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CIRC 19F  
 RECAP SHEET  
 (as of May 2, 1975)

Title: Effort to reverse the signs and symptoms of Parkinsonism with L-Dopa

Spon.Phys.: G.C. Cotzias  
 Prin.Invest: Papavasiliou  
 Mendez

APPROVALS

<u>CIRC</u>	<u>DEPT.</u>
	Initial
3/6/72	3/11/72
	Recertification
3/19/73	3/26/73
	Recertification
5/13/74	5/15/74

No Investigational Consent required.

IND 3911-Dihydroxyphenylalanine inactive in view of commercial availability of compound.

The Medical Research Center  
 Brookhaven National Laboratory  
 Upton, L. I., New York

REPOSITORY Records Holding Area Bldg. 494  
 COLLECTION Clinical Committee - Investigations and  
 BOX No 4 uses of Radioisotopes  
 FOLDER CIRC # 197F

1179901

October 7, 1975

George C. Cotzias, M.D.  
Neurology Department  
Cornell Medical Center  
1300 York Avenue  
New York, New York 10021

Dear Dr. Cotzias,

Effective today, I have inactivated the following CIRC's:

CIRC 19F-Effort to Reverse the Signs and Symptoms of Parkinsonism  
with L-Dopa. IND#3911

CIRC 64R-Administration of 3,4 dihydroxyphenylacetic acid (DOPAC)  
to Patients with Parkinsonism. IND# 7699

CIRC 98 -Piperidine Hydrochloride as an Adjunct to the Treatment  
of Parkinsonism with Levodopa. IND# 9768

When your active CIRC's become due for Annual Recertification, they  
will be reviewed and if no further study is anticipated, they will also  
be declared inactive.

Would you please send me a copy of your letter to the FDA stating  
that the corresponding IND's (3911,7699 and 9768) are no longer being  
used at Brookhaven.

Sincerely,

Robert B. Aronson, Ph.D.  
Associate Chairman

RBA/ck

1179902

Title: Effort to reverse the signs and symptoms of Parkinsonism with L-Dopa

*Inter-activate as per memo  
(No Return) R.B. Aronson  
10/17/75*

To: Dr. Cotzias

Date: May 29, 1975  
~~May 2, 1975~~

Please indicate below whether this proposal is continuing or inactive. If continuing, complete the entire form, and attach to this sheet copies of any reports submitted to the FDA, HEW, or other Granting Agency (in connection with this proposal and the IND numbers given), since the last CIRC approval date. Also please add any additional information which may be of use to the Committee in its deliberations. If inactive, merely sign and return this form.

If this form is not returned by June 16, 1975 ~~May 19, 1975~~, approval of the proposal will automatically be discontinued.

(See attached recap sheet)

*R.B. Aronson*

R.B. Aronson, Ph.D., Associate Chairman

May 29, 75  
Date

To R.B. Aronson,

CIRC PROPOSAL NUMBER \_\_\_\_\_ IS: Continuing  Inactive

Proposed substantive changes are attached \_\_\_\_\_

Adverse effects that have been first noted since the last approval include:

Since the last approval \_\_\_\_\_ patients have been submitted to the experimental regimen.

The Sponsoring Physician as of this date is \_\_\_\_\_

The following changes in Investigators should be noted: \_\_\_\_\_

The following IND #'s have been obtained for specific compounds used in this proposal:

Compound \_\_\_\_\_ IND # \_\_\_\_\_ Compound \_\_\_\_\_ IND # \_\_\_\_\_

The investigational consent form(s) used in this project are numbered \_\_\_\_\_ and copies are attached. Patients involved in this study are referrals from or also studied at the following institution(s)

Attach statement from institution(s) indicating the review committee approval is current.

Signed \_\_\_\_\_  
Principal Investigator Date

\_\_\_\_\_  
Sponsoring Physician Date

1179903

Minutes CIRC Meeting

13 May 1974

Present: E.A. Popenoe, H.R. Connell, R.A. Love, P.S. Papavasiliou,  
G.A. Price, N.P. Rathvon, Jr., U. Reincke

Absent: L.D. Hamilton

The meeting was held in the Small Conference Room of the Medical Research Center. Dr. Popenoe opened the meeting at 1400.

The minutes of the previous meeting, 1 April 1974, were accepted as distributed.

The following communications were received and duly noted:

- 1) Copy of the letter to the FDA requesting amendment to IND 10402 to use thallium-201 as thallos chloride provided by the New England Nuclear Corp., Boston, Mass.
- 2) Memo to Dr. Cronkite from Dr. Popenoe re whole-body counting dated 23 April 1974.
- 3) Copy of letter to FDA from Dr. Atkins to include Dr. Shreeve as an investigator on IND 7677.

CIRC#19F was reviewed for recertification and approved without qualification.

CIRC#114 was approved but not unanimously. N.P. Rathvon, Jr. dissented.

CIRC#115 was approved without qualification.

The Committee next discussed the proposed new CIRC forms and suggests the following changes:

Clinical Investigation Proposal  
CIRC form 2-1

Paragraph B. - More space be made available for presenting the information requested.

Paragraph D. - Include legal competence of the patient  
Indicate other investigative programs the patient is participating in  
Provide more space for presenting the information requested

Supplementary Information on Radionuclide Administration  
CIRC form 2-3

Paragraph A. - Include total amount of activity to be administered  
Question 5

1179904

CIRC Status Memo. CIRC form #4

Change in wording

From: "Adverse effects that have not already been reported to the Department Chairman include:"

To: "Adverse effects that have been first noted since the last approval include:"

The meeting was adjourned at 1500.

Respectfully submitted,



Helen R. Connell

1179905

HOSPITAL OF THE MEDICAL RESEARCH CENTER,  
BROOKHAVEN NATIONAL LABORATORY  
Upton, New York 11973

CIRC No. 19F

CLINICAL INVESTIGATION AUTHORIZATION FORM

TITLE: Effort to reverse the signs and symptoms of parkinsonism with L-dopa.

PURPOSE OF REVIEW:

- INITIAL
- ADDENDUM
- REVISION
- RECERTIFICATION
- REACTIVATION

TO CHAIRMAN, CIRC:  
THE PROPOSAL FOR CLINICAL INVESTIGATION IDENTIFIED BY THE ABOVE CIRC NUMBER AND TITLE IS FORWARDED HERewith FOR REVIEW AND RECOMMENDATION.

E.P. Cronkite 3 May '74  
E.P. CRONKITE, M.D., Chairman, Medical Department Date

TO CHAIRMAN, MEDICAL DEPARTMENT:  
THE CIRC REVIEWED THE ABOVE IDENTIFIED PROPOSAL ON May 13, 1974 AND RECOMMENDS Recertification  
WITH THE FOLLOWING MODIFICATIONS:

None

<u>Eduin A. Popenoe</u> E.A. POPENOE, Chairman	<u>N. Peter Rathvon, Jr.</u> N.P. RATHVON, JR., Alt. Chairman	<u>Helen R. Connell</u> H.R. CONNELL
<u>L.D. Hamilton</u> G.A. PRICE	<u>P.S. Papavasiliou</u> P.S. PAPAVASILIOU	<u>R.A. Love</u> R.A. LOVE
<u>D.N. Slatkin</u> D.N. SLATKIN, Alternate	<u>A.P. Wolf</u> A.P. WOLF, Alternate	<u>U. Reincke</u> U. REINCKE

TO Drs. Cotzias, Papavasiliou & Mendez,

THE ABOVE TITLED AND NUMBERED PROPOSAL IS Approved SUBJECT TO THE FOLLOWING:

No Investigational Consent required.

