity, insomnia and blurred vision. In no cases were the side effects or laboratory findings sufficiently severe to cause the drug to be withdrawn.

The first changed induced by Largactil came in the area of affect (anxiety and depression), followed by changes in the arousal parameter (excitement). During this 6-week study period symptoms denoting mental integration (delusions, hallucinations, thought disorder) showed little change.

Opinion: Therapeutic in newly admitted schizophrenics. (Symptoms of perceptual and thought disorder improve long after symptoms of excitement and affect have improved.)

III. (4) Early Drug Evaluation with Majeptil in Acute Psychiatric Patients.

(Pre-clinical and clinical studies with chronic psychiatric patients suggested psychotropic properties of the compound.)

Majeptil was administered to 5 newly admitted manic-depressive, manic patients for a period of 3 weeks.

Evaluation was based on clinical observations and a battery of tests and examinations: laboratory; physical; the Verdun Side Effect Check List and Target Symptom Rating Scale completed at regular intervals.

Majeptil was administered with a dosage schedule of 30 mgs. daily, in three divided doses. This dosage was maintained for a few days (3 to 5 days) until a hyperkinetic-hypertonic syndrome became prominent. Then the medication was withdrawn until the disappearance of marked extrapyramidal manifestations. 'Chemoshock' was repeated three times.

4 of the 5 patients showed excellent and 1 good results to Majeptil therapy. There was no failure in our small group. This prominent action of the drug in this diagnostic category suggests a special role for this compound in the treatment of manic patients.

Opinion: Therapeutic in newly admitted manics.

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

III. (5) Early Drug Evaluation with R-1625 in Acute Psychiatric Patients.

(Pre-clinical and clinical studies with chronic psychiatric patients suggested antipsychotic properties of the compound.)

A clinical trial was carried out over a 6-week period with 10 newly admitted schizophrenic patients.

Evaluation was based on a battery of tests and examinations: laboratory; physical. The patients were interviewed and assessed on three rating scales (The Verdun Target Symptom, Depression and Sociability Rating Scales). Immediately after arrival and before receiving medication they were administered a short battery of psychophysical tests selected from the Verdun Psychophysical Battery (Reaction Time, Tapping Speed, Cancellation Time and Stroop Test).

The physical measurements and ratings were done weekly during the 6-week trial period and laboratory and psychophysical tests were repeated after 3 and again after 6 weeks.

In all cases R-1625 was used freely in the dosage from 10 to 100 mgs. daily.

2 of the 10 patients were taken off R-1625 during the trial period, the first after 1 week because of side effects on taking 12 mgs. daily (nausea, vomiting, tremor) and the other was discharged from the hospital at the end of the fourth week at which time her score on all three scales was '0'. The global impression of the ward staff was that she had improved greatly.

On Figure VI the weekly significant changes (Sign test) of the three rating scales are presented.

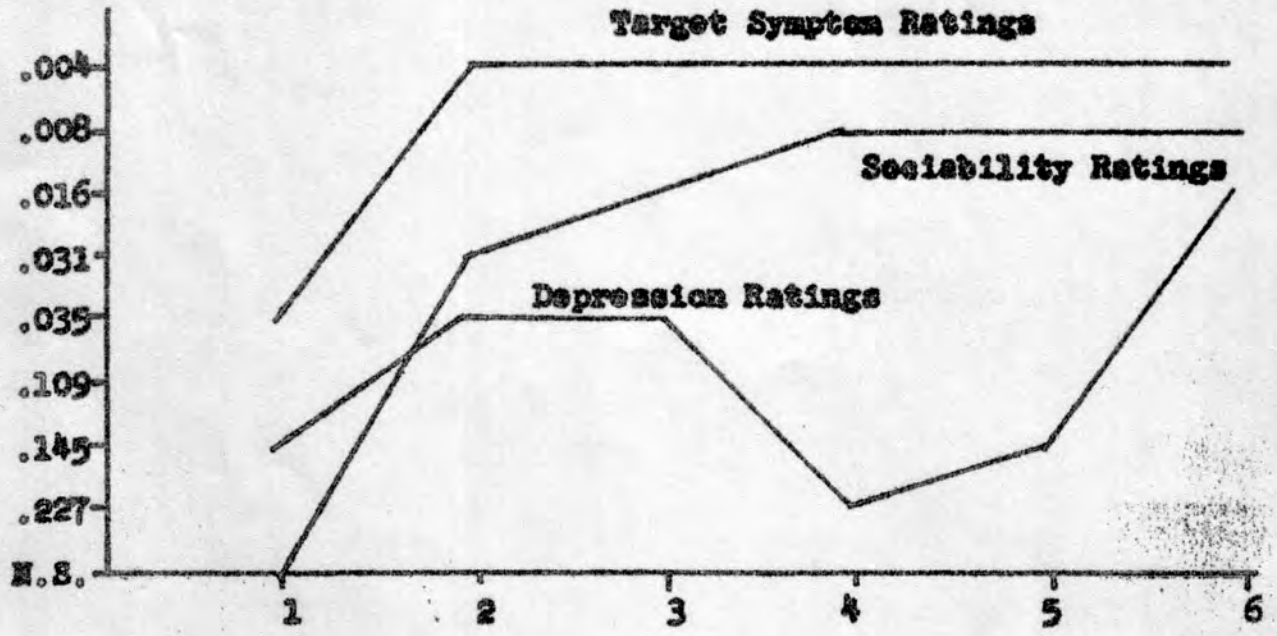


FIGURE VI.

This shows that on the Target Symptom Rating Scale there was significant improvement at the end of the 1st week ($p = .035$) becoming more expanded at the end of the 2nd week ($p = .004$) and continuing on this level of probability until the end of the trial. On the Depression Rating Scale there was significant improvement at the end of the second week ($p = .035$) and this became more marked in the 6th week ($p = .016$). On the Sociability Rating Scale there were significant changes at the end of the second week ($p = .031$) which became more pronounced at the end of the 4th week ($p = .008$) and remained so until the end of the trial.

The individual target symptom which showed the most marked changes at the end of the 2nd week was excitement ($p = .031$); at the end of the 6th week there was significant change in the following areas: hostility ($p = .008$), object relations ($p = .016$), social response, suspiciousness, anxiety, all at the $p = .031$ level of confidence. Among the psychophysical tests only the reaction time was significantly decreased in 6 patients at the end of the 6-week period. Other changes were inconsistent.

At the end of the trial all of the 8 patients were considered to have improved slightly, 4 moderately and 4 markedly.

The most common side effect was drowsiness which occurred in 6 patients. This was followed by constipation in 5 and tremors in 4. Nausea occurred in 2 and vomiting in 1 case and was sufficiently severe to cause the drug to be withdrawn. Other side effects included: dry mouth (3), stuffy nose (2), unsteady gait (2), and excessive salivation (2).

The order of changes induced by R-1625 was as follows: the first changes came in the area of arousal, followed by changes in the affective (anxiety and depression) parameter. During this 6-week study period symptoms referring to mental integration (delusions, hallucinations, thought disorder) showed little alteration.

Opinion: Therapeutic in newly admitted schizophrenics.

III. (6) Early Drug Evaluation with Surmontil in Acute Psychiatric Patients.

(Pre-clinical and clinical studies with chronic psychiatric patients suggested antidepressant effect of the compound.)

