

DEPARTMENT OF VETERANS AFFAIRS

TREATMENT SERVICES

NOV 26 1953

APPLICATION TO CARRY OUT A RESEARCH PROJECT

NOTE: Application to be made in quadruplicate. All copies to be forwarded to the Secretary, Advisory Board on Medical Research and Education.

1. NAME OF APPLICANT **Dr. R.G.B. Gilbert,
Dr. Louis Lamoureux** DATE October 13, 1953.
2. POSITION HELD BY APPLICANT **Consultants in Anaesthesia, Queen Mary Veterans Hospital.**
3. SHORT TITLE OF PROPOSED PROJECT **- D.V.A. Project 31-53.
"Largactil Study" (Poulenc RP 1560).**

4. OUTLINE OF PROPOSED RESEARCH AND ITS OBJECTIVE

Definite objectives remain the same, but method of approach has been modified.

Objectives - 1) To discover hypothermic potentialities.

2) To investigate the drug a) In normal unanaesthetized individuals.

b) In anaesthetized patients

i) as premedicant -

ii) as adjuvant to other agents.

c) By its use in special groups of patients, i.e., intractable pain.

d) By animal experimentation.

Method of approach -

- See Interim Report -

5. RÉSUMÉ OF PRESENT STATE OF KNOWLEDGE AND PREVIOUS WORK BY THE APPLICANT RELATIVE TO THE PROPOSED RESEARCH WITH REFERENCES TO ESSENTIAL PUBLICATIONS

See Interim Report, which includes latest references.

31-53

6. ESTIMATE OF TIME REQUIRED TO COMPLETE PROJECT - A further eight (8) months
viz + Until July 31, 1954.
7. IN WHAT HOSPITAL, LABORATORY, ETC. DOES APPLICANT PROPOSE TO CARRY OUT THE PROJECT
Queen Mary Veterans Hospital
8. CONCISE STATEMENT AS TO ADEQUACY OF HOSPITAL, LABORATORY, ETC. EQUIPMENT
As before -
Now awaiting - 1) Ventilation Meter (expect within next few days).
2) Multipolar thermocouple (expect in two months).
Also utilizing Department of Pharmacology, McGill University for animal study.
9. ESTIMATE OF COST (OVER AND ABOVE NORMAL HOSPITAL, LABORATORY, TREATMENT, ETC. REQUIREMENTS)

(A) EQUIPMENT: (LIST APPARATUS OR MATERIALS REQUIRED, AND COST OF EACH ITEM)

No further equipment is envisaged as being necessary at
the moment.

\$ _____

(B) PERSONNEL: (LIST STAFF REQUIRED WITH POSITIONS, NAMES, QUALIFICATIONS AND RATES OF REMUNERATION OF THOSE WHO WILL BE SPECIALLY EMPLOYED IN THE RESEARCH PROJECT)

Adequate until March 31, 1954, when additional remuneration for
Dr. Allen B. Dobkin - Resident Fellow, will be necessary at \$333.33/month,
four (4) months.

\$ 1333.32
1333.32

(C) INDIVIDUALS TO BE STUDIED: (TRAVELLING, MAINTENANCE IN AND OUT OF HOSPITAL, LOSS OF WAGES, ETC. OVER AND ABOVE NORMAL INVESTIGATION AND TREATMENT REQUIREMENTS OF ENTITLED VETERANS OR OTHERS)

Local volunteers only being used -

If funds could be provided as an additional
inducement, it might be welcome -

\$ 150.00

(D) OTHER:

\$ 1483.32

ESTIMATED TOTAL COST

\$ _____

NOTE: ADD APPENDED SHEETS IF NECESSARY FOR ANY OF ABOVE SECTIONS.

10. IS THIS PROJECT RECEIVING SUPPORT FROM ANY OTHER SOURCE? No.
IF SO - SPECIFY

R. B. Clark

SIGNATURE OF APPLICANT

RECOMMENDED BY:

October 13, 1953.

DATE _____

R. B. Clark

SIGNATURE OF CHIEF OF SERVICE

SERVICE

RECOMMENDED BY:

DATE Nov. 20, 1953

W. H. Stanley

SIGNATURE OF CHAIRMAN, HOSPITAL COMMITTEE ON CLINICAL RESEARCH

DATE _____

APPROVED

NOT APPROVED

DIRECTOR GENERAL OF TREATMENT SERVICES

INTERIM REPORT ON D.V.A. PROJECT 31-53 - LARGACTIL STUDY

October 15, 1953.

NOV 26 1953

by: Allen B. Dobkin, M.D.,
and the
Staff Anaesthetists.

Investigation was undertaken to study the reported advantagenous effects of RP 4560, (known as Largactil) for premedication, and for potentiation of the effects of commonly employed sedative-hypnotic, analgesic and anaesthetic drugs.

In order to evaluate the effects of this substance, the first four weeks of the study were spent in close association with Dr. Rene Létienne, and general observations were made as to its use as a supplement to anaesthesia. During this time it was realized that complicity with other anaesthetic drugs made it impossible to evaluate the specific effects of RP 4560.

The study was therefore arranged as follows:

1. Physiological study of a group of normal healthy volunteers -

Under the direction of Dr. Dobkin, five persons have been studied to date, before and after the intravenous use of various therapeutic doses of RP 4560.

The data was accurately collected with the assistance of -

1. An experienced graduate nurse who was in full time attendance during the study and made clinical notes of the procedures and charted vital signs. The same nurse was present at each study and was kindly arranged for by the Nursing Office of Queen Mary Veterans Hospital.
2. Two experienced technicians trained in taking electroencephalograms and electrocardiograms. Direction for eliciting the most pertinent data and interpretation of the electroencephalograms was kindly provided by Dr. D. Lloyd-Smith. Dr. Palmer reviewed the E.C.G.'s.
3. B.M.R. studies were carried out by Dr. Allen Dobkin.
4. Arterial blood samples were analyzed for oxygen and carbon dioxide content by the Respiratory Function Laboratory under the direction of Dr. Ronald Place.
5. Electrolyte, acid-base and metabolic blood studies were analyzed in the Biochemistry Laboratories under the direction of Dr. A.H. Neufeld.

LARGACTIL STUDY - (cont'd.)

This data thus far indicates -

- a) There is a moderate lowering of body temperature, usually 1.5°F. orally and 2.0°F. rectally and on skin surface. This will be checked at a later date with accurate recording thermometers which have been on order for three-and-one-half months but have not arrived.
- b) B.M.R.'s have indicated a rise in oxygen consumption. Clinically and by arterial blood samples, it is evident that it had FALLEN. This may be explained by the fact that marked depression occurs in respiratory musculature and brings in the probable error due to resistance in the measuring device (Sanborn Metabolator). This is being studied further.
- c) There is moderate depression of rate and depth of respiration clinically. This will be more accurately investigated upon arrival of a ventilation meter now on order. This fact appears to be in absolute contradiction to the statement made by previous observers.
- d) No significant disturbance has been observed in the blood electrolytes which were studied (Serum: Na, K, PO₄, Cl).
- e) There is a slight fall in arterial oxygen content and slight rise in arterial CO₂ content with slight variable changes in the CO₂CP. No accurate pH data was available. Hematocrit and Hemoglobin estimation remained stable. Oxygen and CO₂ alterations reflect a depression of respiration.
- f) There is no significant effect on metabolism as indicated by Blood Urea Nitrogen and Blood Sugar.
- g) This substance causes marked drying effect on mucous membranes and reduces sweating. This action appears to be as effective clinically as atropine.
- h) When large doses are used intravenously vasomotor stability appears to be distinctly impaired with clear data showing orthostatic hypotension with E.E.G. evidence suggestive of cerebral ischemia during the peak action of this substance. With small oral and intramuscular doses, this effect is not seen.
- i) When large doses are used intravenously, there is a slight disturbance in cardiac rhythm. This is a sinus arrhythmia, and is accentuated by placing the patient in the upright posture.
- j) E.E.G. shows a typical pattern of drowsiness. Clinically, the substance exhibits a strong hypnotic effect. The state induced is different from that of morphine in that the patient may be easily aroused and is hypersensitive to sudden stimulation.

LARGACTIL STUDY - (cont'd.)

- k) There appears to be a disturbance in neuromuscular conduction evidenced by skeletal muscle paresis, noted mainly in the facial muscles (Ptosis, diplopia, weak masseters), upper extremities (Dynamometer studies) and lower intercostals.
- l) There is also a marked papillary constriction probably due to paresis of the dilator pupillae (sympathetic).
- m) There is probably a marked depression on gastric motility and secretion of gastric juices indicated by loss of appetite in these subjects and relief of pain in patients with ulcer (to be reported at a later date when more data is available and further studies carried out).
- n) There is a disturbance in micturation lasting more than 12 hours, probably due to parasympathetic inhibition.
- o) The possible reversal of effects of this substance has been tested with Benzedrine, Dexedrine, Caffeine-Sodium Benzoate, Tensilon and Prostigmin, all with no clinical effect. These will be studied more extensively.
- p₄ RP 4560 has topical anaesthetic effects on mucous membranes of the mouth. It is proposed to study an additional 10 - 15 normal subjects. This will be undertaken when permission is granted by Colonel P. Tremblay, to test army personnel, and if funds are available as inducement to local personnel.

II. A controlled study is now under way to investigate the effectiveness of RP 4560 as a premedicating drug. It is proposed to study 300 cases; with this substance as the sole premedicant. Control of data is kept with a questionnaire in order to maintain uniformity of observations and to facilitate tabulation of results.

III. A study is in progress to investigate the potentiating effect of this substance in General Anaesthesia; to investigate the sedative effect during Spinal Anaesthesia; and to investigate the stabilizing effect on blood pressure in patients who are in shock, and who are under the influence of total spinal for upper abdominal and thoracic surgery.

IV. A limited number of patients were administered this substance post-operatively to potentiate the effects of analgesics (morphine and demerol). This was claimed to have deleterious effect due to an apparent increase in pulmonary complications. This was attributed to the fact that the patients felt weak, drowsy, and were immobile when under the influence of this substance. This phase of the investigation has therefore been abandoned for the present.

LARGACTIL STUDY - (cont'd.)

- V. A series of patients with intractable pain and with pain requiring large doses of morphine, demerol and methadon (due to such conditions as inoperable bronchogenic carcinoma and other terminal conditions), are being studied. To date, it has been possible almost to eliminate the strong analgesics in a few cases. This series is being extended.
- VI. Animal experiments have been carried out with the kind assistance of Professor K.I. Melville of the Department of Pharmacology at McGill University. These will be continued as the necessity arises to elicit data that is not applicable to clinical study. To date, three studies have been made. These have ruled out a myoneural junction blocking effect by this substance of the competitive or curare type. There appears to be some depression of the spinal cord and medulla which may be analagous to the Myanesin type of block. The Depolarizing or Decamethonium type of block may be possible. (See reports on animal studies).

NO CROSS CLINICAL REACTIONS HAVE BEEN OBSERVED DURING THE USE OF A WIDE RANGE OF DOSAGE OF THIS SUBSTANCE.

The studies to date indicate that RP 4560 has the following pharmacological effect -

1. Sedative - Hypnotic - Similar to but stronger than Benadryl, Pyribenzamine and Phenergan.
2. Blocks or inhibits the release of Acetylcholine (reversible).
 - 1) At parasympathetic ganglia and postganglionic nerves - indicated by decreased sweating, salivation and probable depression of gastric secretion, and gastric and G.I. spasm (Hexamethonium effect), and blocked innervation of the detrusor muscle of the bladder. May prevent motion sickness (as well as phenergan, dramamine and atropine).
 - 2) Neuromuscular block to skeletal muscle not related to d-Tubocurrarine or Gallamine, possibly related to Decamethonium or Succinylcholine and probably caused by inhibition of Acetylcholine release (described by Paton as "deficiency of transmitter"). Ref: Anaesthesia, Vol. 8, No. 3 - July, 1953.
 - 3) Block of sympathetic ganglia - similar to hexamethonium and indicated by orthostatic hypotension, elevated P and T waves in electrocardiogram (lead II) and tachycardia during general anaesthesia.
3. Local anaesthetic effect topically. Possibly also locally when injected.

LARGACTIL STUDY - (cont.)