E.P. Cronkite 15 May '74  
E.P. CRONKITE, M.D., Chairman, Medical Department Date

CIRC Form 1 10/4/73 5/15/74  
Form 1936B

Copy to: Harrison, Clinic, Chanana, Cotzias, Papavasiliou + Mendez

HOSPITAL OF THE MEDICAL RESEARCH CENTER,  
BROOKHAVEN NATIONAL LABORATORY  
Upton, New York 11973

CIRC STATUS MEMO

CIRC No.

19F

APR 17  
APR 29 1974

Title:

Effort to reverse the signs and symptoms of parkinsonism with L-dopa.

To: Dr. Cotzias

Date: 3/13/74

Please indicate below whether this proposal is continuing or inactive. If continuing, complete the entire form, and attach to this sheet copies of any reports submitted to the FDA, HEW, or other Granting Agency (in connection with this proposal and the IND numbers given), since the last CIRC approval date. Also please add any additional information which may be of use to the Committee in its deliberations. If inactive, merely sign and return this form.

If this form is not returned by 3/31/74, approval of the proposal will automatically be discontinued.

R.B. Aronson

MAR 14 '74

R.B. Aronson, Ph.D., Associate Chairman

Date

To R.B. Aronson,

CIRC PROPOSAL NUMBER 19F IS: Continuing  Inactive

Proposed substantive changes are attached -

Adverse effects that have not already been reported to the Department Chairman include: -

Since the last approval \* 7 patients have been submitted to the experimental regimen.

The Sponsoring Physician as of this date is George C. Cotzias, M.D.  
*\* -> Delete name + add*

The following changes in Investigators should be noted: P.S. Papavasiliou + George Mentzer

The following IND #'s have been obtained for specific compounds used in this proposal:

Dihydroxyphenylalanine

Compound \_\_\_\_\_ IND# 3911 Compound \_\_\_\_\_ IND# \_\_\_\_\_

Note: IND 3911 is inactive in view of commercial availability of compound

The investigational consent form(s) used in this project are numbered \_\_\_\_\_ and copies are attached.

Patients involved in this study are referrals from or also studied at the following institution(s) \_\_\_\_\_

Attach statement from institution(s) indicating the review committee approval is current.

Signed George C. Cotzias  
Principal Investigator Date April 10 1974

George C. Cotzias  
Sponsoring Physician Date \_\_\_\_\_

1179907

Minutes CIRC Meeting

19 March 1973

Present: S. Cohn, R. A. Love, G. A. Price, N. P. Rathvon, Jr., J. S. Robertson

The Committee met at 1400 in the Van Slyke Memorial Room.

The minutes of the previous meeting, 12 March 1973 were accepted as distributed.

CIRC 98

The Committee found the proposed dose schedule unclear, there being no time specified for the transition from 60 mg/day increments to 20% increments. Dr. Mena was called in and explained that the transition would occur when the dose reached 1 gram per day. The question of whether an upper limit of an increment of 1 gram/day should be set was discussed but not made a recommendation. A revised wording clarifying the dose schedule was suggested.

CIRC 19F

Reapproved without qualification.

CIRC 74

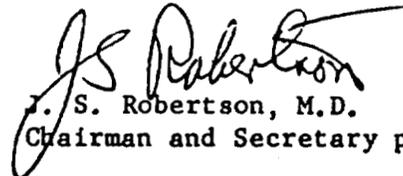
Reapproved without qualification.

CIRC 47

The radiation dose calculations were reviewed. It was recommended that the dose in rads be stated on the consent form.

The meeting adjourned at 1515.

Respectfully submitted,

  
J. S. Robertson, M.D.  
Chairman and Secretary protem

1179908

CIRC No. 19F

CLINICAL INVESTIGATION AUTHORIZATION FORM

TITLE:

Effort to reverse the signs and symptoms of Parkinsonism  
with L-Dopa

PURPOSE OF REVIEW:

- INITIAL
- ADDENDUM
- REVISION
- RECERTIFICATION
- REACTIVATION

TO CHAIRMAN, CIRC:

THE PROPOSAL FOR CLINICAL INVESTIGATION IDENTIFIED BY THE ABOVE CIRC NUMBER AND TITLE IS FORWARDED HERewith FOR REVIEW AND RECOMMENDATION.

*E.P. Cronkite*

22 Feb 73

E.P. CRONKITE, M.D., Chairman, Medical Department

Date

TO CHAIRMAN, MEDICAL DEPARTMENT:

THE CIRC REVIEWED THE ABOVE IDENTIFIED PROPOSAL ON 19 March 1973 AND RECOMMENDS approval  
WITH THE FOLLOWING MODIFICATIONS: - none -

<i>J.S. Robertson</i> J.S. ROBERTSON, Chairman	G.C. COTZIAS, Alternate Chairman	<i>H.R. Connell</i> H.R. CONNELL
<i>S.H. Cohn</i> S.H. COHN	E.A. POPENOE, Alternate	<i>R.A. Love</i> R.A. LOVE
<i>Glen D. Price</i> G. PRICE	G. CHIKKAPPA	<i>N.P. Rathvon, Jr.</i> N.P. RATHVON, JR.
D.N. SLATKIN, Alternate	A.P. WOLF, Alternate	

TO Drs Cotzias, Papanicolaou, Monro, and Mendez

THE ABOVE TITLED AND NUMBERED PROPOSAL IS approved SUBJECT TO THE FOLLOWING:

1179909

*E.P. Cronkite*

26 Mar 73

E.P. CRONKITE, M.D., Chairman, Medical Department

Date

cc. Drs Cotzias, Papanicolaou, Monro, Mendez + Dadd  
Clinic. A. Harrison

CIRC STATUS MEMO

Title: Effort to reverse the signs and symptoms of Parkinsonism with L-Dopa

To: Dr. Cotzias,

Date: 2/13/73

Please indicate below whether this proposal is continuing or inactive. If continuing, complete the entire form, and attach to this sheet copies of any reports submitted to the FDA, HEW, or other Granting Agency (in connection with this proposal and the IND numbers given), since the last CIRC approval date. Also please add any additional information which may be of use to the Committee in its deliberations. If inactive, merely sign and return this form.

If this form is not returned by 2/28/73, approval of the proposal will automatically be discontinued.

*Please Answer each question*

*R B Aronson*

R.B. Aronson, Ph.D., Associate Chairman

13 Feb. '73  
Date

To R.B. Aronson,

CIRC PROPOSAL NUMBER 19F IS:

Continuing

Inactive

Proposed substantive changes are attached \_\_\_\_\_

Adverse effects that have not already been reported to the Department Chairman include:

none

Since the last approval 20 patients have been submitted to the experimental regime.