A clinical trial was carried out with Surmontil over an 8-week period with 20 newly-admitted depressed patients (manic-depressive, depressed 6; involutional melancholia 3; schizoaffective psychosis 3; neurotic depressive reaction 8).

Evaluation was based on a battery of tests and examinations: laboratory; physical; the Verdun Target Symptom and Depression Rating Scales, completed at regular intervals.

Medication was given in the dosage of 150 to 300 mgs. daily in three divided doses.

Of the 20 patients 8 did not complete the full trial period. 2 patients were discharged at an early date, 1 with good improvement and 1 against advice. Drug administration in 3 cases was discontinued because of insufficient effect after 3 weeks, and in 2 cases because of adverse effect, in 1 patient because of toxic confusional state and in another because of hypote

Findings on the two rating scales were tested for signifance with two non-parametric tests (the Sign and Wilcoxon tests). on the Verdun Target Sym tom Rating Scale changes in the total symptomatology of the population were significant at the .01 level of confidence from the 1st week after medication until the end of the drug trial. Although the drug was effective within a week the gross quantitative drop in symptomatology took place between the 2nd and 4th week of drug administration. Five specific target symptoms showed improvement during the trial: depression and thought disturbance were reduced from the 2nd week (both at the .01 level of confidence), anxiety and suspiciousness from the 3rd week (the first at the .01 and the second at the .02 level of confidence). Excitement was reduced

from the 4th week (.05 level of confidence). On the Verdun Depression Rating Scale changes in the total symptomatology were significant, (at the .01 level of confidence) a week after medication until the end of the trial. The specific depression scale items showed improvement as follows: mood, facial expression, retardation improved significantly from the first week (the first 2 on the .01 and the third at the .02 level of confidence). Depressive ideation was reduced and sleep improved from the 2nd week (both at the .01 level of confidence). 9 patients gained weight (mean gain 9 pounds during the trial period). The most frequent side effect was tremor (5), dry mouth (4), blurred vision (4), drowsiness (3), palpitations (3) and headache (3). All other clinical side effects occurred in 1 patient: toxic confusional state, hypotension, skin rash, dizziness, tension.

Further analysis of our findings indicated that the drug is most effective in the treatment of involutional depressions, somewhat less effective in manic depressive and reactive depressions and least effective in schizoaffective depressions.

Opinion: Therapeutic in newly admitted depressed patients.

III. (7) Early Drug Evaluation with Tarasan in Acute Psychiatric Patients.

(Pre-clinical and clinical studies with chronic psychiatric patients suggested antipsychotic properties of the compound.)

A clinical trial was carried out with Tarasan over a 6-week period with 10 newly admitted schizophrenic patients.

Evaluation was based on a battery of tests and examinations: laboratory; physical. The patients were interviewed and assessed on three rating scales (the Verdun Target Symptom, Depression and Sociability Rating Scales).

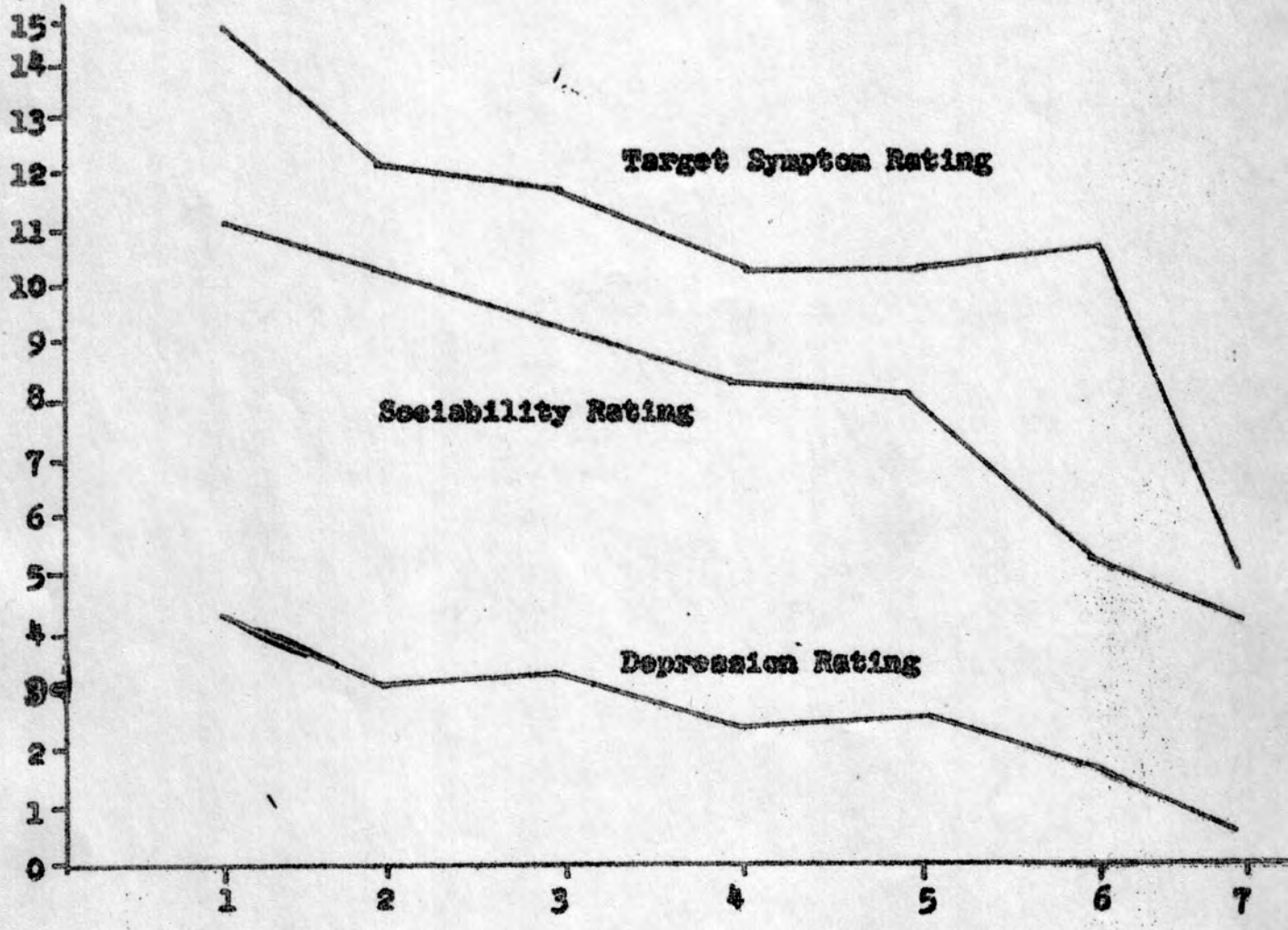
Immediately after arrival and before receiving medication a short battery of psychophysical tests selected from the Verdun Psychophysical Battery (Reaction Time, Tapping Speed, Cancellation Time and Stroop Test) were administered.

The physical measurements and ratings were done weekly during the 6-week trial period and laboratory and psychophysical tests were repeated after 3 weeks and again after 6 weeks.

In all cases Tarasan was used in the dosage range from 50 to 1000 mgs. daily.

Of the 10 patients 4 had to be taken off medication because of uncontrollable behavior in this dosage range; one of them after the 1st week, one after the 3rd and two after the 5th week of medication.

