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.

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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).

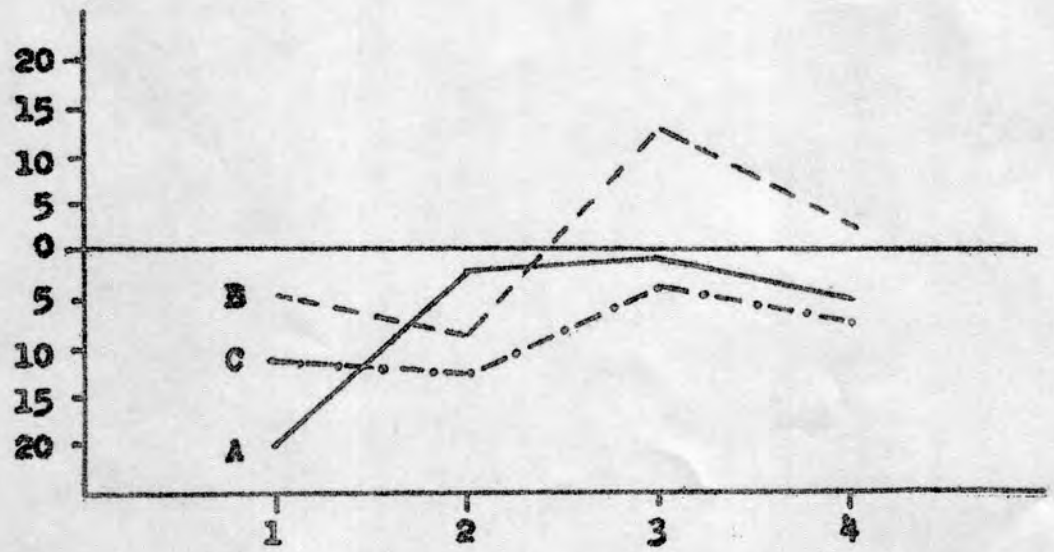

FIGURE I.

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.

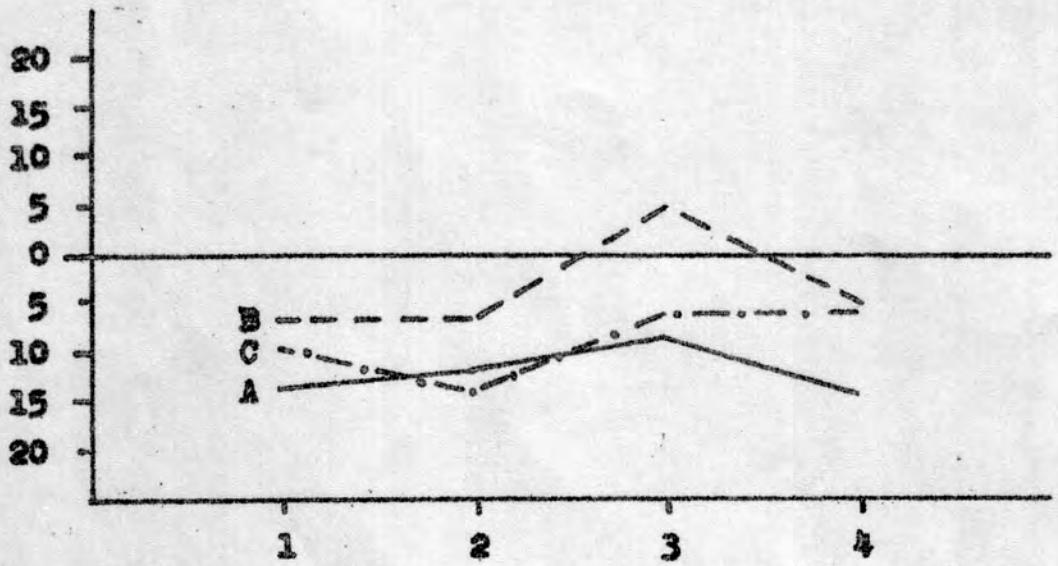

FIGURE II.