The Sponsoring Physician as of this date is Cotzias

The following changes in Investigators should be noted: Delete Drs Duby and Lawrence and add Drs. I. Menz and J. Mendez.

The following IND #'s have been obtained for specific compounds used in this proposal:

Compound Dihydroxyphenylalanine IND # 3911 Compound \_\_\_\_\_ IND # \_\_\_\_\_  
*Note: IND 3911 inactive in view of commercial availability of compound 11/1/73*

The investigational consent form(s) used in this project are numbered 19F and copies are attached.

Patients involved in this study are referrals from or also studied at the following institution(s)  
No "also studied" but constant referrals from all over

Attach statement from institution(s) indicating the review committee approval is current.

Signed George I. Cotzias Feb 22 73 George I. Cotzias Feb 2 73  
Principal Investigator Date Sponsoring Physician Date

1179910

HOSPITAL OF . . . MEDICAL RESEARCH CENTER,  
BROOKHAVEN NATIONAL LABORATORY  
Upton, New York 11973

CLINICAL INVESTIGATION AUTHORIZATION FORM

Purpose of Review: Initial  Revision  Continuing  Addendum

Title: EFFORT TO REVERSE THE SIGNS AND SYMPTOMS OF PARKINSONISM  
WITH L-DOPA

CIRC#

19F

Assigned  
on (date)

11/1/66

To Chairman, CIRC,

The proposal for clinical investigation identified by the above CIRC number and title is forwarded herewith for review and recommendation.

*E. P. Cronkite*

16 Feb '72

E.P. Cronkite, M.D., President of Staff

Date

To President of Staff,

The Clinical Investigation and Uses of Radiosotopes Committee reviewed the above identified proposal on 6 March 72 and recommends approval with the following modifications:

*J. S. Robertson*

J. S. Robertson, Chairman

*S. H. Cohn*

S. H. Cohn

*Glenn A. Price*

G. Price

G.C. Cotzias, Alt. Chairman

E.A. Popenoe, Alternate

G. Chikkappa

H.R. Connell

*Orlando H. Love*

R.A. Love

N.P. Rathvon, Jr.

S.E. Duby, Alternate

A.P. Wolf, Alternate

To D. C. Cotzias,

The above titled and numbered proposal is approved subject to the following:

*A special investigational consent form is not required for standard use of L-DOPA*

*E. P. Cronkite*

11 Mar '72

E.P. Cronkite, M.D., President of Staff

Date

C I R C

MINUTES

The committee met in the small conference room of the BNL Medical Department at 1400 on 6 March 1972.

The following proposals were considered and approved:

<u>CIRC No.</u>	<u>Principal Investigator</u>
19 F	Cotzias
47	Chikkappa
74	Chikkappa
80	Cotzias

The following proposal was disapproved:

81	Cotzias
----	---------

Proposal 81 is really a modification applicable to both CIRC 19F and CIRC 57. Difficulties are foreseen if CIRC 81 is used as the only identifying proposal in a patient's record. Difficulties are also foreseen if CIRC 81 is to be reviewed in the future without simultaneous review of CIRC 19 F and CIRC 57. Aside from the question of CIRC 81 being justifiable as an independent proposal, the committee questioned whether the dietary aspects of this study require committee action.

The committee will be glad to reconsidered the proposal if so requested.

  
J. S. Robertson  
Chairman, CIRC

1179912

BROOKHAVEN NATIONAL LABORATORY

MEMORANDUM

DATE: 2/18/72

TO: CIRC Committee (Dr. Robertson)

FROM: R.B. Aronson, Ph.D. *R.B. Aronson*

SUBJECT: CIRC Meeting

The following proposals are enclosed for consideration by the CIRC Committee at the next meeting to be held in the Small Conference Room at 2:00 PM on March 6, 1972:

CIRC # 19F

~~2~~  
47

74

80

81

RBA/ck  
Enclosures

1179913

CLINICAL INVESTIGATION AUTHORIZATION FORM

Purpose of Review: Initial  Revision  Continuing  Addendum

Title: EFFORT TO REVERSE THE SIGNS AND SYMPTOMS OF PARKINSONISM  
WITH L-DOPA

CIRC# 19F  
Assigned on (date) 11/1/66

To Chairman, CIRC,

The proposal for clinical investigation identified by the above CIRC number and title is forwarded herewith for review and recommendation.

E. P. Cronkite 16 Feb 72  
E.P. Cronkite, M.D., President of Staff Date

To President of Staff,

The Clinical Investigation and Uses of Radiosotopes Committee reviewed the above identified proposal on \_\_\_\_\_ and recommends \_\_\_\_\_ with the following modifications:

J.S. Robertson, Chairman

G.C. Cotzias, Alt. Chairman

H.R. Connell

S.H. Cohn

E.A. Popenoe, Alternate

R.A. Love

G. Price

G. Chikkappa

N.P. Rathvon, Jr.

S.E. Doby, Alternate

A.P. Wolf, Alternate

To \_\_\_\_\_,

The above titled and numbered proposal is \_\_\_\_\_ subject to the following:

*No investigational consent or addition to application for participation in study required*

E.P. Cronkite, M.D., President of Staff. Date

MEMORANDUM

DATE: 10 February 1972

TO: Dr. J. S. Robertson - Chairman CIRC

FROM: George C. Cotzias, M.D.

SUBJECT: CIRC 19F "EFFORT TO REVERSE THE  
SIGNS AND SYMPTOMS OF PARKINSONISM WITH L-DOPA"

I request that CIRC 19F be reactivated. Although Levodopa became an approved drug and our IND #3911 was no longer necessary, we continue the administration of Levodopa. In order to comply with Dr. Cronkite's memo of 27 February 1971 "Identification of Patients by CIRC #" 19F will be used to identify patients receiving Levodopa.

Dr. E. P. Cronkite  
Distribution: Medical Record Librarian  
Mr. H. Pate  
Mr. Finn  
Dr. R. Aronson  
Mrs. C. Kerr  
Dr. Papavasiliou  
Dr. Duby  
Dr. Lawrence  
Dr. Mena

1179915

BROOKHAVEN NATIONAL LABORATORY,

MEMORANDUM

DATE: Feb. 10, '72

TO: Dr. Cotzias

FROM: R.B. Aronson, Ph.D.

SUBJECT: CIRC Proposal 19F

In compliance with recent FDA and HEW notices requiring periodic reviews of clinical research projects, your CIRC proposal, number 19F is scheduled for review soon. Please indicate at the bottom of the page if this proposal should be continuing or placed on the inactive list.

This proposal was last reviewed and approved by the Committee on 2/22 1971. Do you wish to make any substantive changes in your proposal? no

Have you noticed any adverse effects during the experimental program which have not already been reported to the Department Chairman's Office? no. Please include the nature and frequency of such effects.

We need some numbers to be put on top of records. 19F looks like a good one.

Approximately how many patients have been submitted to the experimental regime since the last approval? \_\_\_\_\_

The Sponsoring Physician on this proposal is G.C. Cotzias, M.D.. Has there been a change of Sponsoring Physician or Responsible Investigators? No.