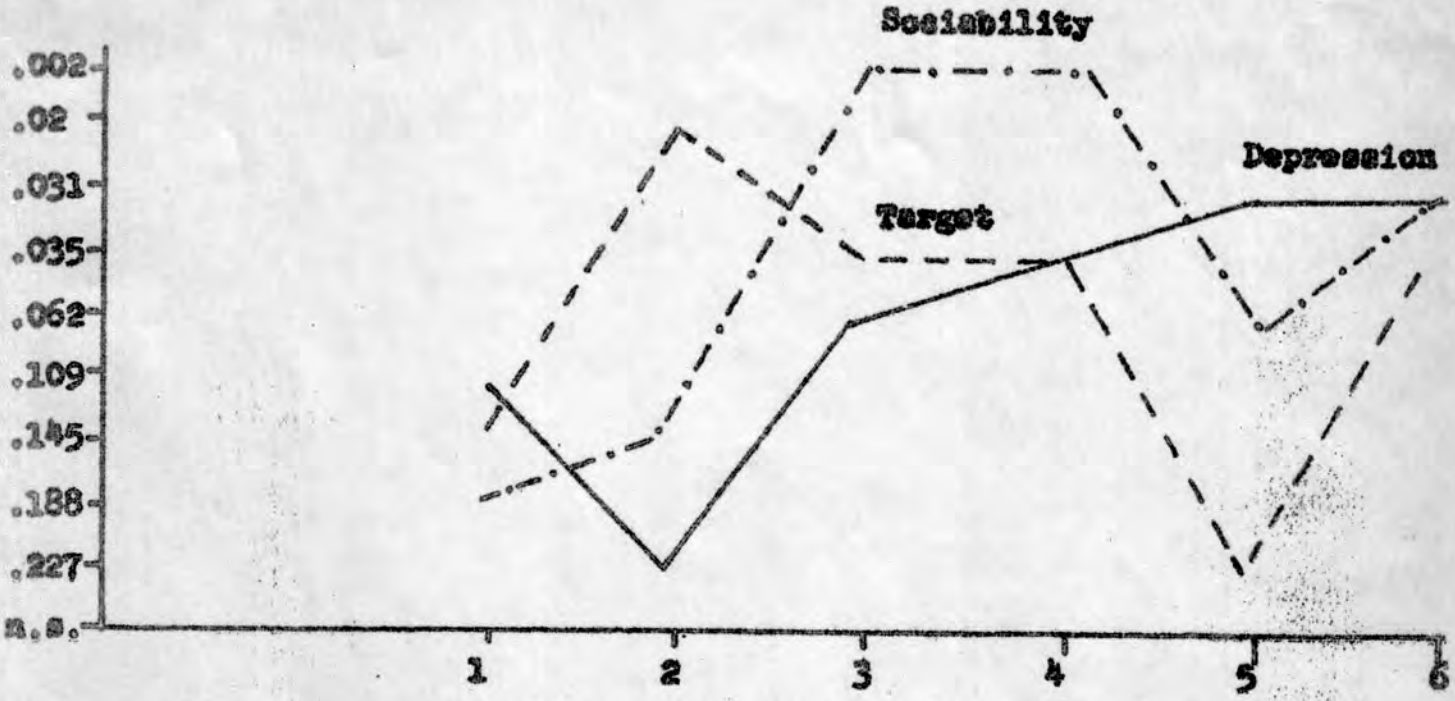
The weekly mean scores for symptomatology on the three rating scales all show a gradual decline (Figure VII) over the 6-week period. Only in the 5th week on the Target Symptom Rating Scale is there some interruption of this downward trend.



Weekly Mean Ratings.

FIGURE VII.

The statistical significance (Sign test) of these changes is shown in Figure VIII.



Significance of Changes in Weekly Ratings.

FIGURE VIII.

On the Target Symptom Rating Scale there is a significant improvement ($p \geq .02$) at the end of the second week. There is some reduction in the level of significance ($p = .035$) with a marked drop in the 5th week ($p = .227$). By the 6th week the previous level had been restored ($p = .031$). On the Depression Rating Scale there was a gradual increase of significance from the 2nd week ($p = .227$) to the 6th week ($p = .031$). On the Sociability Rating Scale the first significant changes took place in the 3rd week ($p = .02$).

The individual target symptoms which show the most striking improvement are in the 3rd week: excitement ($p = .08$), suspiciousness ($p = .016$), in the 6th week depression ($p = .031$), delusions ($p = .188$), suspiciousness ($p = .344$), anxiety ($p = .344$), improvement in object relations ($p = .344$).

Among the psychophysical tests the mean results of the Cancellation test (time and error both) show a significant decrease.

The commonest side effects were vertigo and drowsiness which were reported by 6 patients, dry mouth, constipation, insomnia and nausea reported by 5. 4 patients had coated tongue, 3 stuffy nose, another headache and 3 anorexia. Other side effects included fainting, tremors, skin rash in 2. 1 patient had blurred vision and watering eyes and another a grand male seizure.

The order of changes induced by Taraxan is as follows: the first changes came in the area of arousal followed by changes in the area of affectivity (anxiety and depression). Towards the end of the study changes began in the area of mental integration.

Opinion: Therapeutic in newly admitted schizophrenics.

III. (8) Early Drug Evaluation with Valium in Acute Psychiatric Patients.

(Pre-clinical and clinical studies with chronic psychiatric patients suggested possible tranquillizing properties of this drug.)

A clinical trial was carried out with Valium over an 8-week period with 15 newly admitted schizophrenic patients.

Evaluation was based on a battery of tests and examinations: laboratory; physical; the Verdun Target Symptom Rating Scale; completed at regular intervals.

Valium was administered in a dosage range of 30 to 90 mgs. daily in three divided doses.

The trial was originally designed for 8 weeks but 10 of the patients had to be taken off the drug within 3 weeks and 1 in the 4th week of the trial because of inadequate control of undesirable behavior and absence of any therapeutic effect on the psychotic manifestations.

Analysis of our findings indicated that the drug did have some beneficial effect in reducing anxiety.

Opinion: Ineffective in newly admitted schizophrenics.

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

IV. COMPARATIVE STUDIES ON THE RELATIVE EFFECTIVENESS OF COMPOUNDS.

IV. (1) The Comparative Effectiveness of Tofranil, G-35020 and Ensidon

30 chronic hospitalized psychotic patients with depressive mood change or apathy, equally subdivided into three groups, were administered Tofranil, G-35020 and Ensidon for a period of 12 weeks.

Evaluation was based on clinical observations and a battery of tests and examinations: laboratory (Table VIII); physical (Table IX); the Verdun Target Symptom (Table XI) and Depression Rating Scales (Table XII) and the Verdun Side Effect Check List (Table X).

Administration of medication during the experimental trial was single blind and followed an increasing dosage schedule (100 to 200 mgs. daily in 4 divided doses).

No toxic effect in the laboratory tests was revealed. On the physical tests, blood pressure dropped significantly in the G-35020 group ($p > .001$, Sign test); while in the Ensidon group it started to rise but not frequently enough to reach significance. The Tofranil group showed no pattern of change. On the other hand, pulse rates rose significantly in the Tofranil group ($p > .01$) and fell in the Ensidon group ($p > .01$) while the G-35020 group did not show any pattern of change.