4. By block of Acetylcholine release, may effect a redistribution of heat and cold receptors in skin and mucous membranes causing a fall in body temperature. Hypothalamic effect is not likely. Reference 4.

RECENT REFERENCES -

1. J.P.E.T. July, 1953 - Comparative study of Phenothiazine derivatives (Supported by NRC grant).
2. Acta Pharm. et Toxic Vol. 9, Fasc 2 - Activity of Basically Substituted Derivatives of Phenothiazine, Atropine, Papaverine and other Spasmolytic Drugs against Barium and Acetylcholine induced spasms in guinea pigs and rat ileum (Dahlbom, Edlund, Ekstrand). Shows Benothiazine reduce spasm in manner similar to hexamethonium.
3. Idem Protective Effect of Phenothiazine Derivative against Poisoning by the Irreversible cholinesterase inhibitor Tabun (Bo Holmstedt et al). This paper suggests antimuscarinic and antinicotinic effect of phenothiazine plus protective action by preventing destruction of enzyme anticholinesterase.
4. Idem Hartz and Riskaer. Effects of Antihistamine on Vestibular function in guinea pigs.
5. Acta Physiological Scandinavica Vol. 28, Fasc. 2 - 3 (30-5-53) E. Dodt, A.P. Skouby and Y. Zotterman. The effect of Cholinergic Substances on the Discharges from Thermal Receptors.

This paper demonstrates that Acetylcholine (in minute amounts) shifts the temperature range of the steady discharge of cold fibers towards the warm side and increases the rate of the stationary discharge of the receptors inside the normal range of temperature. The observed slight lowering of body temperature during RP 4560 may be indicative of a reversal of this effect by inhibiting Acetylcholine release.

6. Physiology and Pharmacology of Vomiting. H.L. Borison and S.C. Wang. Pharmacological Review. Vol. 5, No. 2, June, 1953.
7. Neuropharmacology of Peripheral Nerve - James E.P. Teran, Pharmacological Reviews, Vol 4, No. 2 - June, 1952.
8. Idem, The Methonium Compounds. W.D.M. Paton, E.J. Samais (Sept. 1952.).

LARGACTIL STUDY - (con...)

Further studies to be undertaken - (not yet in progress) -

1. A clinical study of the alleviation of post-operative nausea and vomiting has been proposed. Reference - French Literature -
J.A.M.A. Oct. 3, 1953, Vol. 153, No. 5.
Doctors Friend and Cummins.
2. Study of pulmonary ventilation effects and B.M.R. effects - Awaiting ventilation meter.
3. RP 4560, atropine and hyoscine to be compared for effects on secretions.
4. Animal investigation of possible depolarizing action at Myoneural junction. (Decamethonium - like action) - cats required.
5. Clinical study of effects on, a) gastric motility, b) gastric secretion, c) gastric acidity comparing RP 4560, Banthine, Probanthine, Gentrine and Atropine.
6. Clinical study of effects on kidney function and on micturition.
7. Test topical (? local) anaesthetic potency and toxicity of RP 4560.
8. Compare RP 4560, dramamine and gravol effects on motion sickness and post-operative nausea and vomiting. Reference C.M.A.J. Oct. 1953, Vol. 69, No. 4.
9. Compare bronchodilating effect of isopropyl adrenalin with RP 4560.

Clinical study of liver function has been in progress by other local investigators and will not be repeated.

Allen B. Dobkin M.D.
Allen B. Dobkin, M.D.,
Research Fellow in Anaesthesia.

R.G.B. Gilbert
R.G.B. Gilbert, M.D.,
Consultant,
Department of Anaesthesia.

DEPARTMENT OF VETERANS AFFAIRS
TREATMENT SERVICES

APPLICATION TO CARRY OUT A RESEARCH PROJECT

NOTE: Application to be made in quadruplicate. All copies to be forwarded to the Secretary, Advisory Board on Medical Research and Education.

1. NAME OF APPLICANT **Dr. R.G.B. Gilbert**
Dr. Louis Lamoureux DATE June 8th, 1953.
2. POSITION HELD BY APPLICANT **Consultants in Anaesthesia, Q.M.V.H.**
3. SHORT TITLE OF PROPOSED PROJECT
Hibernation in Anaesthesia by use of 'Largactil' (Poulenc, 4560 R.P.)
4. OUTLINE OF PROPOSED RESEARCH AND ITS OBJECTIVE
Objects: (1) To study the hibernation properties of Largactil in man.
(2) To assess whether such response is beneficial.
(3) If it is so, to determine what types of case its use could be of maximum advantage.
- Method of approach:**
(1) Observations to be made on (a) A selected group (b) A control group.
(2) Subjects to be given as near a standard premedication and anaesthetic as possible.
(3) Observation details:
(a) Clinical - Preoperative, Perioperative, Postoperative.
(b) Investigative.
(i) Temperature - Skin, Rectal, Muscle.
(ii) Oxygen utilization studies.
(iii) Arterial oxygen saturation.
(iv) CO₂ combining power.
(v) E.K.G. recordings. (Such observations to be made before operation - 30", 60", 2 hrs., 4 hrs., and 24 hrs. following commencement).
(vi) Possibly also tidal exchange.

Note: It is planned to do one patient per day.

5. RÉSUMÉ OF PRESENT STATE OF KNOWLEDGE AND PREVIOUS WORK BY THE APPLICANT RELATIVE TO THE PROPOSED RESEARCH WITH REFERENCES TO ESSENTIAL PUBLICATIONS

Clinical observations only have for the most part been carried out with this drug, except for E.K.G.'s (L.L.)

It would appear that -

- (1) Less anaesthetic agent is necessary.
- (2) Respiration is stimulated.
- (3) Less postoperative use of analgesics is necessary.
- (4) Mental reaction following operation may be temporarily altered in a "lobotomized" manner.

It is our desire to substantiate clinical impressions and to gain some definite knowledge as to the organismal response.

References: Alluams, R. Anaesésie et Analgésie IX, 2:261 - June 1952.
Deschamps, A. La Presse Médicale 60, 43:944 - June 1952.
Forster, S. et al. Anesthésie et Analgésie IX, 2:250 - June 1952.
Laborit, H. L'anesthésie facilitée par les synergies médicamenteuses.
" " La Presse Médicale 60, 10:204 (1952) Masson et Cie - Paris '52
" " Anesthésie et Analgésie IX, 2 (supplément) - June 1952.
" " La Presse Médicale 60, 60:1256 (Sept. 1952).
Hudon, F. Paper read before Canadian Anaesthetist Soc. Ont. Div. April '53

6. ESTIMATE OF TIME REQUIRED TO COMPLETE PROJECT
(To be combined with Dextran project) 1 year.
7. IN WHAT HOSPITAL, LABORATORY, ETC. DOES APPLICANT PROPOSE TO CARRY OUT THE PROJECT
Queen Mary Veterans Hospital, Montreal, P.Q.
8. CONCISE STATEMENT AS TO ADEQUACY OF HOSPITAL, LABORATORY, ETC. EQUIPMENT
It would seem to be adequate with the cooperation of Dr. R.E.G. Place and his Respiratory Function facilities, except for simultaneous temperature recordings.
9. ESTIMATE OF COST (OVER AND ABOVE NORMAL HOSPITAL, LABORATORY, TREATMENT, ETC. REQUIREMENTS)

(A) EQUIPMENT: (LIST APPARATUS OR MATERIALS REQUIRED, AND COST OF EACH ITEM)

Danish cost

1. Electric Universal thermometer, Type T.E. 3	975 Kr.	\$141.00
2. Connection box type F.E.	265 Kr.	38.00
3. Specific electrodes - 8 in all H ₂ , H ₃ , K ₂ , R ₁ - two of each	65 Kr. each	75.00
4. Estimated agents fees, freight, etc.	520 Kr.	80.00
5. Miscellaneous		66.00
		<u>\$ 400.90</u>

(B) PERSONNEL: (LIST STAFF REQUIRED WITH POSITIONS, NAMES, QUALIFICATIONS AND RATES OF REMUNERATION OF THOSE WHO WILL BE SPECIALLY EMPLOYED IN THE RESEARCH PROJECT)

1. Research Fellow in Anaesthesia.

It is hoped Dr. Allen B. Dobkin will undertake this.
Dr. Dobkin is a Toronto graduate of 1949. He has done 1 yr. Rotating internship. 1 yr. senior in Surgery. 2 years with Dr. Ralph Knight of the University of Minnesota where he has taken part in nine research projects.
(Available July 1st)

H 600
3600 to ~~\$4000~~
\$

(C) INDIVIDUALS TO BE STUDIED: (TRAVELLING, MAINTENANCE IN AND OUT OF HOSPITAL, LOSS OF WAGES, ETC. OVER AND ABOVE NORMAL INVESTIGATION AND TREATMENT REQUIREMENTS OF ENTITLED VETERANS OR OTHERS)

Entitled patients only.

\$

(D) OTHER:

\$

ESTIMATED TOTAL COST

\$ ~~4000~~ to ~~\$5000~~
4400

NOTE: ADD APPENDED SHEETS IF NECESSARY FOR ANY OF ABOVE SECTIONS.

Richard B. Plunk
SIGNATURE OF APPLICANT

RECOMMENDED BY:

DATE June 24/53

[Signature]
SIGNATURE OF CHIEF OF SERVICE

Surgery
SERVICE

RECOMMENDED BY:

DATE June 25/53

MTS Farby
SIGNATURE OF CHAIRMAN, HOSPITAL COMMITTEE ON CLINICAL RESEARCH

DATE

APPROVED
NOT APPROVED

DIRECTOR GENERAL OF TREATMENT SERVICES

DEPARTMENT OF VETERANS AFFAIRS

NOV 26 1953

TREATMENT SERVICES

APPLICATION TO CARRY OUT A RESEARCH PROJECT

NOTE: Application to be made in quadruplicate. All copies to be forwarded to the Secretary, Advisory Board on Medical Research and Education.

1. NAME OF APPLICANT **Dr. R.G.B. Gilbert,
Dr. Louis Lamoureux** DATE October 13, 1953.
2. POSITION HELD BY APPLICANT **Consultants in Anaesthesia, Queen Mary Veterans Hospital.**
3. SHORT TITLE OF PROPOSED PROJECT - **D.V.A. Project 31-53.
"Largactil Study" (Poulenc RP 4560).**

4. OUTLINE OF PROPOSED RESEARCH AND ITS OBJECTIVE

Definite objectives remain the same, but method of approach has been modified.

- Objectives - 1) To discover hypothermic potentialities.
2) To investigate the drug a) In normal unanaesthetized individuals.
b) In anaesthetized patients
i) as premedicant -
ii) as adjuvant to other agents.
c) By its use in special groups of patients, i.e., intractable pain.
d) By animal experimentation.

Method of approach -

- See Interim Report -

5. RÉSUMÉ OF PRESENT STATE OF KNOWLEDGE AND PREVIOUS WORK BY THE APPLICANT RELATIVE TO THE PROPOSED RESEARCH WITH REFERENCES TO ESSENTIAL PUBLICATIONS

See Interim Report, which includes latest references.

31-53

6. ESTIMATE OF TIME REQUIRED TO COMPLETE PROJECT - A further eight (8) months
viz + Until July 31, 1954.
7. IN WHAT HOSPITAL, LABORATORY, ETC. DOES APPLICANT PROPOSE TO CARRY OUT THE PROJECT
Queen Mary Veterans Hospital
8. CONCISE STATEMENT AS TO ADEQUACY OF HOSPITAL, LABORATORY, ETC. EQUIPMENT
As before -
Now awaiting - 1) Ventilation Meter (expect within next few days).
2) Multipolar thermocouple (expect in two months).
Also utilizing Department of Pharmacology, McGill University for animal study.
9. ESTIMATE OF COST (OVER AND ABOVE NORMAL HOSPITAL, LABORATORY, TREATMENT, ETC. REQUIREMENTS)

(A) EQUIPMENT: (LIST APPARATUS OR MATERIALS REQUIRED, AND COST OF EACH ITEM)

No further equipment is envisaged as being necessary at
the moment.