Please add Dr. Simone Duby and Dr. William H. Lawrence as investigators.

If you have obtained IND numbers from the FDA in connection with this proposal please list on a separate sheet the compounds and corresponding IND numbers, and attach.

Please attach to this sheet copies of any reports submitted to the FDA, HEW, or other Granting Agency (in connection with this proposal and the IND numbers given above), since the last CIRC approval date.

Please add any additional information which may be of use to the Committee in its deliberations. Include a copy of the Patient Consent Form now in use for this study.

CIRC PROPOSAL NUMBER 19F IS: Continuing

Inactive

Signed George C. Cotzias Date Feb 11 '71

Please return this completed form to Dr. R.B. Aronson as soon as possible.

1179916

Minutes CIRC Meeting

22 February 1971

Members present: Drs. Cohn, Klopper, Love, Robertson and Steck

Absent: Dr. Hamilton

The Committee met at 1430 in the Small Conference Room of the Medical Research Center.

Proposals CIRC#64 and #65 by Cotzias et al, for the use of DOPAC and  $\beta$ -(3,4 dihydroxyphenyl)-DL-lactic acid in studies of patients with Parkinsonism and dysyonia were considered. The proposals were passed with the following changes requested:

In CIRC#64, under potential hazards, the names of the sources of the toxicity information cited should be given, and where LD<sub>50</sub>'s are mentioned, the time in hours or days should be indicated.

In CIRC#65, on page 2, the third limit under the protocol should be changed to mean 8.0 grams per day.

The Committee also received copies of three letters from Dr. Cotzias to the FDA notifying them of discontinuance of clinical trials previously authorized under IND's 3911, 4734 and 4987. The corresponding CIRC proposals are accordingly considered to be inactive.

A letter was received from Dr. Atkins indicating that the 4 dose per year restriction put on CIRC#63 could operate to deprive a patient of the use of a procedure which would give a lower radiation dose than the alternative using <sup>131</sup>I. It is accordingly recommended that the restriction be modified to include the phrase, "Except when it is clearly in the interest of the patient involved to exceed this restriction."

Respectfully submitted,

J. S. Robertson, M.D.

/ck

cc: CIRC Committee

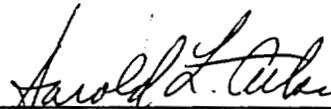
Mr. Finn

1179917

The Committee on Clinical Investigations and Use of Radioisotopes  
hereby approves the program with the following title:

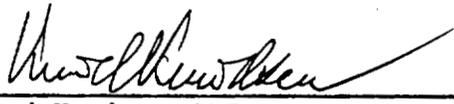
EFFORT TO REVERSE THE SIGNS AND SYMPTOMS OF  
PARKINSONISM WITH L-DOPA

CIRC # 19-f has been assigned to this program.

  
George S. Cotzias, M.D., Chairman  
Harold L. Atkins

  
Lewis M. Schiffer, M.D.

  
Herbert Savel, M.D.

  
Knud Knudsen, M.D.

Date: November 4, 1966

Place: Medical Research Center  
Brookhaven National Laboratory  
Upton, New York 11973

1179918

vB

V.P. Bond, M.D., Cha

Date: Nov. 4, 1966

FORM FOR INITIATION OR REVIEW OF CLINICAL  
INVESTIGATIVE PROGRAMS

CIRC # 19-f

(Submit original only to Department Chairman)

- A. Title of the proposal: EFFORT TO REVERSE THE SIGNS AND SYMPTOMS OF PARKINSONISM WITH L-DOPA
- B. Sponsoring physician(s): G.C. Cotzias
- C. Responsible investigator(s): G.C. Cotzias and P.S. Papavasiliou
- D. Brief description of the study, including its general goals and purpose, and pertinent information on past studies: (Attach additional sheets if necessary.)

The attached manuscript, accepted for publication by the New England Journal of Medicine, reports a completed study of the Parkinsonian's responses to  $\beta$ -MSH, D-L Dopa, and D-L Phenylalanine.  $\beta$ -MSH caused some aggravation of symptomatology and so did fairly large, sudden doses of D-L Phenylalanine, whereas slow increments of the latter failed to affect the one patient studied. In view of this these two agents were discontinued. D-L Dopa, on the other hand, had some beneficial effect in about half the patients studied. The effect was sustained over several months provided that the dose was higher

(CONTINUED ON NEXT PAGE)

- E. Reasons why the investigation(s) are to be performed on human subjects.  
Animal studies have been conducted in the past and are being initiated again. These bear on toxicity and anticipate possible mechanisms of tachyphylaxis, if this should occur in man. Animals do not have Parkinsonism. Therefore, studies on improvement of this disease must be conducted on humans.
- F. Type of patient in which the study is to be done (including approximate number of subjects, if known; special restrictions or requirements; method of obtaining consent; etc.):

The patients to be studied will be advanced Parkinsonians, since only they had responded to D-L Dopa. The dose necessary will be determined empirically, but it is anticipated to lie between 2 and 8 gm. a day. Special restrictions are: 1) Presence of decompensated cardiovascular disease of any kind. 2) Presence of major mental aberrations. 3) Presence of blood dyscrasia or abnormalities.

1179919

(CONTINUED ON NEXT PAGE)

- G. 1. Are drugs not in the U. S. Pharmacopoeia (USP) or the NNR being used or contemplated for use? Yes  No
2. Is an unusual use of a drug(s) accepted by the USP or NNR contemplated? (An example would be the use of an accepted drug in dosages far exceeding the recommended limits or for purposes distinctly different from the usual indications cited.) Yes  No
3. Are any biological products to be administered that do not bear on their containers or labels notation of approval by the Biological Control Division of the National Institutes of Health? Yes  No
4. Is external or internal radiation other than accepted diagnostic or therapeutic procedures to be administered? Yes  No
5. Are any (other) unusual procedures being performed or proposed which in your judgment may entail a special hazard - particularly a hazard above and beyond any imposed by accepted diagnostic and therapeutic measures for that patient? Yes  No
6. Are any radioisotopes to be administered to human beings? Yes  No
- a. If yes, are the radioisotopes to be used solely within the limits of procedures, specifically described in the USP? Yes  No
- Describe the radioisotopic preparation(s):
- b. Or are the radioisotopes to be used only in accordance with a project previously approved by the former Radioisotope Committee of this Department? Yes  No
- Note the project number: H-49 and CIRC 19 thru 19e

IF ANY OF QUESTIONS 1 THROUGH 5 ARE ANSWERED AFFIRMATIVELY, a detailed analysis of the potential hazards must be appended, including pertinent bibliographic citations and other relevant information.

IF QUESTION 6 IS ANSWERED AFFIRMATIVELY, a completed supplementary form for Radioisotope Administration to Human Beings must be appended. However, this form need not be filed provided that question 6a or 6b is also answered affirmatively. A separate form must be submitted for each radioisotopic species to be administered.