Results of the psychiatric ratings indicated certain clinical trends, but were not consistent enough to reach statistical significance. Total Target Symptom ratings indicated slight general improvement in the condition of 7 of the 10 Tofranil subjects. In the G-35020 group no trend was evident, but 5 patients improved, 4 became worse and 1 remained unchanged. The Ensidon group showed approximately the same proportion of changes as the G-35020 group: 5 patients improved, 3 became worse and 2 remained the same.

In the Tofranil group, 6 patients showed a decrease in depressive symptoms from the 6th week on the trial period and in the G-35020 group, the same improvement was noted from the 10th to the 12th weeks of the trial. The Ensidon group again showed no consistent trend. Tension and irritability however showed an increase in 40% of the patients in each group.

On the basis of our study with the three experimental compounds Tofranil appeared to have the strongest psychotropic (anti-depressive and antipsychotic) effect, although these effects were relatively slight. G-35020 showed a slight antidepressant effect late in the trial and Ensidon had no notable effect on psychiatric symptoms.

Opinion: Order of antidepressant potency: Tofranil, G-35020, Ensidon.

IV. (2) The Comparative Effectiveness of R-1625 and Permitil.

A comparative 6-week clinical trial was conducted on 30 female psychotic patients with R-1625 and Permitil. Patients for this study were selected on the basis of the chronicity of their illness and inadequate response to previous therapies. They were subdivided into 2 groups, matched as to age and length of hospitalization.

The following tests were conducted: laboratory; physical. Their psychopathology was assessed by rating scales containing items under the headings of emotion, perception, thought process, thought content, motivation, sleep, appetite.

One group was placed on R-1625 and the other on Permitil medication in dosages increasing within 4 weeks from 3 x 1 to 3 x 4 mgs. and 3 x .5 to 3 x 2.0 mgs. respectively.

Both medications appeared to improve symptoms related to the parameter of mental integration. R-1625 appeared to be superior in counteracting perceptive disorders. It should be noted however that both compounds produced therapeutic effects in both areas. The sleep disturbances of 5 patients improved while they were on R-1625, while the activity (motivation) of 3 patients improved while on Permitil. Our trial suggested that R-1625 may be preferable where hyperactivity and agitation are associated with pathology of perception and insomnia, while Permitil may be preferable where apathy and withdrawal are associated with thought disorder (Table XXI).

Improvement was shown in:	Haloperidol	Permitil
Emotion	1	3
Perception	7	3
Thought Process	5	10
Thought Content	7	5
Motivation	0	3
Sleep	5	0
Appetite	2	0

Table XXI

This study revealed no organ toxicity with either of these compounds. The principal clinical side effects were drowsiness with R-1625 (4), insomnia with Permitil (3), extrapyramidal symptoms with both (9).

Opinion: Equally antipsychotic but areas of maximal effectiveness different.

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

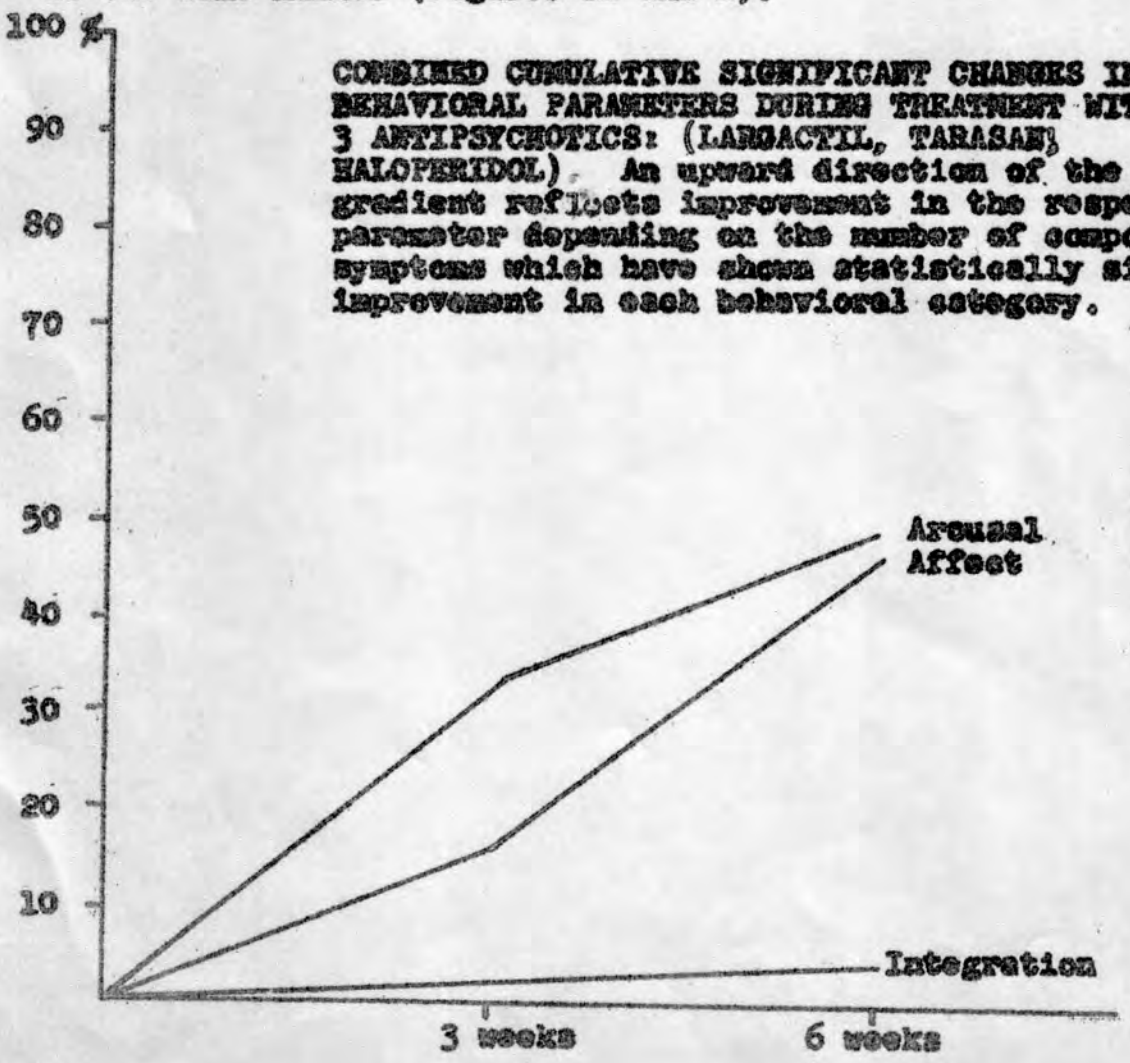
IV. (3) The Comparative Effectiveness of R-1625, Largactil and Tarasan.

30 newly admitted schizophrenic patients equally divided into 3 categories were administered R-1625, Largactil and Tarasan for a period of 6 weeks.

The following tests were conducted: laboratory; physical. The patients were closely followed by clinicians for day-to-day manifestations of their psychotic condition, and at weekly intervals their behavior and mental status were recorded on the Verdun Target Symptom, Depression and Sociability Rating Scales. The behavioral manifestations recorded were brought together under 3 categories which designate 3 parameters of mental functioning. The 3 parameters on which we oriented our observations were: 1. arousal, 2. affect and 3. integration.

The three drugs used were R-1625 representing the butyrophenones, Largactil representing the phenothiazines, and Tarasan representing the thioxanthenes. They were administered in the following dosages: R-1625, 10 to 100 mgs., Largactil 900 to 4000 mgs. and Tarasan 50 to 1000 mgs., daily.