\$ _____

(B) PERSONNEL: (LIST STAFF REQUIRED WITH POSITIONS, NAMES, QUALIFICATIONS AND RATES OF REMUNERATION OF
THOSE WHO WILL BE SPECIALLY EMPLOYED IN THE RESEARCH PROJECT)

Adequate until March 31, 1954, when additional remuneration for
Dr. Allen B. Bobkin - Resident Fellow, will be necessary at \$333.33/month,
four (4) months.

\$ 1333.32
\$ 1333.32

(C) INDIVIDUALS TO BE STUDIED: (TRAVELLING, MAINTENANCE IN AND OUT OF HOSPITAL, LOSS OF WAGES, ETC.
OVER AND ABOVE NORMAL INVESTIGATION AND TREATMENT REQUIREMENTS OF ENTITLED VETERANS OR OTHERS)

Local volunteers only being used -

If funds could be provided as an additional
inducement, it might be welcome -

\$ 150.00

(D) OTHER:

\$ _____
\$ 1183.32

ESTIMATED TOTAL COST

\$ _____

NOTE: ADD APPENDED SHEETS IF NECESSARY FOR ANY OF ABOVE SECTIONS.

10. IS THIS PROJECT RECEIVING SUPPORT FROM ANY OTHER SOURCE? No.
IF SO - SPECIFY


SIGNATURE OF APPLICANT

RECOMMENDED BY:

October 13, 1953.

DATE _____


SIGNATURE OF CHIEF OF SERVICE

SERVICE

RECOMMENDED BY:

DATE Nov. 20. 1953


SIGNATURE OF CHAIRMAN, HOSPITAL COMMITTEE ON CLINICAL RESEARCH

APPROVED

DATE _____

NOT APPROVED

DIRECTOR GENERAL OF TREATMENT SERVICES

INTERIM REPORT ON D.V.A. PROJECT 31-53 - LARGACTIL STUDY

October 15, 1953.

by: Allen B. Dobkin, M.D.,
and the
Staff Anaesthetists.

NOV 26 1953

Investigation was undertaken to study the reported advantageous effects of RP 4560, (known as Largactil) for premedication, and for potentiation of the effects of commonly employed sedative-hypnotic, analgesic and anaesthetic drugs.

In order to evaluate the effects of this substance, the first four weeks of the study were spent in close association with Dr. Rene Létienne, and general observations were made as to its use as a supplement to anaesthesia. During this time it was realized that complicity with other anaesthetic drugs made it impossible to evaluate the specific effects of RP 4560.

The study was therefore arranged as follows:

1. Physiological study of a group of normal healthy volunteers -

Under the direction of Dr. Dobkin, five persons have been studied to date, before and after the intravenous use of various therapeutic doses of RP 4560.

The data was accurately collected with the assistance of -

1. An experienced graduate nurse who was in full time attendance during the study and made clinical notes of the procedures and charted vital signs. The same nurse was present at each study and was kindly arranged for by the Nursing Office of Queen Mary Veterans Hospital.
2. Two experienced technicians trained in taking electroencephalograms and electrocardiograms. Direction for eliciting the most pertinent data and interpretation of the electroencephalograms was kindly provided by Dr. D. Lloyd-Smith. Dr. Palmer reviewed the E.C.G.'s.
3. E.M.R. studies were carried out by Dr. Allen Dobkin.
4. Arterial blood samples were analyzed for oxygen and carbon dioxide content by the Respiratory Function Laboratory under the direction of Dr. Ronald Place.
5. Electrolyte, acid-base and metabolic blood studies were analyzed in the Biochemistry Laboratories under the direction of Dr. A.H. Neufeld.

31-53

(cont'd. page 2.)

003251

LARGACTIL STUDY - (cont'd.)

2.

This data thus far indicates -

- a) There is a moderate lowering of body temperature, usually 1.5°F. orally and 2.0°F. rectally and on skin surface. This will be checked at a later date with accurate recording thermometers which have been on order for three-and-one-half months but have not arrived.
- b) B.M.R.'s have indicated a rise in oxygen consumption. Clinically and by arterial blood samples, it is evident that it had **FALLEN**. This may be explained by the fact that marked depression occurs in respiratory musculature and brings in the probable error due to resistance in the measuring device (Sanborn Metabolator). This is being studied further.
- c) There is moderate depression of rate and depth of respiration clinically. This will be more accurately investigated upon arrival of a ventilation meter now on order. This fact appears to be in absolute contradiction to the statement made by previous observers.
- d) No significant disturbance has been observed in the blood electrolytes which were studied (Serum: Na, K, PO_4 , Cl).
- e) There is a slight fall in arterial oxygen content and slight rise in arterial CO_2 content with slight variable changes in the CO_2CP . No accurate pH data was available. Hematocrit and Hemoglobin estimation remained stable. Oxygen and CO_2 alterations reflect a depression of respiration.
- f) There is no significant effect on metabolism as indicated by Blood Urea Nitrogen and Blood Sugar.
- g) This substance causes marked drying effect on mucous membranes and reduces sweating. This action appears to be as effective clinically as atropine.
- h) When large doses are used intravenously vasomotor stability appears to be distinctly impaired with clear data showing orthostatic hypotension with E.E.G. evidence suggestive of cerebral ischemia during the peak action of this substance. With small oral and intramuscular doses, this effect is not seen.
- i) When large doses are used intravenously, there is a slight disturbance in cardiac rhythm. This is a sinus arrhythmia, and is accentuated by placing the patient in the upright posture.
- j) E.E.G. shows a typical pattern of drowsiness. Clinically, the substance exhibits a strong hypnotic effect. The state induced is different from that of morphine in that the patient may be easily aroused and is hypersensitive to sudden stimulation.

(cont'd. page 3)

003252

LANGACTIL STUDY - (cont'd.)

- k) There appears to be a disturbance in neuromuscular conduction evidenced by skeletal muscle paresis, noted mainly in the facial muscles (Ptosis, diplopia, weak masseters), upper extremities (Dynamometer studies) and lower intercostals.
- l) There is also a marked papillary constriction probably due to paresis of the dilator pupillae (sympathetic).
- m) There is probably a marked depression on gastric motility and secretion of gastric juices indicated by loss of appetite in these subjects and relief of pain in patients with ulcer (to be reported at a later date when more data is available and further studies carried out).
- n) There is a disturbance in micturation lasting more than 12 hours, probably due to parasympathetic inhibition.
- o) The possible reversal of effects of this substance has been tested with Benzedrine, Dexedrine, Caffeine-Sodium Benzoate, Tensilon and Prostigmin, all with no clinical effect. These will be studied more extensively.
- p) RP 1560 has topical anaesthetic effects on mucous membranes of the mouth. It is proposed to study an additional 10 - 15 normal subjects. This will be undertaken when permission is granted by Colonel P. Tremblay, to test army personnel, and if funds are available as inducement to local personnel.

II. A controlled study is now under way to investigate the effectiveness of RP 1560 as a premedicating drug. It is proposed to study 300 cases, with this substance as the sole premedicant. Control of data is kept with a questionnaire in order to maintain uniformity of observations and to facilitate tabulation of results.

III. A study is in progress to investigate the potentiating effect of this substance in General Anaesthesia; to investigate the sedative effect during Spinal Anaesthesia; and to investigate the stabilizing effect on blood pressure in patients who are in shock, and who are under the influence of total spinal for upper abdominal and thoracic surgery.

IV. A limited number of patients were administered this substance post-operatively to potentiate the effects of analgesics (morphine and demerol). This was claimed to have deleterious effect due to an apparent increase in pulmonary complications. This was attributed to the fact that the patients felt weak, drowsy, and were immobile when under the influence of this substance. This phase of the investigation has therefore been abandoned for the present.

LANGACTIL STUDY - (cont'd.)

V. A series of patients with intractible pain and with pain requiring large doses of morphine, demerol and methadon (due to such conditions as inoperable bronchogenic carcinoma and other terminal conditions), are being studied. To date, it has been possible almost to eliminate the strong analgesics in a few cases. This series is being extended.

VI. Animal experiments have been carried out with the kind assistance of Professor K.I. Melville of the Department of Pharmacology at McGill University. These will be continued as the necessity arises to elicit data that is not applicable to clinical study. To date, three studies have been made. These have ruled out a myoneural junction blocking effect by this substance of the competitive or curare type. There appears to be some depression of the spinal cord and medulla which may be analogous to the Hyalozin type of block. The Depolarizing or Decamethonium type of block may be possible. (See reports on animal studies).

NO CROSS CLINICAL REACTIONS HAVE BEEN OBSERVED DURING THE USE OF A WIDE RANGE OF DOSAGE OF THIS SUBSTANCE.

The studies to date indicate that RP 4560 has the following pharmacological effect -

1. Sedative - Hypnotic - Similar to but stronger than Benadryl, Pyribenzamine and Phenergan.
2. Blocks or inhibits the release of Acetylcholine (reversible).
 - 1) At parasympathetic ganglia and postganglionic nerves - indicated by decreased sweating, salivation and probable depression of gastric secretion, and gastric and G.I. spasm (Hexamethonium effect), and blocked innervation of the detrusor muscle of the bladder. May prevent motion sickness (as well as phenergan, dramamine and 8thSpino).
 - 2) Neuromuscular block to skeletal muscle not related to d-Tubocurarine or Gallamine, possibly related to Decamethonium or Succinylcholine and probably caused by inhibition of Acetylcholine release (described by Paton as "deficiency of transmitter"). Ref: Anaesthesia, Vol. 8, No. 3 - July, 1953.
 - 3) Block of sympathetic ganglia - similar to hexamethonium and indicated by orthostatic hypotension, elevated P and T waves in electrocardiogram (lead II) and tachycardia during general anaesthesia.
3. Local anaesthetic effect topically. Possibly also locally when injected.

LARGACTIL STUDY - (cont'd)

4. By block of Acetylcholine release, may effect a redistribution of heat and cold receptors in skin and mucous membranes causing a fall in body temperature. Hypothalamic effect is not likely. Reference 4.

RECENT REFERENCES -

1. J.P.E.T. July, 1953 - Comparative study of Phenothiazine derivatives (Supported by NRC grant).
2. Acta Pharm. et Toxic Vol. 9, Fasc 2 - Activity of Basically Substituted Derivatives of Phenothiazine, Atropine, Papaverine and other Spasmolytic Drugs against Barium and Acetylcholine induced spasms in guinea pigs and rat ileum (Bahlbom, Edlund, Ekstrand). Shows Phenothiazine reduce spasm in manner similar to hexamethonium.
3. Idem Protective Effect of Phenothiazine Derivative against Poisoning by the Irreversible cholinesterase inhibitor Tabun (Bo Holmstedt et al). This paper suggests antismuscarinic and antinicotinic effect of phenothiazine plus protective action by preventing destruction of enzyme anticholinesterase.
4. Idem Hartz and Riskaer. Effects of Antihistamine on Vestibular function in guinea pigs.
5. Acta Physiological Scandinavica Vol. 28, Fasc. 2 - 3 (30-5-53) E. Dødt, A.P. Skouby and Y. Zetterman. The effect of Cholinergic Substances on the Discharges from Thermal Receptors.

This paper demonstrates that Acetylcholine (in minute amounts) shifts the temperature range of the steady discharge of cold fibers towards the warm side and increases the rate of the stationary discharge of the receptors inside the normal range of temperature. The observed slight lowering of body temperature during RP 4560 may be indicative of a reversal of this effect by inhibiting Acetylcholine release.

6. Physiology and Pharmacology of Vomiting. H.L. Borison and S.C. Wang. Pharmacological Review. Vol. 5, No. 2, June, 1953.
7. Neuropharmacology of Peripheral Nerve - James E.P. Toman, Pharmacological Reviews, Vol 4, No. 2 - June, 1952.
8. Idem, The Methonium Compounds. W.B.M. Paton, E.J. Samais (Sept. 1952.).

LARGACTIL STUDY - (cont.)