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.

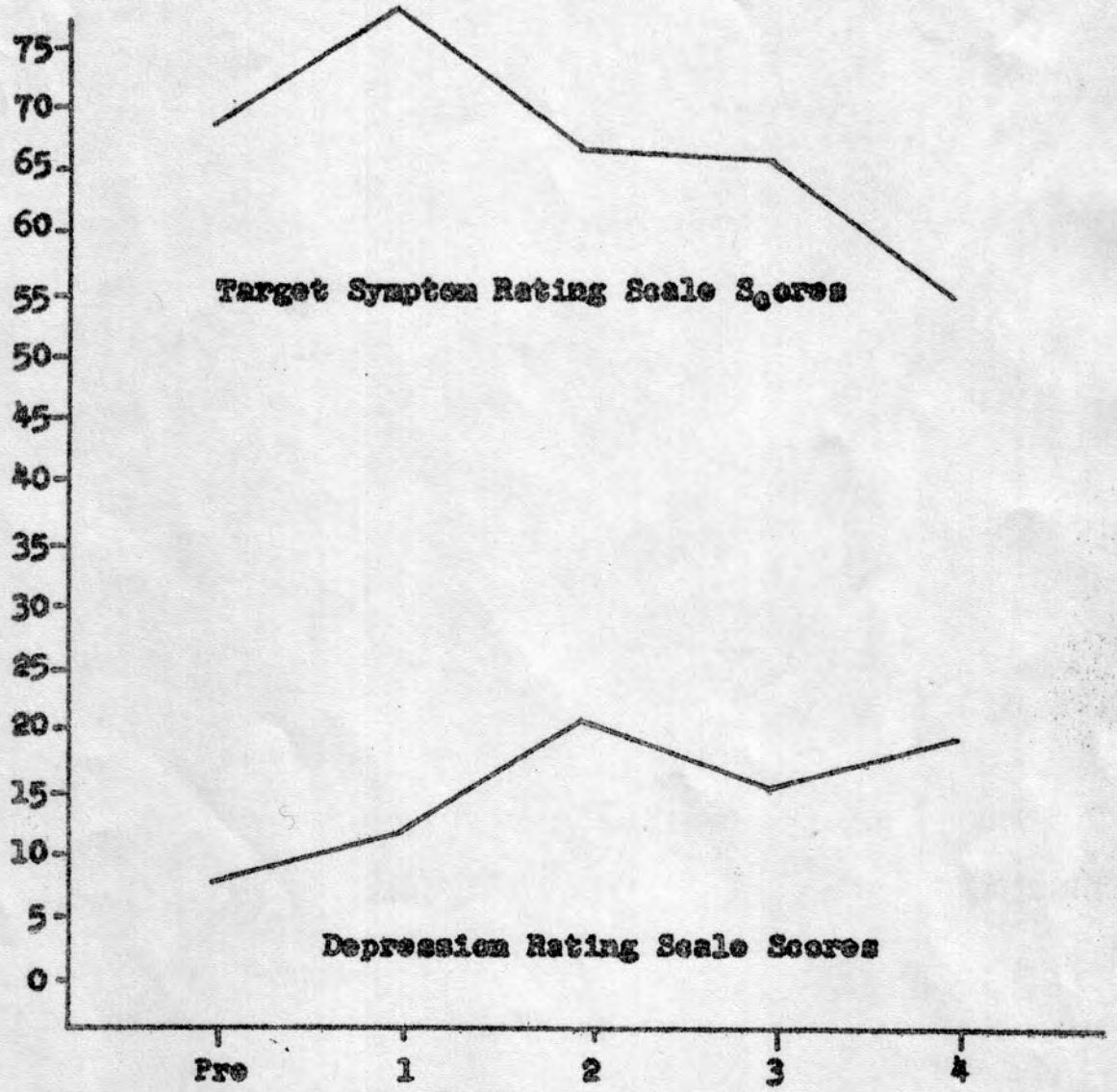

FIGURE III.

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