Each group of patients receiving an antipsychotic drug reacted in the same manner (Figures IX and X).



COMBINED CUMULATIVE SIGNIFICANT CHANGES IN BEHAVIORAL PARAMETERS DURING TREATMENT WITH 3 ANTIPSYCHOTICS: (LARGACTIL, TARASAN, HALOPERIDOL). An upward direction of the gradient reflects improvement in the respective parameter depending on the number of component symptoms which have shown statistically significant improvement in each behavioral category.

FIGURE IX.

INDIVIDUAL CUMULATIVE SIGNIFICANT CHANGES IN BEHAVIORAL PARAMETERS DURING TREATMENT WITH 3 DIFFERENT ANTIPSYCHOTICS.

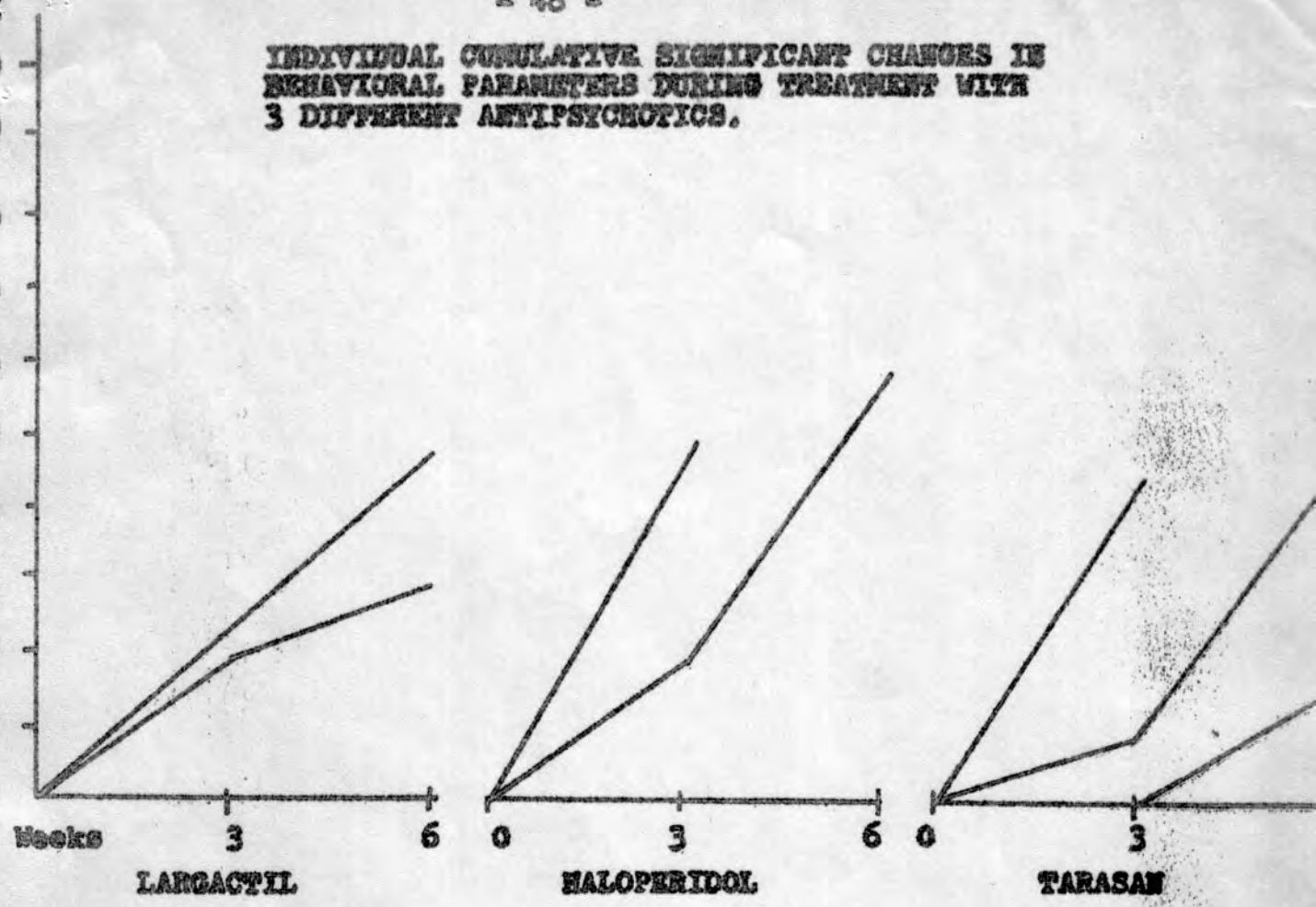


FIGURE X.

There was a rapid improvement of symptoms on the arousal parameter as excitement and agitation subsided soon after pharmacotherapy commenced. This was followed by a less rapid but still dramatic improvement in the sphere of affect which became evident in a lessening of anxiety, tension and depression and in greater accessibility of the patients. However the most specific psychotic symptoms such as hallucinations, delusions and thought disorder were hardly affected at all in the first 6 weeks of treatment with the 3 antipsychotic compounds. There were among the 30 patients of our sample some in whom such fundamental improvement did occur, but in the close follow-up studies of the whole sample on a quantitative basis, the changes observed on the integration parameter were not large enough to become statistically significant.

The pattern of improvement over this time showed a very similar distribution of the therapeutic effects in each of our 3 groups of schizophrenic patients, suggesting a similar mode of action for each of the three chemically different major tranquillizers.

A slight effect on the integration parameter, due to improvement in the symptom of delusions, appeared only in the group treated with Taractan, but the number of patients was very small. Hence the over-all similarity of sequential symptom reduction is probably more significant than the one slight difference since this might well have been due to sampling. It should also be noted that the group receiving Largactil, and exhibiting the least improvement, was composed of patients with higher pre-treatment morbidity ratings than the other two groups, since patients were assigned to the different drugs as they were admitted to the hospital and were not matched for degree of initial pathology.

Opinion: Equally effective. Order of effect: arousal, affectivity, mental integration.

(Ban, T.A., Stonehill, E. and Lehmann, H.E. Butyrophenones in Psychiatry. Symposium, L'Annonciation, Quebec. Jan. 10/64. In Press.)

IV. (4) The Comparative Effectiveness of R-1625, McN-JR-2498 and McN-JR-3345 in Chronic Psychiatric Patients.

The experimental compounds were administered in succession for 8-week periods each to 15 chronic schizophrenic patients, following a Latin square design.

Evaluation was based on clinical observations and a battery of tests and examinations: laboratory; physical; the Verdun Side Effect Check List and the Verdun Target Symptom Rating Scale.

The drugs were administered in increasing dosages from 1.5 to 30 mgs. in 3 divided doses for the R-1625 and McN-JR-2498 groups, and from 60 mgs. to 600 mgs. for the McN-JR-3345 group.

A comparison of the pre-trial total symptomatology scores at the end of the first 8-week period showed a significant improvement ($p \leq .01$) (Wilcoxon and Sign-Ranks test). The total score then became significantly worse when medication was stopped for two weeks ($p > .05$) and again a significant improvement ($p = .01$) occurred during the second 8-week period of medication. This pattern was repeated in the third trial period, i.e. there was exacerbation of symptoms during the 2-week inter-trial medication-free period and a significant improvement ($p > .01$) in the total symptom rating scores for the third trial period on the drugs. These findings are presented in Figure XI.