Further studies to be undertaken - (not yet in progress) -

1. A clinical study of the alleviation of post-operative nausea and vomiting has been proposed. Reference - French Literature -
J.A.M.A. Oct. 3, 1953, Vol. 153, No. 5.
Doctors Friend and Cummins.
2. Study of pulmonary ventilation effects and B.M.R. effects - Awaiting ventilation meter.
3. RP 4560, atropine and hyoscine to be compared for effects on secretions.
4. Animal investigation of possible depolarizing action at Myoneural junction. (Decamethonium - like action) - cats required.
5. Clinical study of effects on, a) gastric motility, b) gastric secretion, c) gastric acidity comparing RP 4560, Banthine, Probanthine, Centriline and Atropine.
6. Clinical study of effects on kidney function and on micturition.
7. Test topical (? local) anaesthetic potency and toxicity of RP 4560.
8. Compare RP 4560, dramamine and gravol effects on motion sickness and post-operative nausea and vomiting. Reference C.M.A.J. Oct. 1953, Vol. 69, No. 4.
9. Compare bronchodilating effect of isopropyl adrenalin with RP 4560.

Clinical study of liver function has been in progress by other local investigators and will not be repeated.

Allen B. Dobkin M.D.

Allen B. Dobkin, M.D.,
Research Fellow in Anaesthesia.

R.C.B. Gilbert

R.C.B. Gilbert, M.D.,
Consultant,
Department of Anaesthesia.

DEPARTMENT OF VETERANS AFFAIRS

TREATMENT SERVICES

APPLICATION TO CARRY OUT A RESEARCH PROJECT

NOTE: Application to be made in quadruplicate. All copies to be forwarded to the Secretary, Advisory Board on Medical Research and Education.

Dr. R.G.B. Gilbert
Dr. Louis Lamoureux

1. NAME OF APPLICANT

DATE June 8th, 1953.

2. POSITION HELD BY APPLICANT

Consultants in Anaesthesia, Q.M.V.H.

3. SHORT TITLE OF PROPOSED PROJECT

Hibernation in Anaesthesia by use of 'Largactil' (Poulenc, 4560 R.P.)

4. OUTLINE OF PROPOSED RESEARCH AND ITS OBJECTIVE

- Objects:** (1) To study the hibernation properties of Largactil in man.
(2) To assess whether such response is beneficial.
(3) If it is so, to determine what types of case its use could be of maximum advantage.

Method of approach:

- (1) Observations to be made on (a) A selected group (b) A control group.
- (2) Subjects to be given as near a standard premedication and anaesthetic as possible
- (3) Observation details:
 - (a) Clinical - Preoperative, Perioperative, Postoperative.
 - (b) Investigative.
 - (i) Temperature - Skin, Rectal, Muscle.
 - (ii) Oxygen utilization studies.
 - (iii) Arterial oxygen saturation.
 - (iv) CO₂ combining power.
 - (v) E.K.G. recordings. (Such observations to be made before operation - 30", 60", 2 hrs., 4 hrs., and 24 hrs. following commencement).
 - (vi) Possibly also tidal exchange.

Note: It is planned to do one patient per day.

5. RÉSUMÉ OF PRESENT STATE OF KNOWLEDGE AND PREVIOUS WORK BY THE APPLICANT RELATIVE TO THE PROPOSED RESEARCH WITH REFERENCES TO ESSENTIAL PUBLICATIONS

Clinical observations only have for the most part been carried out with this drug, except for E.K.G.'s (I.L.)
It would appear that -

- (1) Less anaesthetic agent is necessary.
- (2) Respiration is stimulated.
- (3) Less postoperative use of analgesics is necessary.
- (4) Mental reaction following operation may be temporarily altered in a "lobotomized" manner.

It is our desire to substantiate clinical impressions and to gain some definite knowledge as to the organismal response.

References: Alluane, R. Anaesthésie et Analgésie IX, 2:261 - June 1952.
Deschamps, A. La Presse Médicale 60, 43:944 - June 1952.
Forster, S. et al. Anaesthésie et Analgésie IX, 2:250 - June 1952.
Laberit, H. L'anesthésie facilitée par les synergies médicamenteuses.
" " La Presse Médicale 60, 10:204 (1952) Masson et Cie - Paris '51
" " Anaesthésie et Analgésie IX, 2 (supplément) - June 1952.
" " La Presse Médicale 60, 60:1256 (Sept. 1952).
Hudon, F. Paper read before Canadian Anaesthetist Soc. Ont. Div. April '53

6. ESTIMATE OF TIME REQUIRED TO COMPLETE PROJECT
(To be combined with Dextran project) 1 year.
7. IN WHAT HOSPITAL, LABORATORY, ETC. DOES APPLICANT PROPOSE TO CARRY OUT THE PROJECT
Queen Mary Veterans Hospital, Montreal, P.Q.
8. CONCISE STATEMENT AS TO ADEQUACY OF HOSPITAL, LABORATORY, ETC. EQUIPMENT
It would seem to be adequate with the cooperation of Dr. R.E.G. Place and his Respiratory Function facilities, except for simultaneous temperature recordings.
9. ESTIMATE OF COST (OVER AND ABOVE NORMAL HOSPITAL, LABORATORY, TREATMENT, ETC. REQUIREMENTS)

(A) EQUIPMENT: (LIST APPARATUS OR MATERIALS REQUIRED, AND COST OF EACH ITEM)

	Danish cost	
1. Electric Universal thermometer, Type T.E. 3	975 Kr.	\$141.00
2. Connection box type F.E.	265 Kr.	38.00
3. Specific electrodes - 8 in all	65 Kr. each	75.00
H ₂ , H ₃ , K ₂ , R ₁ - two of each		
4. Estimated agents fees, freight, etc.	520 Kr.	80.00
5. Miscellaneous		66.00
		\$ 400.00

(B) PERSONNEL: (LIST STAFF REQUIRED WITH POSITIONS, NAMES, QUALIFICATIONS AND RATES OF REMUNERATION OF THOSE WHO WILL BE SPECIALLY EMPLOYED IN THE RESEARCH PROJECT)

1. Research Fellow in Anaesthesia.

It is hoped Dr. Allen B. Dobkin will undertake this.
Dr. Dobkin is a Toronto graduate of 1949. He has done 1 yr. Rotating internship. 1 yr. senior in Surgery. 2 years with Dr. Ralph Knight of the University of Minnesota where he has taken part in nine research projects.
(Available July 1st)

H100
3600 to \$4800
\$

(C) INDIVIDUALS TO BE STUDIED: (TRAVELLING, MAINTENANCE IN AND OUT OF HOSPITAL, LOSS OF WAGES, ETC. OVER AND ABOVE NORMAL INVESTIGATION AND TREATMENT REQUIREMENTS OF ENTITLED VETERANS OR OTHERS)

Entitled patients only.

\$

(D) OTHER:

\$ 4400

4000 to \$5000

ESTIMATED TOTAL COST

\$

NOTE: ADD APPENDED SHEETS IF NECESSARY FOR ANY OF ABOVE SECTIONS.

Richard Bluh N
SIGNATURE OF APPLICANT

RECOMMENDED BY:

DATE

June 24/53

SIGNATURE OF CHIEF OF SERVICE

SERVICE

RECOMMENDED BY:

DATE

June 25/53

SIGNATURE OF CHAIRMAN, HOSPITAL COMMITTEE ON CLINICAL RESEARCH

DATE

APPROVED

NOT APPROVED

DIRECTOR GENERAL OF TREATMENT SERVICES

Ottawa 2, Ont., August 23, 54.
D.F.P.S. (Financial Division).

Project 31-53 --
Hibernation in Anaesthesia by use of
'Largactil' (Poulenc, 4560 R.P.)

3-84(T.5)

Advice has been received that there is a surplus of \$345.00 under Object 460, in the above-named project, which has been terminated in Montreal. Will you please take the necessary action to recall this money from the District and credit it to Vote 5, Object 460.

GAW/em

W
G. A. Winfield, M.D.,
Secretary,
Advisory Board for Medical Research
and Education.

c.c. S.T.M.O.,
Montreal, P.Q.

INTRA-DEPARTMENT
CORRESPONDENCE

DEPARTMENT OF VETERANS AFFAIRS

Secretary,
Advisory Board for Medical
Research and Education.

Queen Mary Veterans Hospital.
MONTREAL, August 16, 1954. 19

TO

MARK YOUR REPLY:

For attention of : Dr. G.A. Winfield

For attention of

SUBJECT ; Dr. A.B. Dobkin - Project 31-53

File No. 3-84

We have been informed that Dr. Dobkin terminated the above Project in June and after discussion with Dr. D.H. Starkey he recommended that the cheque for \$345.00 for the month of July be returned to Treasury Office for cancellation.

The cheque is therefore being returned to District Treasury Officer today.

"NN

(Jules Mercier)
(JULES MERCIER) M.D.,
Senior Treatment Medical Officer.

c.c. Dr. D.H. Starkey

2. D.F.P.S. (Financial Division).

May we now show this as a recovery in Vote 5?

G. A. Winfield, M.D.

3.

A. Winfield.

*This would be an automatic credit to Vote 5. Obj. 4.
Do you wish to withdraw \$45. from Montreal.*

Ottawa 2, Ont., May 21,

54.

Dr. J. Mercier,
S.T.M.O.,
Queen Mary Veterans' Hospital,
Montreal, P.Q.

Visit of Dr. Dobkin to
Atlantic City.

3-84 (T.5)

Reference my memo of May 20, addressed to Dr. R.G.B.
Gilbert.

Attached herewith please find copies of DVA-TS 60
which are returned for your disposal.

5
G. A. Winfield, M.D.,
Secretary,
Advisory Board for Medical Research
and Education.

Ottawa 2, Ont., May 20,

54.

Dr. R.G.B. Gilbert,
Queen Mary Veterans' Hospital,
Montreal, P.Q.

Project 51-53 --
Hibernation in Anaesthesia by use of
'Largactil' (Poulenc, 4560 R.P.)

3-84(T.5)

Further to my communication of April 13. I have now been advised by the members of the Board that they feel unable to support the request that Dr. Dobkin proceed to Atlantic City at Departmental expense. I may say that the decision was taken partly because Dr. Dobkin will terminate his employment with the Department on July 1st, also because no provision was made for this expenditure when the project was put forward, and finally the applications were received too late for consideration.

I think I should tell you that the Board are generally against allocating research funds against research projects.

GAW/EM

c.c. S.T.M.O., Montreal, P.Q.

c.c. Chairman,
Clinical Research Committee,
Queen Mary Veterans' Hospital.

W
G. A. Winfield, M.D.,
Secretary,
Advisory Board for Medical Research
and Education.

Ottawa 2, Ont., April 13, 19 54.

TO Dr. D.H. Starkey,
Queen Mary Veterans' Hospital, MARK YOUR REPLY:
Montreal, P.Q.

For attention of

For attention of

Project 31-53 --
SUBJECT Hibernation in Anaesthesia by use of File No. 3-84(T.5)
'Largactil' (Poulenc, 4560 R.P.).

Dr. A.B. Dobkin is employed as a Research Fellow on the above-named project. He will terminate his fellowship in July.

On April 12 a request was received for Dr. Dobkin to attend the Federation Proceedings of the American Physiological and American Pharmacological Society in Atlantic City, April 12-15, and his expenses of \$150 be charged to the project.

No provision was made in the project for this expenditure and the application was received much too late. The object of his visit is said to be to obtain vital information related to his research project regarding the Physiology and Pharmacology of phenothiazine derivatives as they apply to use in prevention and treatment of shock (traumatic) and their use in association with Anaesthesia and Surgery.

I have written Dr. Gilbert pointing out that no provision was made for this expenditure and that the application was received much too late. I am, however, forwarding this for the consideration of the Board.

GAW/em

G. A. Winfield
G. A. Winfield, M.D.,
Secretary,
Advisory Board for Medical Research
and Education.

*Mrs Newfield & Daney
concur with Dr. Starkey's
view that we cannot
support this request
for non-contaminating staff*
MHS

University of Toronto

FACULTY OF MEDICINE

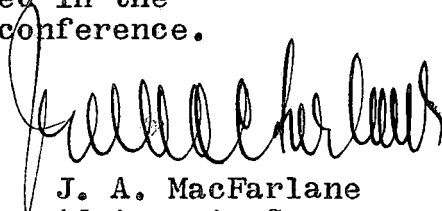
TORONTO 5, CANADA

OFFICE OF THE DEAN

April 28, 1955

Memorandum for Dr. Winfield

I do not believe that travelling expenses should be made a charge against a research project. However, even if there should be a decision to charge some travelling expenses either to the project or to other special funds, Dr. Dobkin should have applied in the ordinary way before the conference.