George C. Cotjian  
Sponsoring Physician

Committee on Clinical Investigations and  
Uses of Radioisotopes

Approval recommended  Date 11/7/62

Disapproval  Date \_\_\_\_\_

V. P. Bond

V. P. Bond, M. D.  
Chairman, Medical Department

1179920

6/25/63  
mlk

D. (continued)

than those encountered in the literature. In some instances the therapeutic effect was indeed dramatic. Ill effects encountered fell into three categories: 1) Occasional anorexia or nausea, mostly transitory. 2) Three instances of involuntary athetoid movements which appeared when the therapeutic effect was marked. 3) Four instances of granulocytopenia, which became reversed when the amino acid was stopped.

The experiences of Birkhäuser and Hornykiewicz, of McGeer and Zeldowicz and of Fehling (ref. 15,16,17,18 of attached preprint) as well as that of Barbeau alluded to on earlier Circ. #19a, show that about 1/2 of the dose is needed to achieve about the same results if one used L-Dopa instead of D-L.

It is possible that your approval of #19a covers the use of L-Dopa, but we respectfully request an additional judgement.

The reasons for using L-Dopa are that the side effects of the D-L compound might be less pronounced with the L. The L compound, being the natural one, is expected to be less toxic than the D-L. However, in mice being given orally D,L and D-L Dopa in various amounts for periods up to 24 weeks, no toxicity was encountered, with any of the compounds. Possible differences in toxicity are to be defined in a study involving rats and mice now initiated. The compound was purchased from the Nutritional Biochemicals Corporation because we have had good experience with their products and feel that <sup>they</sup> can be trusted.

Since it was thought during my absence that document 19a covered L-Dopa, this amino acid was started on four patients, but it will be discontinued if your committee so decides. All four patients showed rather striking sustained therapeutic effects on their Parkinsonism. Of these, one showed a granulocytopenia with 2300-2800 total circulating granulocytes. For about two weeks, this has not changed although the amino acid was continued. The granulocytopenia was evident only in the morning. Dopa was now shifted to the night

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D. (continued)

instead of the day to determine whether the diurnal rhythm of the granulocytes is changed by this agent. During the last three days the white cell counts, performed during morning and afternoon, have been normal. However, there have been seen bone marrow changes which consist primarily of some vacuolization of the corresponding cells.

*F. E.*

A special requirement is that there be little doubt of the diagnosis. Post encephalitic, idiopathic and arteriosclerotic varieties of the disease will not be separated from each other.

Consent is obtained verbally in the Outpatient Department and repeated on the wards from both the patient and his next-of-kin. We try to overstate the dangers of this experimental therapy and to understate the probability of long-lasting success. The patients know the nature of the drugs and their dangers. They are being informed of their progress. They are reassured that if they do not participate in the project they will not be discriminated against.

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QUESTION 1: Known hazards from this amino acid include: 1) Induction of nausea or anorexia. 2) Induction of mild athetoid movements. 3) Induction of granulocytopenia. All three have been reversible up to now.

QUESTION 6: N. A.

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AROMATIC AMINO ACIDS AND MODIFICATION OF PARKINSONISM

George C. Cotzias, M.D., Melvin H. Van Woert, M.D.  
and Lewis M. Schiffer, M.D.

Medical Research Center  
Brookhaven National Laboratory  
Upton, New York 11973

This work was supported by the U.S. Atomic Energy Commission

*New England J. Med.*

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## INTRODUCTION

The known biochemical abnormalities in Parkinson's disease consist of: (a) a decrease of melanin pigment in the substantia nigra (1,2) and (b) a decrease of some biogenic amines in the substantia nigra and the corpus striatum (3). These two defects might be interrelated, as suggested by the fact that in both melanocytes (4) and sympathetic cells (5) tyrosine is hydroxylated to dihydroxyphenylalanine, a common precursor in the synthesis of both melanin and catecholamines. Furthermore, both melanocytes and sympathetic cells originate from the neural crest (6).

It was suggested earlier (7, 8) that the interrelationships between melanogenesis and extrapyramidal disease might be of fundamental importance. It was noted that chronic exposure to at least two chemicals, namely manganese and phenothiazine compounds may induce extrapyramidal manifestations. Manganese was shown to accumulate in the various melanin granules analyzed (9,10), a property which is shared by phenothiazines (11). In addition, metals such as manganese interact in vitro with phenothiazines to give semi-quinone free radicals, similar to those present in normal melanin (12).

In the present work an effort was made to ameliorate the known biochemical abnormalities in patients with Parkinson's disease. Initially the effect of melanocyte stimulating hormone (MSH) was investigated. This agent increases melanin deposition at least in the integumental melanocytes (13) and it was hoped that it might similarly affect the pigmented cells of the brain. Furthermore, this peptide has increased the amplitude of evoked monosynaptic potentials in the spinal cord of the cat (14). It became apparent however, that the Parkinsonian state was reversibly aggravated by the administration of

this hormone. A serviceable working hypothesis compatible with this finding might be that the hormone was shifting dihydroxyphenylalanine (DOPA), the precursor of melanins and biogenic amines, from the brain to the integument. Therefore, it was considered desirable to investigate the therapeutic potential of DOPA, particularly since the early reports of short-lived improvement (15) were disputed by later studies (16,17,18). By administering higher doses than previously reported, a rather striking sustained improvement was observed in several patients. Some of the patients developed a depression of the circulating granulocytes and marked vacuolization of the corresponding bone marrow cells. Similar hematological complications associated with either phenylalanine deficiency or chloramphenicol toxicity have been reversed by phenylalanine (19, 20). Excesses of this amino acid have also increased the dopamine concentration in rat brain (21), while low dopamine concentrations have been linked with the pathogenesis of human Parkinsonism (3). Therefore, this amino acid was also administered. The present paper presents the sum of these findings and discusses their relationship to the therapy of Parkinsonism.

#### MATERIALS AND METHODS

Clinical material: Seventeen patients with Parkinsonism were admitted to this study. All had been referred to us by their physicians, after treatment with several standard antiparkinsonian medications, including two who had been subjected to cryopallidectomy. All were studied as in-patients in the metabolic wards for several to many months. Some of the Parkinsonians had previously participated in therapeutic studies of their disease (22). Three non-Parkinsonians were included as controls. The patients were made aware of the nature and consequences, but not of the timing of the regimens.

Drugs and dosages: The melanocyte stimulating hormone ( $\beta$ -MSH) was generously supplied by Armour Laboratories. Its activity was  $2 \times 10^9$  units (Shizume-Lerner) per gm. (10 mg/vial). It was administered intramuscularly in two equal doses dissolved in 1 ml of 16% gelatin. The doses were slowly increased but did not exceed 40 mg/day. The periods of  $\beta$ -MSH administration were bracketed by periods of injecting the gelatin as a placebo twice daily.

D,L-phenylalanine and D,L-dihydroxyphenylalanine (DOPA) were studied because of the great expense of the L-compounds. These amino acids were obtained from the Nutritional Biochemicals Corporation. They were made up in pink capsules containing 100, 200 or 500 mg. The same capsules filled with lactose served as placebo. As a rule, the total number of capsules was kept constant during the evaluation of both the placebo and the amino acid.

In all studies these agents were started at a small dose and were gradually increased while the placebo was simultaneously decreased.