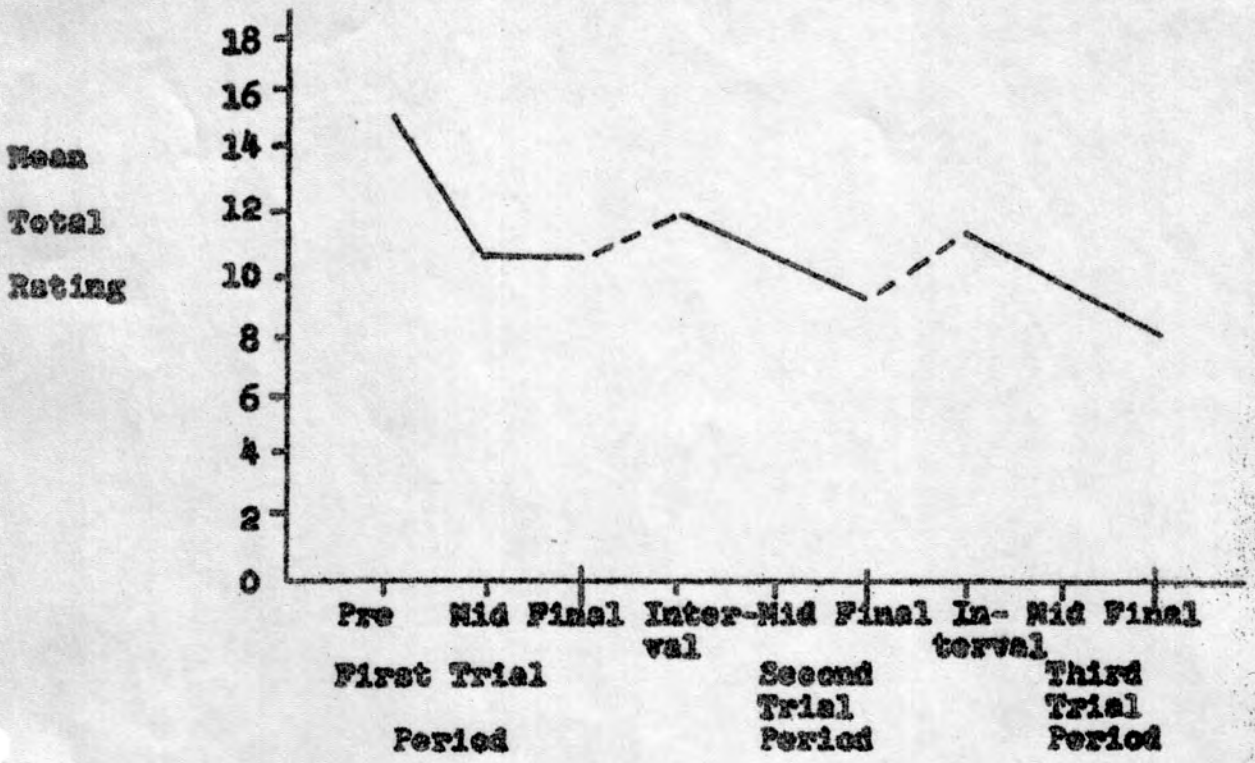


FIGURE XI.

A comparison for each drug between the pre-trial total symptom ratings and the ratings at the end of the 8-week period is presented in Figure XII.

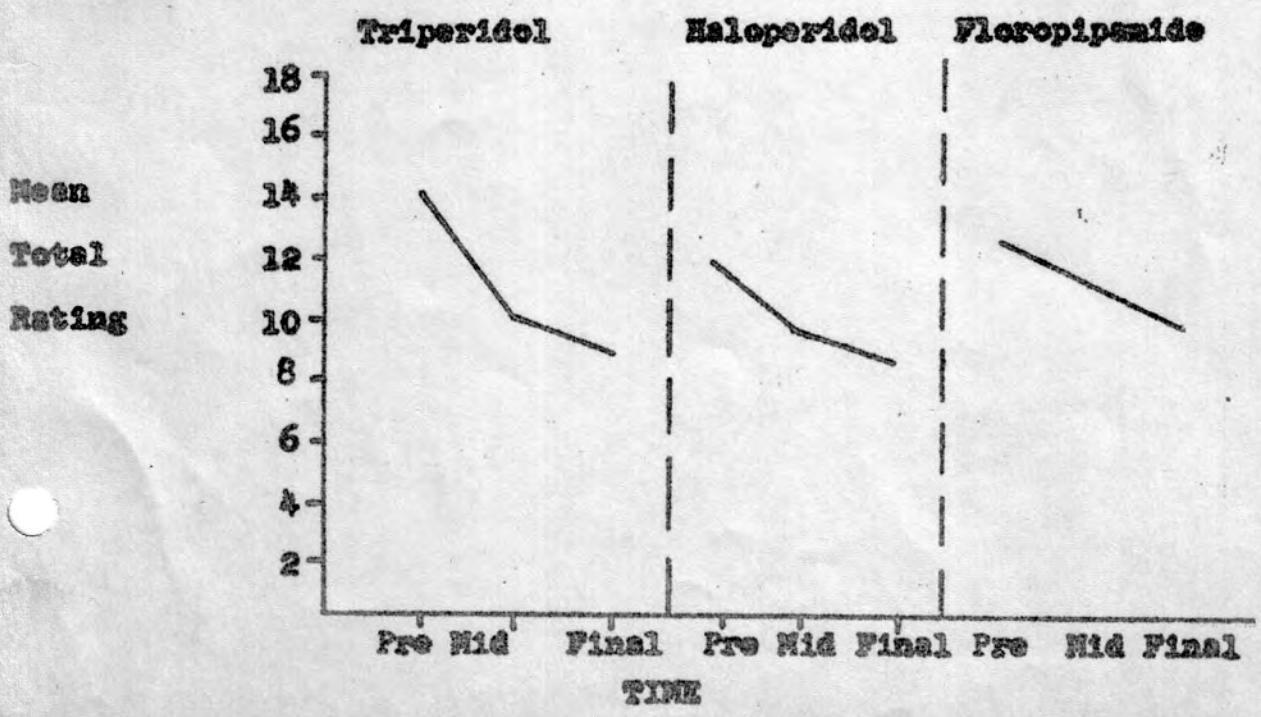


FIGURE XII.

The 3 drugs differed in the time required to effect a significant decrease of improvement in symptomatology. MeN-JR-2498 showed a significant improvement ($p < .01$) in the Target Symptom Scale for the pre-trial rate and the rating to the end of the 4th week. From the 4th to the 8th week there was a further but non-significant improvement in total symptom rating scales. R-1625 effected a less significant ($p \geq .05$) improvement for the first half of the trial period and a non-significant improvement for the second half of the trial. A further improvement from the pre-trial to final ratings was significant at the .01 level of confidence. A comparison of the pre- and mid-trial ratings for MeN-JR-3345 showed a non-significant improvement in symptoms which continued on this basis during the second half of the trial period. However in this case the total change from the pre-trial to the final ratings reached the .01 level of significance.

An analysis of these specific target symptoms showed that only certain symptoms were effected by the drug (Table XXII).