J. A. MacFarlane
Adviser in Surgery

Hold for Mr. Smith

University of Toronto

TORONTO 5, CANADA

File No. 3-84(T.5)

DEPARTMENT OF MEDICINE
100 COLLEGE ST.

April 26, 1954

TO Dr. G.A. Winfield, Secretary,
Advisory Board for Medical Research and Education,
Department of Veterans Affairs, Ottawa.

RE: Project 31-53 (Dr. A.B. Dobkin, Montreal)--
Hibernation in Anaesthesia by Use of 'Largactil'

It is reasonable that Dr. Dobkin should wish to attend the meeting of the American Physiological and Pharmacological Society to hear papers on the pharmacology of Largactil and to gain more information by personal discussion with people interested.

Since he has attended the meeting and gave no opportunity for his request to be considered in time he might be told that his application would be considered on the receipt of an adequate report describing the "vital information which he has obtained related to his research project" regarding the physiology and pharmacology of phenothiazine derivatives as they apply to use in prevention and treatment of shock (traumatic) and their use in association with anaesthesia and surgery.

It is not stated where Dr. Dobkin is working and it is accordingly not possible to evaluate the adequacy or otherwise of \$150 for his trip.

Ray Farquharson.

R. F. Farquharson,
Adviser in Medicine to DGTS.

Do not approve of making travelling expenses a charge against a research project. In my opinion travelling expenses for the purpose mentioned by the applicant, if approved, should be paid by a separate fund. Do not favour the acceptance of late applications for attendance at meetings.

Duncan Graham
Duncan Graham,

Adviser in Medical Education and
Research to DGTS.

Ottawa 2, Ont., April 13, 19 54.

TO Dr. R.F. Farquharson,
Professor of Medicine,
University of Toronto,
TORONTO, Ontario.

MARK YOUR REPLY:

For attention of

For attention of

Project 31-53 --
SUBJECT Hibernation in Anaesthesia by use of File No. 3-84 (T.5)
'Largactil' (Poulenc, 4560 R.P.).

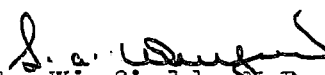
Dr. A.B. Dobkin is employed as a Research Fellow on the above-named project. He will terminate his fellowship in July.

On April 12 a request was received for Dr. Dobkin to attend the Federation Proceedings of the American Physiological and American Pharmacological Society in Atlantic City, April 12-15, and his expenses of \$150 be charged to the project.

No provision was made in the project for this expenditure and the application was received much too late. The object of his visit is said to be to obtain vital information related to his research project regarding the Physiology and Pharmacology of phenothiazine derivatives as they apply to use in prevention and treatment of shock (traumatic) and their use in association with Anaesthesia and Surgery.

I have written Dr. Gilbert pointing out that no provision was made for this expenditure and that the application was received much too late. I am, however, forwarding this for the consideration of the Board.

GAW/em


G. A. Winfield, M.D.,
Secretary,
Advisory Board for Medical Research
and Education.

Queen Mary Veterans Hospital,
Montreal, Que., April 23,

19 54.

TO Advisory Board for Medical Research
and Education,
Department of Veterans Affairs,
Ottawa, Ont.,

MARK YOUR REPLY:

APR 27 1954

For attention of

G.A. Winfield, M.D., Secretary

For attention of

R.G.B. Gilbert, M.D.,

Consultant,

File No.

SUBJECT Research Project 31-53

Dear doctor Winfield:

Thank you for your letter of April 13, 1954, file no. 3-84 (T.5), concerning expenses of a Fellow to attend a convention.

No provision was made in the application concerning this trip as the programme for this particular convention was not even conceived when our Project was started.

I am very aware of the tardiness of this application and only hope that it has not put you out as much as the degree implied in your letter.

Apologizing for troubling you, I remain,

Yours very truly,

Richard Gilbert

R.G.B. Gilbert, M.D.,
Consultant,
Department of Anaesthesia.

RGBG/FM

Read for Board.

Ottawa 2, Ont., April 13, 54.

Drs. Starkey & Farquharson

Project 31-53 --

Hibernation in Anaesthesia by use of
'Largaatil' (Poulenc, 4560 R.P.).

3-84(T.5)

Dr. A.B. Dobkin is employed as a Research Fellow on the above-named project. He will terminate his fellowship in July.

On April 12 a request was received for Dr. Dobkin to attend the Federation Proceedings of the American Physiological and American Pharmacological Society in Atlantic City, April 12-15, and his expenses of \$150 be charged to the project.

No provision was made in the project for this expenditure and the application was received much too late. The object of his visit is said to be to obtain vital information related to his research project regarding the Physiology and Pharmacology of phenothiazine derivatives as they apply to use in prevention and treatment of shock (traumatic) and their use in association with Anaesthesia and Surgery.

I have written Dr. Gilbert pointing out that no provision was made for this expenditure and that the application was received much too late. I am, however, forwarding this for the consideration of the Board.

GAW/em

sw
G. A. Winfield, M.D.,
Secretary,
Advisory Board for Medical Research
and Education.

Ottawa 2, Ont., April 13,

54.

Dr. R.G.B. Gilbert,
Queen Mary Veterans' Hospital,
Montreal, P.Q.

Project 31-53 --

Hibernation in Anaesthesia by use of
'Largactil' (Poulenc, 4560 R.P.)

3-84(T.5)

I received, yesterday, form DVA-TS 60 requesting that Dr. Dobkin attend the Federation Proceedings of the American Physiological and American Pharmacological Society in Atlantic City, April 12-15, and suggesting that his expenses, totalling \$150, be charged against his research project.

In the first place, no provision was made in the application for this trip. In the second place, the application was received much too late to allow the Board to give consideration to this. I am now forwarding a letter to the Board but I must express some doubt as to whether or not they will be prepared to approve this visit.

GAW/em

G. A. Winfield, M.D.,
Secretary,
Advisory Board for Medical Research
and Education.

Ottawa 2, Ont., April 1,

54.

D.F.P.S. (Financial Division).

Project 31-53 --

Hibernation in Anaesthesia by use of
'Largactil' (Poulenc, 4560 R.P.).

3-84(T.5)

The above-named project, in progress at Queen Mary Veterans' Hospital, has been approved for continuation into the coming fiscal year. Will you please, therefore, take the necessary action to release the sum of \$1,335 for remuneration of Dr. Dobkin. The charge is Vote 5, Primary 36, Object 460.

GAW/em

Law
G. A. Winfield, M.D.,
Secretary,
Advisory Board for Medical Research
and Education.

Ottawa 2, Ont., April 1, 54.

Dr. R.G.B. Gilbert,
Queen Mary Veterans' Hospital,
Montreal, P.Q.

Project 31-53 --
Hibernation in Anaesthesia by use of
'Largactil' (Poulenc, 4560 R.P.)

3-84(T.S)

As I informed you on February 11th, the Board approved the continuation of your project with certain revisions. Dr. Dobkin will receive remuneration at the rate of \$333.33 a month for four months. The item of \$150 for volunteers has been deleted. I am, therefore, requesting the release of a total of \$1,335 for Dr. Dobkin's remuneration.

when I note this project will be completed in July and would appreciate a report, in quadruplicate, on the progress made.

GAW/em

c.c. S.T.M.O., Montreal, P.Q.

c.c. Chairman,
Clinical Research Committee,
Queen Mary Veterans' Hospital.

GAW
G. A. Winfield, M.D.,
Secretary,
Advisory Board for Medical Research
and Education.

INTRA-DEPARTMENT
CORRESPONDENCE

DEPARTMENT OF VETERANS AFFAIRS

March 9th, 1954.

TO Dr. R.G. Gilbert & Dr. L. Lamoureux,
Queen Mary Veterans Hospital,
Montreal, P.Q.

MARK YOUR REPLY:

MAR 10 1954

For attention of

For attention of Dr. D.H. Starkey

SUBJECT Requisition for Anaesthesiometer and for
Oscilloscope. (Research Project 31-53).

File No. 3-84-31-53

Owing to an error in bookkeeping, changes were not properly shown in the accounts of this research project and the balance of \$487.70 given to us at the beginning of January should have read \$117.00. This money is, unfortunately, not enough to cover either of the items you are requesting. As neither of these items were listed in the original application and as the Project is supposed to be completed in 4 months' time, would it be possible to borrow what you need or to make other temporary arrangements for acquiring the necessary data?

D.H. Starkey, M.D.,
Chairman,
Clinical Research Committee.

DHS:BMF

*Copy for Dr. Winfield
- for the "record"*

P.A.-

Ottawa 2, Ont., February 12, 54.
D.F.P.S. (Financial Division).

Project 31-53 -
Hibernation in Anaesthesia by use of
'Largactil' (Poulenc 4560 RP)

3-84(T.5)

The above-named project, in progress in Montreal, requires additional funds for equipment. Will you please, therefore, take the necessary action to transfer the sum of \$30.00 from Object 460 to Object 467, Vote 5, Primary 36.

GAW/em

W
G. A. Winfield, M.D.,
Secretary,
Advisory Board for Medical Research
and Education.

Ottawa 2, Ont., February 12, 54.

Dr. D.H. Starkey,
Queen Mary Veterans' Hospital,
Montreal, P.Q.

Project 31-53 --
Hibernation in Anaesthesia by use of
'Largactil' (Poulenc 4560 R.P.)

3-84(T.5)

I have your memorandum of February 10 requesting the transfer from Object 460 to Object 467 of \$30.00. A transfer of \$150.00 was effected on September 21. I will now request a transfer of \$30.00 but I find difficulty in determining why \$30.00 is necessary to pay an account of \$1.30.

It would be appreciated if transfers between objects could be kept at a minimum. This entails considerable work not only in my department but in the Financial Division.

GAW/em

W
G. A. Winfield, M.D.,
Secretary,
Advisory Board for Medical Research
and Education.

TO Secretary,
Advisory Board for Medical Research & Education,
Department of Veterans Affairs,
Ottawa, Ontario.

February 10th, 1954.

MARK YOUR REPLY:

FEB 11 1954

For attention of Dr. G.A. Winfield

For attention of Dr. D.H. Starkey

SUBJECT Research Project 31-53: Studies with Largactil File No. 3-84 (31-53)
Drs. Lamoureux and Gilbert.

Further to my memorandum of February 2nd in respect to available funds for return to Head Office account, it appears that the necessary equipment will amount to \$1.30 more than the grantees' have left in their equipment account. They tried to keep the equipment estimates as close as possible to quoted prices, but it is now found that the Anesthesiometer and the Oscilloscope will cost \$489.00.

Would it be possible to transfer \$30.00 from the unexpended funds voted for salaries, to Object 467 in order to cover their requirements up to April 1st 1954.

D.H. Starkey
D.H. Starkey, M.D.,
Chairman,
Clinical Research Committee.

DHS:BMF

Ottawa 2, Ont., February 11, 54.

Dr. R.G.B. Gilbert,
Queen Mary Veterans' Hospital,
Montreal, P.Q.

Project 31-53 --
Hibernation in Anaesthesia by use of
'Largactil'. (Poulenc RP 4560).

3-84(T.5)

Your project, as named above, was considered by the Advisory Board for Medical Research and Education at their recent meeting and I am to inform you that they have approved of its continuation until July, 1954, with the following revision. The amount of \$150 for payment of local volunteers has been deleted. The Board suggests that cases being investigated under Project 14-54 might be used on this project.

This project now stands at approximately \$1,335 for remuneration of Dr. Dobkin for the four months. These funds will be released early in the fiscal year.

I will be pleased to receive a final report, in quadruplicate, on the termination of this project.

GAW/em
c.c. S.T.M.O., Montreal, P.Q.
c.c. Chairman,
Clinical Research Committee,
Queen Mary Veterans' Hospital.

G. A. Winfield, M.D.,
Secretary,
Advisory Board for Medical Research
and Education.

c.c. Mr. G.A. Armstrong.

003276

DEPARTMENT OF VETERANS AFFAIRS

TREATMENT SERVICES

APPLICATION TO CARRY OUT A RESEARCH PROJECT

31(53)

NOV 26 1953

NOTE: Application to be made in quadruplicate. All copies to be forwarded to the Secretary, Advisory Board on Medical Research and Education.