Laboratory tests: A comprehensive battery of tests selected to detect evidence of drug toxicity was carried out at various intervals. The hematocrit, hemoglobin, total and differential leucocyte counts, Coombs test and platelet counts originally performed every two weeks were done twice a week after abnormalities first became apparent. The total peripheral blood granulocytes per cubic millimeter of blood were calculated by multiplying the white blood count by the percentage of segmented and band neutrophils. Bone marrow aspirates collected in 1% EDTA in saline were examined in 12 patients. They were immediately smeared and stained by the Wright-Giemsa method to avoid degenerative artifacts. Differential vacuole counts were made on 500 to 800 myeloid cells of 13 aspirates from 8 patients. All vacuoles were counted in thin areas of the smears and in places where there was minimal lipid deposition.

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Tests of hepatic and renal function were carried out before therapy and subsequently at two week intervals. The liver function studies included serum protein determination with A/G ratio, serum electrophoresis, serum alkaline phosphatase, bilirubin, cholesterol, cephalin flocculation, SGOT and the bromsulphthalein test. The kidney function tests included urinalysis, creatinine clearance, urea clearance, determination of 24 hour urinary protein and occasional phosphate clearance. Weekly analyses of whole blood manganese (23, 24) serum copper and serum iron were obtained in most cases. Blood glucose, serum electrolytes, serum calcium, phosphorus, uric acid, protein bound iodine and urinary 5-hydroxyindoleacetic acid,  $\text{FeCl}_3$  test for indoles and 24 hour urinary glucose by glucose oxidase and Benedict's reaction were determined intermittently. Serum amino acid analyses before and during phenylalanine and dihydroxyphenylalanine administration are in progress.

Clinical evaluation: Semidaily visits and periodic physical examinations were conducted in all instances. Handwriting, the number of steps required to walk 10 meters and the observed facility to sit down or stand up, to pick up an object from the floor and to draw a straight line were tested periodically. Cog-wheel phenomenon, rigidity, tremor, festination, dysarthria, salivation, muscle strength and mental state were evaluated regularly, while on placebo and while on the compounds tested. Cinematographic records were obtained both before and during therapy in several instances.

#### RESULTS

Clinical: As is shown on Table I, the melanocyte stimulating hormone ( $\beta$ -MSH) was given to six patients. Other drugs had been withdrawn in five of these and the neurological manifestations had reached a plateau. In the other patient (#6) this was impossible due to emergence of dysphagia. All patients

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developed initially abdominal cramps and diarrhea which disappeared after a few days in all but one individual. In the latter patient (#4) the hormone was stopped. Increased pigmentation of the skin gradually developed, most noticeably over the arms and face.

The progressive increments of the hormone induced an increase in Parkinsonian manifestations: tremor appeared or became aggravated while muscular strength, posture, gait and associated movements became further impaired. Salivation emerged in one case, but in none was rigidity changed to an appreciable degree.

In the repeated trials of D,L-DOPA eight\* of the sixteen patients showed either complete sustained disappearance or marked amelioration of their individual manifestations of Parkinsonism. These included tremor, cogwheel phenomenon, rigidity, loss of associated movements, muscular weakness, festination, salivation and loss of facial expression. The dose required for improvement was possibly a function of the body mass (Table I). As the dose of D,L-DOPA was gradually increased the improvement was first noted in the rigidity and only at higher levels was there a decrease or disappearance of tremor. The decrease in tremor was reflected in the electrocardiograms taken under identical conditions before and during therapy with D,L -DOPA. The improvement in the handwriting of one patient is shown in Fig. 1. In another patient (#9), mental confusion associated with garrulity was markedly improved on this drug. This was particularly striking because every standard antiparkinsonian agent tried by several physicians had either aggravated this patient's mental confusion or had induced visual and auditory hallucinations. Simultaneously

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\* Case Nos. 1, 6, 7, 8, 9, 10, 16, 17

with motor improvement and disappearance of tremor, another patient (#7) developed euphoria associated with exaggerated facial expression and gesticulation when talking. These manifestations disappeared whenever the D,L-DOPA was discontinued and the full syndrome re-emerged.

In patient #6, DOPA controlled dysphagia, tremor and weakness, none of which had been significantly affected by full doses of Artane, Parsidol, Phenergan or Cogentin. Intermittant athetoid movements of the tongue were seen in this latter case only while on DOPA. Moderate athetoid movements of all four extremities were exhibited also by patient #17. Patients #10 and #16 had been subjected earlier to cryopallidectomy elsewhere. Euphoria was not a common finding, but the sedation and "drugged" sensation associated with most anti-parkinson therapy was notably absent. In two instances (#2 and #11) although sustained improvement was induced by DOPA, there remained significant degrees of either tremor or rigidity. By sharp contrast, four individuals (#3, #4, #12 and #15) with early unilateral disease remained essentially unimproved. Patient #13 became pale, apathetic and immobile on two trials and was therefore not continued on DOPA. In one (#14) intercurrent fever caused us to stop the drug. The control patients (#18 and #19) showed no discernible mental or physical consequence during administration of D,L-DOPA. Athetoid movements were observed only in patients with Parkinson's disease and only when the therapeutic effect was impressive.

Eight of the sixteen Parkinsonian patients who had received D,L Dihydroxyphenylalanine (DOPA) were subsequently given its precursor compound D, L-Phenylalanine. By contrast, none of these eight patients displayed any discernible improvement in their Parkinson's disease on D,L-Phenylalanine and the majority were adversely affected. Patient #1 received 4 gms of D,L-Phenylalanine at the

time she was enjoying marked improvement from D,L-DOPA. While on this combination she developed tremor, rigidity, weakness and drowsiness so that the phenylalanine was discontinued. Gradual readministration of this amino acid when she was not receiving DOPA induced only a moderate aggravation of her clinical manifestations, even at a dose level of 12.6 gms per day. By contrast she was under sustained full control of her disease with 4.0 gm of DOPA per day. Among the remaining seven patients one (#11) developed akinesia for the first time after receiving phenylalanine, one (#14) showed no significant changes, and the remainder developed minimal to moderate aggravation of their rigidity and tremor. Two control patients, one with congenital hydrocephalus (#19) and the other with rheumatoid arthritis (#20) received respectively 4.8 and 8.0 gms of D,L-phenylalanine daily for about one week without physical or mental changes.

Toxicological: Nausea, faintness and occasional vomiting did occur during DOPA administration, but only with increments larger than 0.5 gm/dose. These symptoms were transitory as a rule and were not encountered with increments of less than 0.2 gm/dose. The hematological changes are discussed below.

Laboratory data: The Parkinsonian patients generally had low serum phosphorus concentrations which were unaffected by the drugs used in this study. The mean and standard deviation of 200 serum phosphorus determinations on these patients was  $3.0 \pm 0.5$  mg% with a range of 1.8 to 4.1 (normal = 3.0 - 4.5 mg% Tausaky & Shorr method). The serum calcium, alkaline phosphatase and 24 hour urinary phosphorus were all normal and unaffected by these drugs.

In two patients, who were on long term therapy with D,L-DOPA, the blood manganese level decreased as shown in Figure 2. The lower plateau was reached in both cases after a period of DOPA administration approximating the life span of the erythrocyte.