	MeN-JR-2498	R-1625	MeN-JR-3345
Excitement	p-0.008	N.S.	p-0.016
Suspiciousness	p-0.031	N.S.	N.S.
Hostility	no change	no change	no change
Anxiety	N.S.	no change	no change
Apathy	N.S.	N.S.	N.S.
Object Relations	p-0.016	N.S.	no change
Hallucinations	N.S.	N.S.	N.S.
Disturbance of Thinking	p-0.016	N.S.	N.S.
Delusions	N.S.	p-0.016	N.S.
Memory	no change	no change	no change
Consciousness	no change	no change	no change
Social Responses	N.S.	N.S.	N.S.

Table XXII.

MeN-JR-2498 brought about significant improvement in excitement ($p = .008$), suspiciousness ($p = .031$), object relations ($p = .016$), disturbance of thinking ($p = .016$). R-1625 effected a significant improvement in the symptom delusions ($p = .016$) and MeN-JR-3345 a significant improvement in the symptom of excitement ($p = .016$). No change was noted with respect to 'memory' and 'consciousness'. The ratings showed other symptoms improved, but not significantly.

Among the physical measures, with the exception of weight, there was no significant change observed during the trial period. Weight changes occurred with 2 of the compounds but in different directions. There was significant loss of weight in the patients on MeN-JR-2498 at the $p < .01$ level of confidence, while patients on MeN-JR-3345 gained weight significantly ($p < .05$).

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.

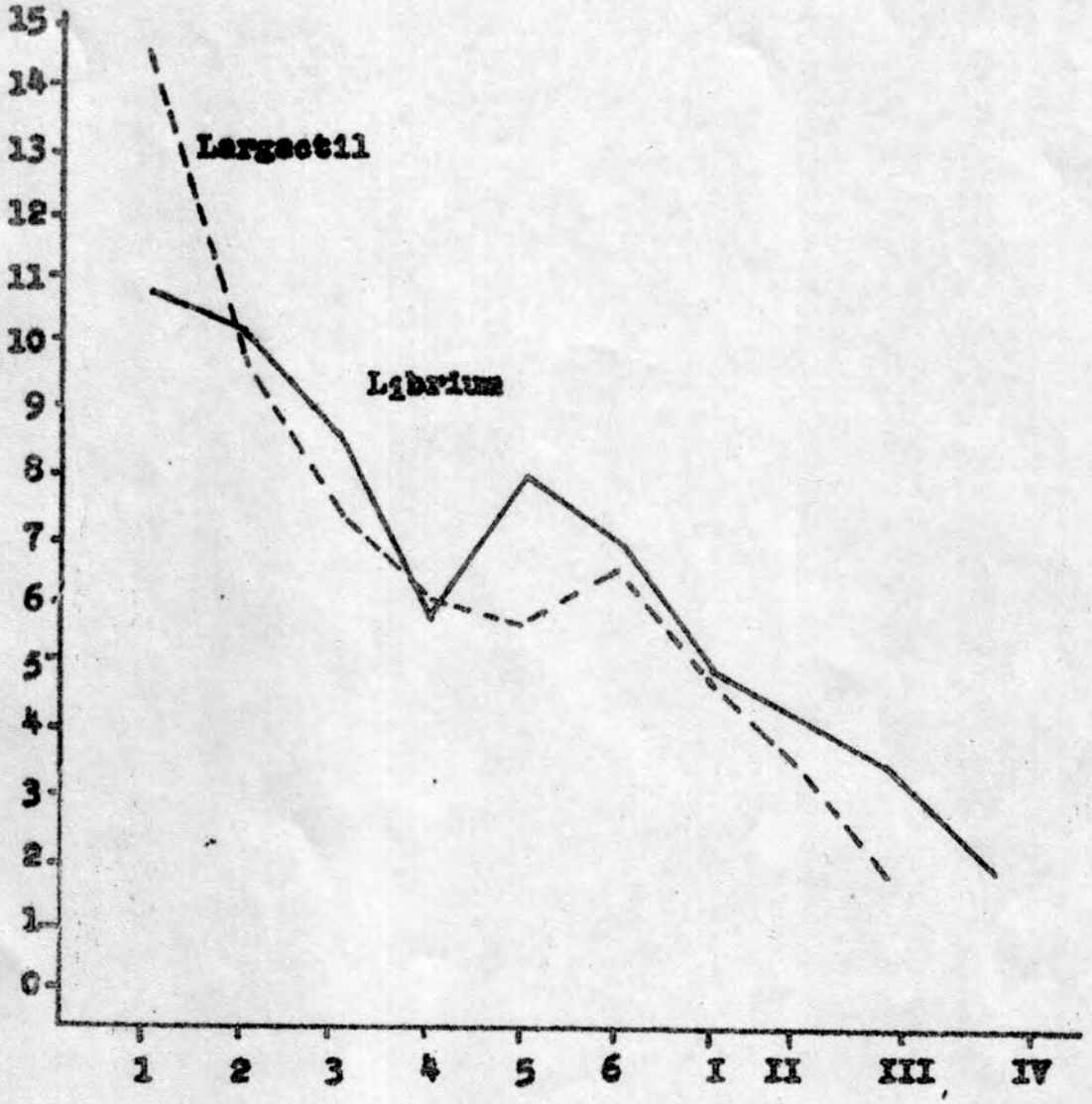


FIGURE XIII.

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).

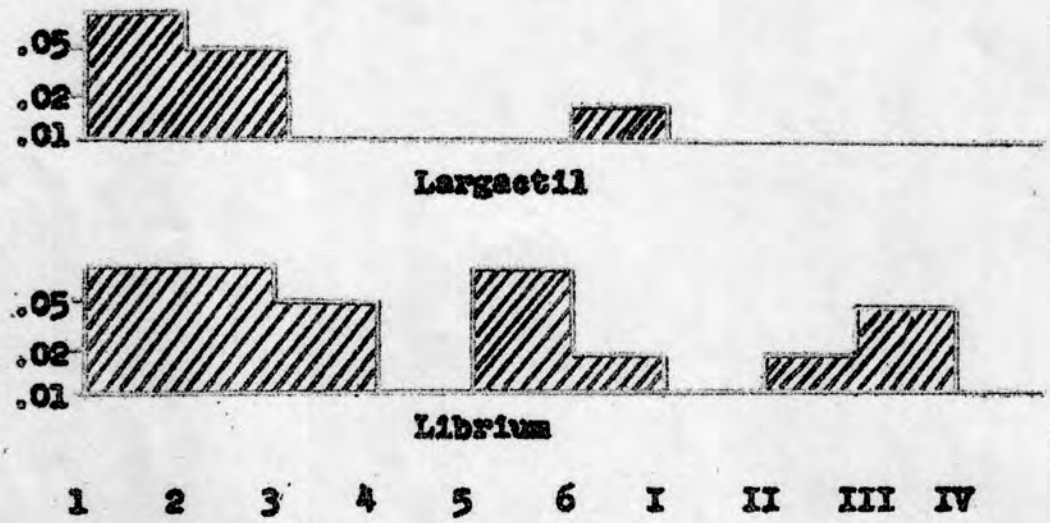


FIGURE XIV.

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.