1. NAME OF APPLICANT Dr. R.G.B. Gilbert,
Dr. Louis Lamoureux DATE October 13, 1953.
2. POSITION HELD BY APPLICANT Consultants in Anaesthesia, Queen Mary Veterans Hospital.
3. SHORT TITLE OF PROPOSED PROJECT - D.V.A. Project 31-53.
"Largactil Study" (Poulenc RP 4560).
4. OUTLINE OF PROPOSED RESEARCH AND ITS OBJECTIVE
Definite objectives remain the same, but method of approach has been modified.
Objectives - 1) To discover hypothermic potentialities.
2) To investigate the drug a) In normal unanaesthetized individuals.
b) In anaesthetized patients
i) as premedicant -
ii) as adjuvant to other agents.
c) By its use in special groups of patients, i.e., intractable pain.
d) By animal experimentation.

Method of approach -
- See Interim Report -

5. RÉSUMÉ OF PRESENT STATE OF KNOWLEDGE AND PREVIOUS WORK BY THE APPLICANT RELATIVE TO THE PROPOSED RESEARCH WITH REFERENCES TO ESSENTIAL PUBLICATIONS

See Interim Report, which includes latest references.

31-53

6. ESTIMATE OF TIME REQUIRED TO COMPLETE PROJECT - A further eight (8) months
viz + Until July 31, 1954.
7. IN WHAT HOSPITAL, LABORATORY, ETC. DOES APPLICANT PROPOSE TO CARRY OUT THE PROJECT
Queen Mary Veterans Hospital
8. CONCISE STATEMENT AS TO ADEQUACY OF HOSPITAL, LABORATORY, ETC. EQUIPMENT
As before -
Now awaiting - 1) Ventilation Meter (expect within next few days).
2) Multipolar thermocouple (expect in two months).
Also utilizing Department of Pharmacology, McGill University for animal study.
9. ESTIMATE OF COSTS (OVER AND ABOVE NORMAL HOSPITAL, LABORATORY, TREATMENT, ETC. REQUIREMENTS)

(A) EQUIPMENT: (LIST APPARATUS OR MATERIALS REQUIRED, AND COST OF EACH ITEM)

No further equipment is envisaged as being necessary at
the moment.

\$ _____

(B) PERSONNEL: (LIST STAFF REQUIRED WITH POSITIONS, NAMES, QUALIFICATIONS AND RATES OF REMUNERATION OF THOSE WHO WILL BE SPECIALLY EMPLOYED IN THE RESEARCH PROJECT)

Adequate until March 31, 1954, when additional remuneration for
Dr. Allen B. Dobkin - Resident Fellow, will be necessary at \$333.33/month,
four (4) months.

\$ 1333.32
1333.32

(C) INDIVIDUALS TO BE STUDIED: (TRAVELLING, MAINTENANCE IN AND OUT OF HOSPITAL, LOSS OF WAGES, ETC. OVER AND ABOVE NORMAL INVESTIGATION AND TREATMENT REQUIREMENTS OF ENTITLED VETERANS OR OTHERS)

Local volunteers only being used -

If funds could be provided as an additional
inducement, it might be welcome -

\$ 150.00

(D) OTHER:

\$ _____

ESTIMATED TOTAL COST

\$ 1483.32

NOTE: ADD APPENDED SHEETS IF NECESSARY FOR ANY OF ABOVE SECTIONS.

10. IS THIS PROJECT RECEIVING SUPPORT FROM ANY OTHER SOURCE? No.
IF SO - SPECIFY

[Signature]

SIGNATURE OF APPLICANT

RECOMMENDED BY:

DATE October 13, 1953.

[Signature]

SIGNATURE OF CHIEF OF SERVICE

SERVICE

RECOMMENDED BY:

DATE Nov. 20, 1953

[Signature]

SIGNATURE OF CHAIRMAN, HOSPITAL COMMITTEE ON CLINICAL RESEARCH

DATE _____

APPROVED

NOT APPROVED

DIRECTOR GENERAL OF TREATMENT SERVICES

INTERIM REPORT ON D.V.A. PROJECT 31-53 - LARGACTIL STUDY

October 15, 1953.

by: Allen B. Dobkin, M.D.,
and the
Staff Anaesthetists.

NOV 26 1953

Investigation was undertaken to study the reported advantagenous effects of RP 4560, (known as largactil) for premedication, and for potentiation of the effects of commonly employed sedative-hypnotic, analgesic and anaesthetic drugs.

In order to evaluate the effects of this substance, the first four weeks of the study were spent in close association with Dr. Rene Létienne, and general observations were made as to its use as a supplement to anaesthesia. During this time it was realized that complicity with other anaesthetic drugs made it impossible to evaluate the specific effects of RP 4560.

The study was therefore arranged as follows:

1. Physiological study of a group of normal healthy volunteers -

Under the direction of Dr. Dobkin, five persons have been studied to date, before and after the intravenous use of various therapeutic doses of RP 4560.

The data was accurately collected with the assistance of -

1. An experienced graduate nurse who was in full time attendance during the study and made clinical notes of the procedures and charted vital signs. The same nurse was present at each study and was kindly arranged for by the Nursing Office of Queen Mary Veterans Hospital.
2. Two experienced technicians trained in taking electroencephalograms and electrocardiograms. Direction for eliciting the most pertinent data and interpretation of the electroencephalograms was kindly provided by Dr. D. Lloyd-Smith. Dr. Palmer reviewed the E.C.G.'s.
3. B.M.R. studies were carried out by Dr. Allen Dobkin.
4. Arterial blood samples were analyzed for oxygen and carbon dioxide content by the Respiratory Function Laboratory under the direction of Dr. Ronald Place.
5. Electrolyte, acid-base and metabolic blood studies were analyzed in the Biochemistry Laboratories under the direction of Dr. A.H. Neufeld.

LARGACTIL STUDY - (cont'd.)

2.

This data thus far indicates -

- a) There is a moderate lowering of body temperature, usually 1.5°F. orally and 2.0°F. rectally and on skin surface. This will be checked at a later date with accurate recording thermometers which have been on order for three- and-one-half months but have not arrived.
- b) B.M.R.'s have indicated a rise in oxygen consumption. Clinically and by arterial blood samples, it is evident that it had FALLEN. This may be explained by the fact that marked depression occurs in respiratory musculature and brings in the probable error due to resistance in the measuring device (Sanborn Metabolator). This is being studied further.
- c) There is moderate depression of rate and depth of respiration clinically. This will be more accurately investigated upon arrival of a ventilation meter now on order. This fact appears to be in absolute contradiction to the statement made by previous observers.
- d) No significant disturbance has been observed in the blood electrolytes which were studied (Serum: Na, K, PO₄, Cl).
- e) There is a slight fall in arterial oxygen content and slight rise in arterial CO₂ content with slight variable changes in the CO₂CP. No accurate pH data was available. Hematocrit and Hemoglobin estimation remained stable. Oxygen and CO₂ alterations reflect a depression of respiration.
- f) There is no significant effect on metabolism as indicated by Blood Urea Nitrogen and Blood Sugar.
- g) This substance causes marked drying effect on mucous membranes and reduces sweating. This action appears to be as effective clinically as atropine.
- h) When large doses are used intravenously vasomotor stability appears to be distinctly impaired with clear data showing orthostatic hypotension with E.E.G. evidence suggestive of cerebral ischemia during the peak action of this substance. With small oral and intramuscular doses, this effect is not seen.
- i) When large doses are used intravenously, there is a slight disturbance in cardiac rhythm. This is a sinus arrhythmia, and is accentuated by placing the patient in the upright posture.
- j) E.E.G. shows a typical pattern of drowsiness. Clinically, the substance exhibits a strong hypnotic effect. The state induced is different from that of morphine in that the patient may be easily aroused and is hypersensitive to sudden stimulation.

LARGACTIL STUDY - (cont'd.)

- k) There appears to be a disturbance in neuromuscular conduction evidenced by skeletal muscle paresis, noted mainly in the facial muscles (Ptosis, diplopia, weak masseters), upper extremities (Dynamometer studies) and lower intercostals.
- l) There is also a marked papillary constriction probably due to paresis of the dilator pupillae (sympathetic).
- m) There is probably a marked depression on gastric motility and secretion of gastric juices indicated by loss of appetite in these subjects and relief of pain in patients with ulcer (to be reported at a later date when more data is available and further studies carried out).
- n) There is a disturbance in micturation lasting more than 12 hours, probably due to parasympathetic inhibition.
- o) The possible reversal of effects of this substance has been tested with Benzedrine, Dexedrine, Caffeine-Sodium Benzoate, Tensilon and Prostigmin, all with no clinical effect. These will be studied more extensively.
- p₁ RP 4560 has topical anaesthetic effects on mucous membranes of the mouth. It is proposed to study an additional 10 - 15 normal subjects. This will be undertaken when permission is granted by Colonel P. Tremblay, to test army personnel, and if funds are available as inducement to local personnel.

II. A controlled study is now under way to investigate the effectiveness of RP 4560 as a premedicating drug. It is proposed to study 300 cases; with this substance as the sole premedicant. Control of data is kept with a questionnaire in order to maintain uniformity of observations and to facilitate tabulation of results.

III. A study is in progress to investigate the potentiating effect of this substance in General Anaesthesia; to investigate the sedative effect during Spinal Anaesthesia; and to investigate the stabilizing effect on blood pressure in patients who are in shock, and who are under the influence of total spinal for upper abdominal and thoracic surgery.

IV. A limited number of patients were administered this substance post-operatively to potentiate the effects of analgesics (morphine and demerol). This was claimed to have deleterious effect due to an apparent increase in pulmonary complications. This was attributed to the fact that the patients felt weak, drowsy, and were immobile when under the influence of this substance. This phase of the investigation has therefore been abandoned for the present.

LARGACTIL STUDY - (cont'd.)

- V. A series of patients with intractable pain and with pain requiring large doses of morphine, demerol and methadon (due to such conditions as inoperable bronchogenic carcinoma and other terminal conditions), are being studied. To date, it has been possible almost to eliminate the strong analgesics in a few cases. This series is being extended.
- VI. Animal experiments have been carried out with the kind assistance of Professor K.I. Melville of the Department of Pharmacology at McGill University. These will be continued as the necessity arises to elicit data that is not applicable to clinical study. To date, three studies have been made. These have ruled out a myoneural junction blocking effect by this substance of the competitive or curare type. There appears to be some depression of the spinal cord and medulla which may be analogous to the Myanesin type of block. The Depolarizing or Decamethonium type of block may be possible. (See reports on animal studies).

NO GROSS CLINICAL REACTIONS HAVE BEEN OBSERVED DURING THE USE OF A WIDE RANGE OF DOSAGE OF THIS SUBSTANCE.

The studies to date indicate that RP 4560 has the following pharmacological effect -

1. Sedative - Hypnotic - Similar to but stronger than Benadryl, Pyribenzamine and Phenergan.
2. Blocks or inhibits the release of Acetylcholine (reversible).
 - 1) At parasympathetic ganglia and postganglionic nerves - indicated by decreased sweating, salivation and probable depression of gastric secretion, and gastric and G.I. spasm (Hexamethonium effect), and blocked innervation of the detrusor muscle of the bladder. May prevent motion sickness (as well as phenergan, dramamine and atropine).
 - 2) Neuromuscular block to skeletal muscle not related to d'Tubocurrarine or Gallamine, possibly related to Decamethonium or Succinylcholine, and probably caused by inhibition of Acetylcholine release (described by Paton as "deficiency of transmitter"). Ref: Anaesthesia, Vol. 8, No. 3 - July, 1953.
 - 3) Block of sympathetic ganglia - similar to hexamethonium and indicated by orthostatic hypotension, elevated P and T waves in electrocardiogram (lead II) and tachycardia during general anaesthesia.
3. Local anaesthetic effect topically. Possibly also locally when injected.

LARGACTIL STUDY - (cont'd.)

4. By block of Acetylcholine release, may effect a redistribution of heat and cold receptors in skin and mucous membranes causing a fall in body temperature. Hypothalamic effect is not likely. Reference 4.