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The remainder of the laboratory examinations were contributory only in that the urines of patients on DOPA became black on standing and showed positive Benedict's but negative glucose oxidase reaction.

Four instances (Case Nos. 1, 4, 6, 7) of granulocytopenia developed during the course of treatment of 16 patients with D,L-DOPA. Two episodes were rapid and 2 gradual; the latter occurring over several months. The total granulocytes decreased to 1800 to 2300/ $\text{mm}^3$  and rose to normal, or near normal, between 1 week and 6 months after cessation of DOPA. There was no direct correlation between duration of treatment or total dose of D,L-DOPA administered, although all instances occurred after more than 200 grams of D,L-DOPA had been consumed. There was no direct evidence of a sensitization type of reaction. Occasional atypical lymphomonocytoid cells were seen in the peripheral blood of D,L-DOPA treated patients, especially in those who developed granulocytopenia.

Quantitative and differential counting of vacuoles in cells of the myeloid series confirmed the first impressions that they were increased in numbers in bone marrows of patients treated with D,L-DOPA. The vacuoles were mostly cytoplasmic, although some overlay nuclei, and were increased in number in the more immature forms of the myeloid series (Fig. 3). The number of vacuoles per cell were also increased in blasts, promyelocytes and myelocytes in 4 patients who were receiving, or had recently received, D,L-DOPA. Two of these patients had concomitant granulocytopenia and one had previously been granulocytopenic. Only occasional vacuoles were seen in erythroid cells and these were not quantified.

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DISCUSSION

The sustained beneficial effects of DOPA reported here are in sharp contrast to some previous reports (16, 17, 18). This difference can be ascribed to the larger, sustained doses used during the present investigation. While small doses of DOPA can reduce rigidity, the larger amounts used here are necessary to eliminate both rigidity and tremor. Some of the most striking results were obtained in patients who had advanced disease for which they had been subjected to intensive conventional medical or surgical therapy prior to this study. The four patients who did not respond significantly to the full regimen exhibited relatively mild unilateral Parkinson's disease.

The mechanisms by which the above effects were brought about remain obscure. The finding of decreased concentrations of dopamine in the brain in Parkinson's disease might have some bearing on the improvement noted in our patients. L-DOPA passes through the blood-brain barrier leading to an increase in dopamine concentration in the brain. It is of interest that the onset of improvement when sufficient DOPA was given was rapid (2-3 hours), while the reestablishment of the base-line state after abruptly terminating the drug, following prolonged therapy, was much longer (4-14 days). Long term therapy with DOPA may well have some effect on the catecholamine storage granules which have been described (25) in certain neuron cells. If increased dopamine was the only mechanism by which improvement was brought about, one would expect effects in the same direction to follow the administration of an earlier precursor, phenylalanine. This was certainly not the case. Since the conversion of phenylalanine to DOPA requires hydroxylation, it is plausible to suggest that defective hydroxylation of this or other aromatic amino acids might emerge as a biochemical error in this disease.

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The mechanisms by which athetoid movements were induced have not been elucidated. These movements were observed only in patients with Parkinson's disease and only when the therapeutic effect of DOPA was marked.

The mode of action of  $\beta$ -MSH in aggravating the Parkinsonian state is also not clear. The stimulation of the skin melanocytes was definite and this could have resulted in a decrease of available DOPA for brain metabolism. Chlorpromazine has also been reported to increase skin pigmentation (26) as well as produce extrapyramidal symptoms (17). Although this explanation remained speculative, no further effort was made to substantiate it in view of the patients' discomfort.

The diminution of the concentration of whole blood manganese might be worthy of comment. The time which elapsed until a new plateau was reached following administration of DOPA had approximated the life span of one generation of erythrocytes. This was compatible with two earlier demonstrations: 1) That manganese becomes incorporated in a manganoporphyrin of human erythrocytes (27); 2) That the exact enantiogram of Figure 2 was obtained after feeding excessive but steady amounts of manganese (Ref. 24, Fig. 2). Many amino acids have significant chelating properties and are able to facilitate metal transport into cells (28). The decrease in blood manganese could result from the redistribution of this metal by DOPA. Further investigations of this hypothesis are planned. Other essential metals have been implicated in the Parkinsonian syndrome (29) as well as in the metabolism of some biogenic amines (30, 31). The low serum phosphorus levels encountered here, coupled with the normal calcium levels, indicate that not only manganese but also magnesium must be studied in the present context.

Administration of D,L-DOPA resulted in granulocytopenia in a sizeable percentage of the patients studied. In no instance did infection occur and all episodes of granulocytopenia were reversed. In 3 of the patients the drug was stopped, and in the fourth, granulocytes rose despite continued therapy. Noted in association with the granulocytopenia was extensive vacuolization of immature cells of the myeloid series. Although there is no direct evidence linking the two findings, it is plausible to assume that they are related. The vacuoles seen in the bone marrow elements are similar to those noted in the erythroid and myeloid cells of patients with phenylalanine deficiency (19) and chloramphenicol-induced erythroid suppression (20).

The sum of the evidence presented indicates that DOPA is an effective agent for certain cases of Parkinsonism, worthy of further investigation. The hematological complications were relatively mild since they consisted of only a mild granulocytopenia and morphologic changes in the bone marrow. Still, caution must be exercised in studying D,L-DOPA. A similar long term study with L-DOPA seems highly warranted as soon as it becomes economically feasible.

#### SUMMARY

Some compounds were selected for study because of their possible effects on abnormal melanogenesis and catecholamine metabolism which occur in Parkinson's disease. These compounds included melanocyte stimulating hormone ( $\beta$ -MSH), D,L-Phenylalanine and D,L-Dihydroxyphenylalanine (DOPA).

$\beta$ -MSH (20-40 mg), given intramuscularly to 6 patients, resulted in an aggravation of their tremor but no significant effect on their rigidity. Oral D,L-Phenylalanine (1.6-12.6 gm) exacerbated both tremor and rigidity in 7 out of 8 patients with Parkinson's disease.

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Of the 16 Parkinsonian patients receiving D,L-DOPA (3-16 gm/day orally), 8 showed either complete or marked sustained improvement of several individual manifestations of Parkinsonism. Rigidity decreased or disappeared at relatively lower doses whereas only at higher levels of DOPA was there a decrease or disappearance of tremor. Two additional patients were also improved but to a lesser degree by this amino acid. A significant side effect following administration of D,L-DOPA was a transient granulocytopenia encountered in four cases. This was associated with extensive vacuolization of the more immature cells in the myeloid series of the bone marrow. Another side effect was the reversible induction of athetoid movements, which was observed thus far only in patients with Parkinson's disease and only when the therapeutic effect was significant.

Although D,L-DOPA emerged as an effective therapeutic agent, the hematological complications indicate that caution must be exercised in further studies of this compound.

#### ACKNOWLEDGEMENTS

Mr. Samuel T. Miller (9,24) and Miss Judith Edwards (24) performed the neutron activation analyses for manganese. The excellence of the support by the nurses under the supervision of Martha Hill, R. N. is gratefully acknowledged. The authors thank Charles I. Goldman, Ph.Ch. for the expert fabrication and supply of the active chemicals and their respective placebos in the forms studied here.