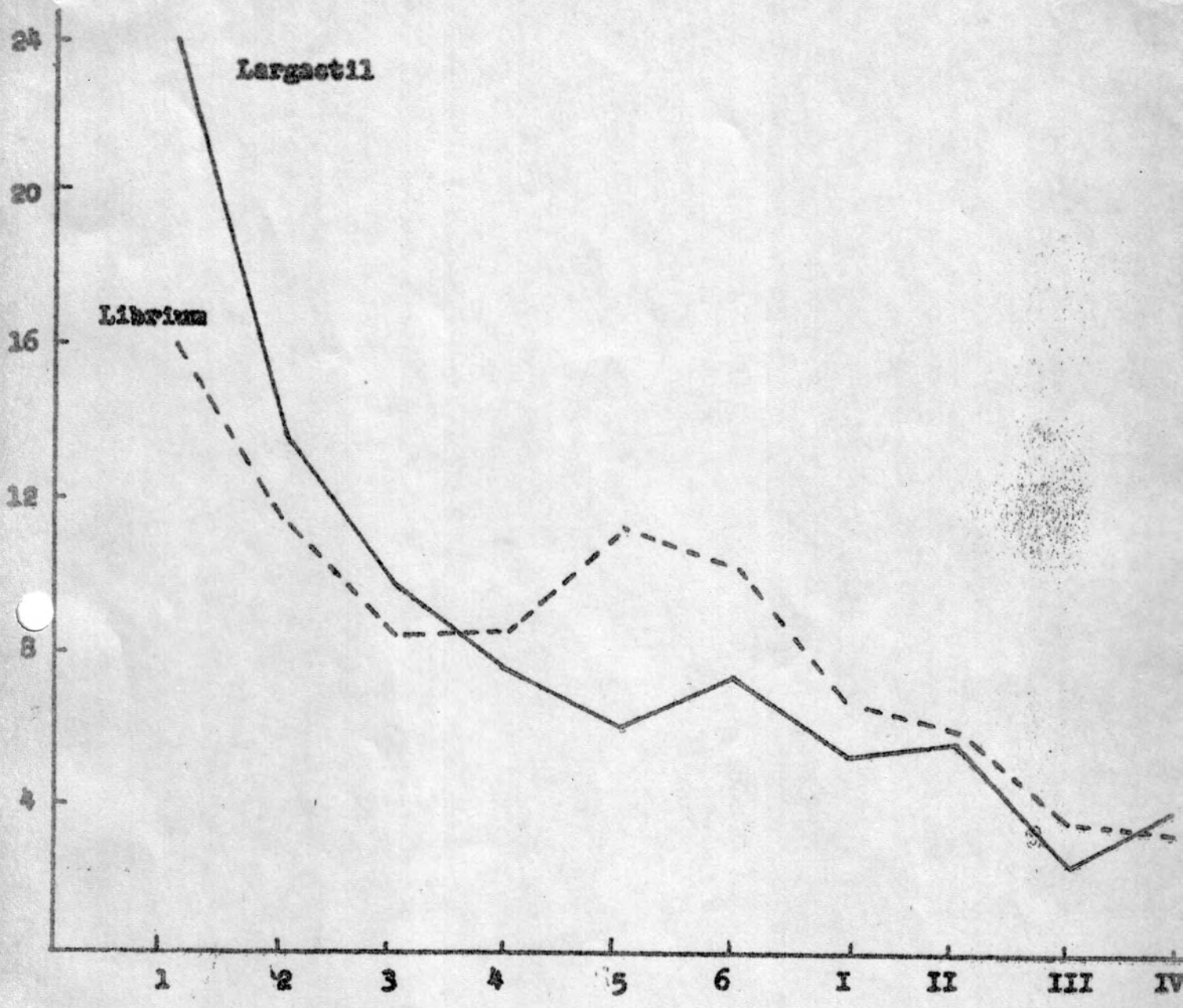


FIGURE XV.

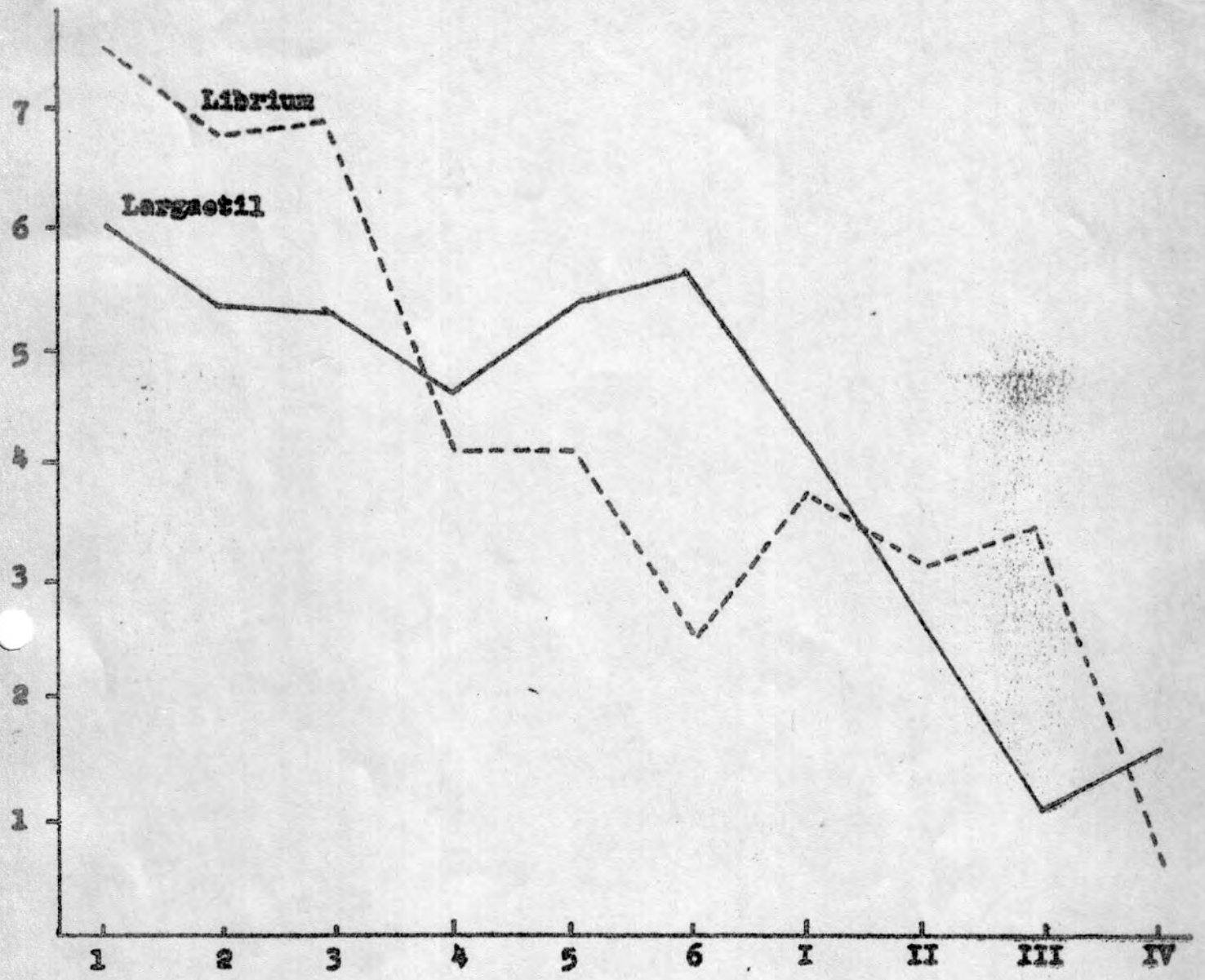


FIGURE XVI.

'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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