RECENT REFERENCES -

1. J.P.E.T. July, 1953 - Comparative study of Phenothiazine derivatives (Supported by NRC grant).
2. Acta Pharm. et Toxic Vol. 9, Fasc 2 - Activity of Basically Substituted Derivatives of Phenothiazine, Atropine, Papaverine and other Spasmolytic Drugs against Barium and Acetylcholine induced spasms in guinea pigs and rat ileum (Dahlbom, Edlund, Ekstrand). Shows Phenothiazine reduce spasm in manner similar to hexamethonium.
3. Idem: Protective Effect of Phenothiazine Derivative against Poisoning by the Irreversible cholinesterase inhibitor Tabun (Bo Holmstedt et al). This paper suggests antimuscarinic and antinicotinic effect of phenothiazine plus protective action by preventing destruction of enzyme anticholinesterase.
4. Idem: Hartz and Riskaer. Effects of Antihistamine on Vestibular function in guinea pigs.
5. Acta Physiologica Scandinavica Vol. 28, Fasc. 2 - 3 (30-5-53) E. Dodt, A.P. Skouby and Y. Zotterman. The effect of Cholinergic Substances on the Discharges from Thermal Receptors.

This paper demonstrates that Acetylcholine (in minute amounts) shifts the temperature range of the steady discharge of cold fibers towards the warm side and increases the rate of the stationary discharge of the receptors inside the normal range of temperature. The observed slight lowering of body temperature during RP 4560 may be indicative of a reversal of this effect by inhibiting Acetylcholine release.

6. Physiology and Pharmacology of Vomiting. H.L. Borison and S.C. Wang. Pharmacological Review. Vol. 5, No. 2, June, 1953.
7. Neuropharmacology of Peripheral Nerve - James E.P. Toman, Pharmacological Reviews, Vol 4, No. 2 - June, 1952.
8. Idem, The Methonium Compounds. W.D.M. Paton, E.J. Zamais (Sept. 1952.).

LARGACTIL STUDY - (cont'd.)

Further studies to be undertaken - (not yet in progress) -

1. A clinical study of the alleviation of post-operative nausea and vomiting has been proposed. Reference - French Literature -
J.A.M.A. Oct. 3, 1953, Vol. 153, No. 5.
Doctors Friend and Cummins.
2. Study of pulmonary ventilation effects and B.M.R. effects - Awaiting ventilation meter.
3. RP 4560, atropine and hyoscine to be compared for effects on secretions.
4. Animal investigation of possible depolarizing action at Myoneural junction. (Decamethonium - like action) - cats required.
5. Clinical study of effects on, a) gastric motility, b) gastric secretion, c) gastric acidity comparing RP 4560, Banthine, Probanthine, Centrine and Atropine.
6. Clinical study of effects on kidney function and on micturition.
7. Test topical (? local) anaesthetic potency and toxicity of RP 4560.
8. Compare RP 4560, dramamine and gravol effects on motion sickness and post-operative nausea and vomiting. Reference C.M.A.J. Oct. 1953, Vol. 69, No. 4.
9. Compare bronchodilating effect of isopropyl adrenalin with RP 4560.

Clinical study of liver function has been in progress by other local investigators and will not be repeated.

Allen B. Dobkin M.D.

Allen B. Dobkin, M.D.,
Research Fellow in Anaesthesia.

R.G.B. Gilbert

R.G.B. Gilbert, M.D.,
Consultant,
Department of Anaesthesia.

INTRA-DEPARTMENT
CORRESPONDENCE

DEPARTMENT OF VETERANS AFFAIRS

Document disclosed under the Access to Information Act
Document divulgué en vertu de la Loi sur l'accès à l'information

Queen Mary Veterans Hospital
Montreal, Qué., Sept. 11, 19 53.

TO Advisory Board for Medical
Research and Education,
Ottawa, Ont.,

MARK YOUR REPLY:

For attention of Dr. G.A. Winfield,
Secretary

For attention of R.G.B. Gilbert, M.D.,

SUBJECT Project 31-53 - Largactil

File No. 124 (AN) 2-5.

Dear doctor Winfield:

I am enclosing a Curriculum Vitae. Dr. Dobkin was unable to commence work here until the 1st of August. I am seeing the authorities here so that his payment will commence from that time.

We are very pleased with the manner in which Dr. Dobkin has commenced his studies under our direction. I will endeavour to give you an interim report from time to time.

I note that a continuance of his service needs reapplication in triplicate by mid-December this year.

Yours sincerely,

R.G.B. Gilbert

R.G.B. Gilbert, M.D.,
Consultant,
Department of Anaesthesia.

RGBG/FM

encl:

c.c. Dr. D.H. Starkey,
Advisor - Laboratories.

① W. Cunningham.
Ph return

James

CURRICULUM VITAE

DOBKIN, Allen, Benjamin

Home Address 209 Major Street, Toronto, Ontario.

Present Address 3955 Dupuis Ave., Montreal 26, Quebec.

Place & Date of Birth Toronto, Ont., June 25, 1923.

Marital Status Married - One child

Nationality Canadian

Father Hyman Dobkin, 209 Major Street, Toronto, Ont.,

Age: 61 Nationality Naturalized Canadian Occupation: Tailor

Mother Gussie Dobkin,

Age: 59 Occupation: Housewife

Brother John Dobkin, Canton, Ohio.,

Age: 39 Nationality: Naturalized American

Occupation: Physician Cardiologist.

Brother Raymond Dobkin, Toronto, Ont.,

Age: 29 Nationality: Canadian (Birth)

Occupation: Executive (Tip Top Tailors)

Wife Edith Dobkin

Son Gary, Richard Dobkin

Age: 7 months.

Education

1. Huron State School, Toronto, Ont., (8 yrs.)
2. Harbord Collegiate Institute, Toronto, Ont., (5 yrs.) Senior Matriculation.
3. University of Toronto Faculty of Arts, (3 yrs.) Bachelor of Arts.
4. University of Toronto Faculty of Medicine (4 yrs.) Doctor of Medicine.
5. Mount Sinai Hospital, Cleveland, Ohio, (1yr.) Rotation Internship.
6. Mount Sinai Hospital, Cleveland, Ohio, (1 yr.) Asst. Resident in Surgery.
7. University of Minnesota - Fellowship in Anaesthesia.

DOBKIN, Allen, Benjamin

Licensure

1. Medical Council of Canada, 1949 (June), No. 10368.
2. Ohio State Board, 1951, No. 17703.
3. Minnesota State Board, 1952, No. 12240.
4. American Board in Anaesthesiology, Part I, - Successfully completed,
July, 1953.

Membership

1. American Society of Anaesthesiologists Inc., No. 5399.
2. Minnesota Society of Anaesthesiologists.
3. American Medical Association, (Junior).

Research Projects Completed

1. Physiological Observations on Patients Subjected to Hexamethonium-Induced Hypotension. (Frederick H. Van Bergen, M.D., Joseph J. Buckley, M.D., and Allen B. Dobkin, M.D.,).

This paper was presented at the University of Minnesota Staff Meeting on March 20, 1953, and an expanded paper will be presented at the A.S.A. Meeting in Seattle in October, 1953.

2. A Study of Post-anaesthetic Hypotension Following Cyclopropane: Its Relationship to Hypercapnia. (Joseph J. Buckley, M.D., Allen B. Dobkin, M.D., Frederick H. Van Bergen, M.D.,).

This paper is in press in Anaesthesiology Journal.

3. Electrocardiographic Abnormalities Encountered During Endotracheal Intubation. (Joseph J. Buckley, M.D., Allen B. Dobkin, M.D., William Evers, M.D., Frederick H. Van Bergen, M.D.,).

This study is complete and is being prepared for publication.

4. Respiratory Acidosis in Patients Suffering From Bulbar Poliomyelitis, (Frederick H. Van Bergen, M.D., Ion Brown, M.D., Allen B. Dobkin, M.D., E.B. Brown, PhD.,).

This paper is being prepared for publication.

5. An evaluation of the Three Indirect Methods of Recording Blood Pressure as Compared with the Direct Intra-arterial Pressure. (Frederick H. Van Bergen, M.D., Allen B. Dobkin, M.D.,).

This paper is being prepared for publication.

6. Respiratory Acidosis During Ether Anaesthesia Utilizing the Mass Spectrometer Alveolar Gas Analysis and Blood Gas Analysis. (Allen B. Dobkin, M.D., Frederick H. Van Bergen, M.D., E.B. Brown, PhD.,).

This study is complete and forms part of my thesis study.

DOBEN, Allen, Benjamin

7. The Effect of Posture Upon Carbon Dioxide and Oxygen Tensions Under Anaesthesia. (Joseph J. Buckley, M.D. William Evers, M.D., Allen B. Dobkin, M.D., Frederick H. Van Bergen, M.D.,).

This study is now in progress.

8. During 1952, I compiled the data from this Hospital's records for the Henry K. Beecher Anaesthesia Death Study which is now being prepared for publication.

Publications

1. March, 1952, - "The Study of Hypercapnia" - University of Minnesota Staff Bulletin.
2. March, 1953, - "Hypotensive Anaesthesia" - University of Minnesota Staff Bulletin.
3. May, 1953, - "Post-anaesthetic Hypotension after Cyclo" - Anaesthesiology Journal.

Others in active preparation.

Teaching Experience

Clinical Instructor in Anaesthesiology - University of Minnesota Hospital - February, 1952 - February, 1953.

Ultimate Career

Practice Anaesthesiology, Academic teaching and research.

Particularly interested - Respiratory Physiology.

Allen B. Dobkin M.D.
.....

ABD/FM

Ottawa 2, Ont., Sept. 21,
D.F.P.S. (Financial Division).

53.

Project 31-53 --
Hibernation in Anaesthesia by use of
'Largactil'.

3-84(T.5)

The above-named project, being undertaken in Queen Mary Veterans' Hospital, requires an additional \$150 for equipment. Will you please, therefore, take the necessary action to transfer this amount from Object 460 to Object 467.

GAW/em

u
G. A. Winfield, M.D.,
Secretary,
Advisory Board for Medical Research
and Education.

Ottawa 2, Ont., Sept. 21,

53.

Dr. R.G.B. Gilbert,
Consultant, Department of Anaesthesia,
Queen Mary Veterans' Hospital,
Montreal, P.Q.

Project 31-53 --

Hibernation in Anaesthesia by use of
'Largactil'.

3-84(T.5)

Reference your memorandum of September 18, please
be advised that I am transferring the sum of \$150 from
Object 460 to Object 467.

GAW/em

س
G. A. Winfield, M.D.,
Secretary,
Advisory Board for Medical Research
and Education.

c.c. Dr. D.H. Starkey,
Queen Mary Veterans' Hospital,
Montreal, P.Q.

BOND

MADE IN CANADA

003290

INTRA-DEPARTMENT
CORRESPONDENCE

DEPARTMENT OF VETERANS AFFAIRS

TO Dr. G.A. Winfield,
Secretary,
Advisory Board for Medical Research & Education,
Department of Veterans Affairs,
Ottawa, Ontario.

September 18th 19 53.

MARK YOUR REPLY:

For attention of

For attention of

SUBJECT Research Project #31-53; Equipment costs

File No. 124-3-84-31 (53)

The observations projected were originally confined to the use of ordinary equipment except for the special observation on patients' temperatures. In the light of recent work it has been found necessary to have more exact information in the field of respiratory physiology, most of which can be tackled with existing facilities in collaboration with Dr. Place. An Oximeter was needed to round out the equipment, and it was thought that this could be obtained within the four-hundred dollars allowed for equipment. Unfortunately we have just been informed that the electrical thermometric equipment being obtained from Denmark is going to cost slightly more than the original estimates indicated.

Our immediate requirements for equipment amount to \$462.30 - \$62.30 above the original estimate. Because the Research Fellow was unable to start work until the 1st of August, the allowance for salary stands at \$330.00 over the amount required.

Would the Advisory Board be agreeable to transferring either the exact sum required or perhaps \$150.00 so that there would be a little amount in the account for small pieces of equipment that might be required unexpectedly in the next few months.

Richard B. Gilbert

R.G.B. Gilbert, M.D.,
Consultant, Department of Anaesthesia.

D.H. Starkey

Recommended: D.H. Starkey, M.D.,
Chairman,
Clinical Investigation Committee.