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LEGEND TO TABLE I

MSH         $\beta$ -MSH melanocyte stimulating hormone  
DOPA        D,L-Dihydroxyphenylalanine  
Phenyl.     D-L-Phenylalanine

\*    Inadequate trial because of fever.

†    Cryopallidectomy

The response to DOPA was scored as:

0	No improvement
+	>10% improvement in performance
++	20-40% improvement in performance
+++	40-60% improvement in performance
++++	> 60% improvement in performance

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TABLE I

Case #	Age - Sex	Duration of Illness (yr)	Drug	Length of Therapy (days)	No. of Times on Placebo	Maximum dose grams	mg/kg	Total Amt (grams)	
<u>PARKINSONIANS</u>									
1	55 F	32	MSH	110	4	0.025			
			DOPA	107	5	6.0	119	282	++++
			Phenyl	50	1	12.6			
2	63 F	2	MSH	68	1	0.040			
			DOPA	34	2	3.0	72	57	++
3	42 M	1 1/2	MSH	24	2	0.035			
			DOPA	108	2	10.0	93		0
			Phenyl	7	1	11.2			
4	57 M	3	MSH	12	2	0.035			
			DOPA	44	2	10.0	128	228	0
5	72 F	10	MSH	64	1	0.020			
6	62 M	11	MSH	120	4	0.035			
			DOPA	347	7	16.0	222	3892	+++
7	61 M	7	DOPA	251	3	9.0	122	1610	++++
			Phenyl	6	1	12.0			
8	60 F	13	DOPA	133	3	12.0	235	577	+++
			Phenyl	12	2	8.0			
9	60 M	8	DOPA	163	3	12.0	195	1282	++++
			Phenyl	1	1	1.6			
10	62 M	5 1/2	DOPA	82	3	16.0	224	687	+++
11	69 F	6	DOPA	45	2	12.0	259	330	++
			Phenyl	3	1				
12	43 M	1	DOPA	33	3	14.0	155	239	0
			Phenyl	4	0	4.0			
13	62 M	15	DOPA	10	1	8.0	122	47	0
14	73 F	3	DOPA	23	6	1.5	24	10	*
			Phenyl	4	0	5.0			
15	59 M	1 1/2	DOPA	38	2	9.5	125	177.4	0
16	65 M	9	DOPA	142	2	12.0	165	1109	+++
17	54 F	6	DOPA	63	2	12.0	216	438.3	+++
<u>CONTROLS</u>									
18	80 F		DOPA	44	0	4.0	51	115	
19	44 F		DOPA	16	0	8.0	188	91	
			Phenyl	7	0	4.8			
20	50 M		Phenyl	5	0	4.0			

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LEGENDS TO FIGURES

FIGURE 1 Handwriting of patient #1 before (A) and during (B) therapy with DOPA. Note increase in size of letters and diminution of tremor.

FIGURE 2 Blood manganese concentrations of patients #6 and #7 as determined by neutron activation analysis. Note that the drop in concentration became complete after the elapse of about 130 days.

FIGURE 3 Photomicrograph of bone marrow smear of patient #7 showing large vacuole in eosinophilic myelocyte (upper left), 4 vacuoles in myelocyte (center), and 3 vacuoles in metamyelocyte (lower right).

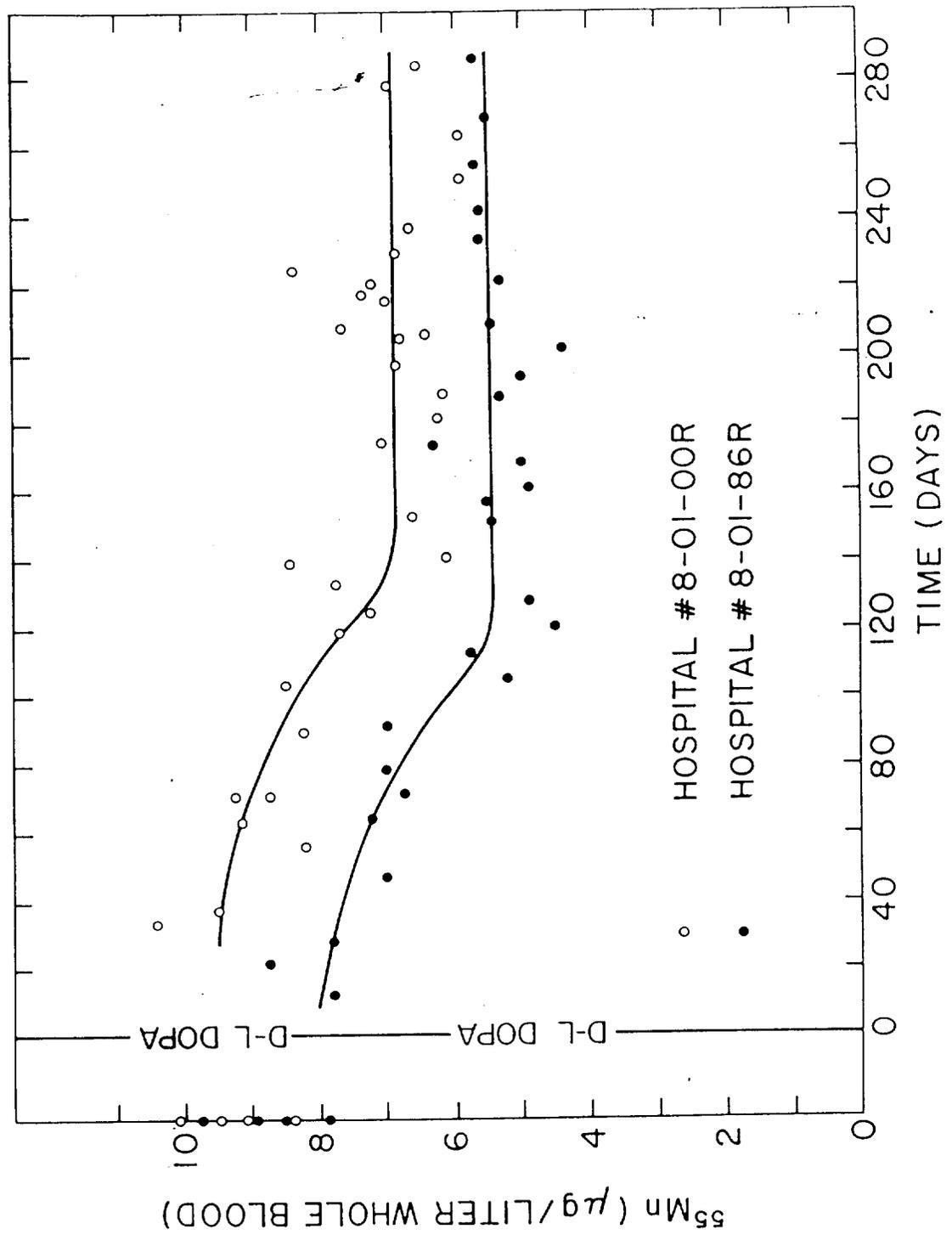


FIGURE 2

449944



FIGURE 3

1179945