RGB:BMF



WILDER PENFIELD, M.D.
Director

EILEEN C. FLANAGAN, B.A., R.N.
Director of Nursing

MISS E. DEBRISAY
Director of Social Service

MONTREAL NEUROLOGICAL
INSTITUTE

HOSPITAL DEPARTMENT

3801 UNIVERSITY STREET
MONTREAL 2, CANADA

J. PRESTON ROBB, M.D.
Executive Assistant

DONALD LLOYD-SMITH, M.D.
Secretary-Registrar

D. C. BAIN, B.A.
Business Manager

Dept. of Anaesthesia.
Queen Mary Veterans' Hospital
Montreal. 28/7/53.

File No - 3-84 (T.G.)

Dear Dr. Winfield,
Thank you so much for
your letter of July 16th. Dr. Hammond
and myself are grateful to you for
facilitating the approval of our Projects.

Through a misunderstanding,
Dr. Dobbin is not available until
August 3rd, at which date he
will join our staff.

I am taking my holiday
during August so that I will not
be on Project -

be able to send you full details
concerning Dr. Dobkin's qualifications
until I return — That is, other
than those already submitted.

However I will make it one
of my first duties, on return.

I have left with him details
of work to be carried out.

Thanking you again

Yours sincerely

Richard B. Platt.

Ottawa 2, Ont., July 14,

53.

Mr. G.A. Armstrong.

Project 31-53 --

Hibernation in Anaesthesia by use of
'Largactil' (Poulenc, 4560, R.P.)

3-84(T.5)

Will you please take the necessary action to authorize the employment of Dr. Allen B. Dobkin, on a casual basis, at the rate of \$4,000 per annum. I believe Dr. Dobkin may have begun his duties on July 1st, but at any rate he should be taken on as soon as he is available. Funds have been released.

GAW/em

G. A. Winfield, M.D.,
Secretary,
Advisory Board for Medical Research
and Education.

Ottawa 2, Ont., July 14, 53.

D.F.P.S. (Financial Division).

Project 31-53 --
Hibernation in Anaesthesia by use of
'Largactil' (Poulenc, 4560, R.P.)

3-84(T.5)

The above-named project has been approved by the
Advisory Board for commencement at Queen Mary Veterans'
Hospital. Will you please, therefore, take the necessary
action to release a total of \$3,400 under Vote 5, as follows:

Object 460	\$ 3,000
Object 467	<u>400</u>
Total	\$ 3,400

GAW/em

G. A. Winfield, M.D.,
Secretary,
Advisory Board for Medical Research
and Education.

Ottawa 2, Ont., July 14, 53.

Dr. R.G.B. Gilbert,
Consultant in Anaesthesia,
Queen Mary Veterans' Hospital,
MONTREAL, P.Q.

Project 31-53 --

Hibernation in Anaesthesia by use of
'Largactil' (Doulenc, 4560 R.P.).

3-84(T.5)

The above-named project, as submitted by you and Dr. Lamoureux, has now been returned by the Advisory Board and I am pleased to inform you that they have approved of this application.

I am, therefore, requesting the release of a total of \$3,400 allocated as follows: \$3,000 for remuneration for Dr. Dobkin at the rate of \$4,000 per annum. This will compensate Dr. Dobkin for the remaining nine months of the fiscal year. \$400 for the purchase of equipment.

It would be appreciated if you would forward the necessary forms concerning Dr. Dobkin's qualifications so that they may be processed by the Civil Service Commission. In the interim I am requesting authority for Dr. Dobkin's employment on a casual basis.

I note that this project is expected to reach completion within one year. If it is proposed to continue it beyond 31 March, 1954, it will be necessary to resubmit it in application form together with a report of progress to date, in triplicate, to reach this office not later than mid-December, 1953. This is essential in order that it may be placed before the Advisory Board at their annual meeting.

GAW/em

c.c. S.T.M.O., Montreal, P.Q.

c.c. Chairman,

Clinical Research Committee,
Queen Mary Veterans' Hospital.

c.c. Mr. G. A. Armstrong.

G. A. Winfield, M.D.,
Secretary,
Advisory Board for Medical Research
and Education.

UNIVERSITY OF TORONTO
DEPARTMENT OF MEDICINE

File No. 3-84-4(T.5)

July 6 1953

MEMORANDUM FOR

JUL 14 1953

Dr. G.A. Winfield, Secretary,
Advisory Board for Medical Research and Education,
Department of Veterans Affairs,
Ottawa, Canada.

Re: Project 31-53 -

Hibernation in anaesthesia by use of 'Largactil'
(Poulenc, 4560 R.P.) - Drs. Gilbert and Lamoureux,
Queen Mary V.H., Montreal.

I should approve this application.

R. F. Farquharson

R. F. Farquharson
Adviser in Medicine to DGTS.

Application approved
10. 7. 53

Duncan Graham

Duncan Graham,
Adviser in Medical Education and
Research to DGTS

I approve the application
10. 7. 53
Duncan Graham

Ottawa 2, Ont., July 8,

53.

Dr. R.F. Farquharson,
Professor of Medicine,
University of Toronto,
TORONTO, Ontario.

Project 31-53 --

Hibernation in Anaesthesia by use of
'Largactil' (Poulenc, 4560 R.P.)

3-84(T.5)

May I now have the comments of the members of
the Board in your area with respect to the above-named
project which was forwarded to you on June 26, please.

GAW/em

G. A. Winfield, M.D.,
Secretary,
Advisory Board for Medical Research
and Education.

Ottawa 2, Ont., June 26, 53.

Dr. R.F. Farquharson,
Professor of Medicine,
University of Toronto,
TORONTO, Ontario.

Project 31-53 --
Hibernation in Anaesthesia by use of
'Largactil' (Poulenc, 4560 R.P.)

3-84-4(T.5)

I am attaching, herewith, application form to carry out the above-named research project. This project will entail a total of \$3,400. I am given to understand that Dr. Dobkin is now proceeding to Montreal. It is proposed to employ him at the rate of \$4,000 per annum with effect 1 July. The Montreal Section of the Board have approved this project and Dr. Warner is very much interested in it. I understand that Dr. Shapley, Adviser in Anaesthesia, is fully conversant with it.

Since there is some urgency in the matter, I would appreciate this being circulated to the members of the Board in your area and returned as early as possible.

GAW/em

G. A. Winfield, M.D.,
Secretary,
Advisory Board for Medical Research
and Education.

DEPARTMENT OF VETERANS AFFAIRS

TREATMENT SERVICES

APPLICATION TO CARRY OUT A RESEARCH PROJECT

NOTE: Application to be made in quadruplicate. All copies to be forwarded to the Secretary, Advisory Board on Medical Research and Education.

Dr. R.G.B. Gilbert

1. NAME OF APPLICANT Dr. Louis Lamoureux

DATE June 8th, 1953.

2. POSITION HELD BY APPLICANT Consultants in Anaesthesia, Q.M.V.H.

3. SHORT TITLE OF PROPOSED PROJECT

(Hibernation in Anaesthesia by use of 'Largactil' (Poulenc, 4560 R.P.))

4. OUTLINE OF PROPOSED RESEARCH AND ITS OBJECTIVE

- Objects: (1) To study the hibernation properties of Largactil in man.
(2) To assess whether such response is beneficial.
(3) If it is so, to determine what types of case its use could be of maximum advantage.

Method of approach:

- (1) Observations to be made on (a) A selected group (b) A control group.
(2) Subjects to be given as near a standard premedication and anaesthetic as possible.
(3) Observation details:
(a) Clinical - Preoperative, Perioperative, Postoperative.
(b) Investigative.
(i) Temperature - Skin, Rectal, Muscle.
(ii) Oxygen utilization studies.
(iii) Arterial oxygen saturation.
(iv) CO₂ combining power.
(v) E.K.G. recordings. (Such observations to be made before operation - 30", 60", 2 hrs., 4 hrs., and 24 hrs. following commencement).
(vi) Possibly also tidal exchange.

Note: It is planned to do one patient per day.

5. RÉSUMÉ OF PRESENT STATE OF KNOWLEDGE AND PREVIOUS WORK BY THE APPLICANT RELATIVE TO THE PROPOSED RESEARCH WITH REFERENCES TO ESSENTIAL PUBLICATIONS

Clinical observations only have for the most part been carried out with this drug, except for E.K.G.'s (L.L.)

It would appear that -

- (1) Less anaesthetic agent is necessary.
(2) Respiration is stimulated.
(3) Less postoperative use of analgesics is necessary.
(4) Mental reaction following operation may be temporarily altered in a "lobotomized" manner.

It is our desire to substantiate clinical impressions and to gain some definite knowledge as to the organismal response.

References: Alluame, R. Anaesésie et Analgésie IX, 2:261 - June 1952.
Deschamps, A. La Presse Médicale 60, 43:944 - June 1952.
Forster, S. et al. Anesthésie et Analgésie IX, 2:250 - June 1952.
Laborit, H. L'anesthésie facilitée par les synergies médicamenteuses.
" " La Presse Médicale 60, 10:204 (1952) Masson et Cie - Paris '51
" " Anesthésie et Analgésie IX, 2 (supplément) - June 1952.
" " La Presse Médicale 60, 60:1256 (Sept. 1952).
Hudon, F. Paper read before Canadian Anaesthetist Soc. Ont. Div. April '53

6. ~~ESTIMATE~~ ESTIMATE OF TIME REQUIRED TO COMPLETE PROJECT
(To be combined with Dextran project) 1 year.
7. IN WHAT HOSPITAL, LABORATORY, ETC. DOES APPLICANT PROPOSE TO CARRY OUT THE PROJECT
Queen Mary Veterans Hospital, Montreal, P.Q.
8. CONCISE STATEMENT AS TO ADEQUACY OF HOSPITAL, LABORATORY, ETC. EQUIPMENT
It would seem to be adequate with the cooperation of Dr. R.E.G. Place and his Respiratory Function facilities, except for simultaneous temperature recordings.
9. ESTIMATE OF COST (OVER AND ABOVE NORMAL HOSPITAL, LABORATORY, TREATMENT, ETC. REQUIREMENTS)

(A) EQUIPMENT: (LIST APPARATUS OR MATERIALS REQUIRED, AND COST OF EACH ITEM)

Danish cost

1. Electric Universal thermometer, Type T.E. 3	975 Kr.	\$141.00
2. Connection box type F.E.	265 Kr.	38.00
3. Specific electrodes - 8 in all H ₂ , H ₃ , K ₃ , R ₁ - two of each	65 Kr. each	75.00
4. Estimated agents fees, freight, etc.	520 Kr.	80.00
5. Miscellaneous		66.00
		<u>\$ 400.00</u>

(B) PERSONNEL: (LIST STAFF REQUIRED WITH POSITIONS, NAMES, QUALIFICATIONS AND RATES OF REMUNERATION OF THOSE WHO WILL BE SPECIALLY EMPLOYED IN THE RESEARCH PROJECT)

1. Research Fellow in Anaesthesia.

It is hoped Dr. Allen B. Dobkin will undertake this.
Dr. Dobkin is a Toronto graduate of 1949. He has done 1 yr. Rotating internship. 1 yr. senior in Surgery. 2 years with Dr. Ralph Knight of the University of Minnesota where he has taken part in nine research projects.
(Available July 1st)

\$ 4000.
\$3600 to \$4800

(C) INDIVIDUALS TO BE STUDIED: (TRAVELLING, MAINTENANCE IN AND OUT OF HOSPITAL, LOSS OF WAGES, ETC. OVER AND ABOVE NORMAL INVESTIGATION AND TREATMENT REQUIREMENTS OF ENTITLED VETERANS OR OTHERS)

Entitled patients only.

\$ _____

(D) OTHER:

\$ 4400

ESTIMATED TOTAL COST

\$ ~~4000 to \$5000~~

NOTE: ADD APPENDED SHEETS IF NECESSARY FOR ANY OF ABOVE SECTIONS.

Richard B. Plu
SIGNATURE OF APPLICANT

RECOMMENDED BY:

DATE

June 24/53

W. B. Baer
SIGNATURE OF CHIEF OF SERVICE

Surgery
SERVICE

RECOMMENDED BY:

DATE

June 25/53

D.H. Bailey
SIGNATURE OF CHAIRMAN, HOSPITAL COMMITTEE ON CLINICAL RESEARCH

DATE

APPROVED

NOT APPROVED

DIRECTOR GENERAL OF TREATMENT SERVICES

003302