

OFFICE OF NAVAL RESEARCH, NEW YORK
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ADDRESS REPLY TO
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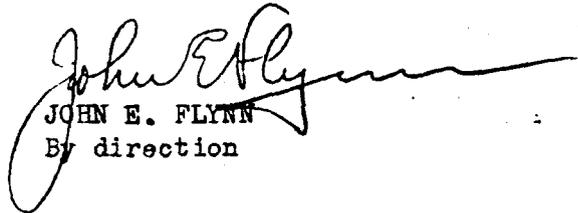
15 March 1955

From: Commanding Officer, Office of Naval Research, New York
To: Chief of Naval Research (Code 444) NAV1.941208.091

Subj: Proposal on "Determination of the Effect of High Dosage
Betatron Irradiation to the Pituitary and Hypothalamus in
Man" from Sloan-Kettering Institute

Encl: (1) 14 cys subj proposal dtd 11 Mar 55

1. Subject proposal is forwarded as enclosure (1). Pertinent comments
from this office will be furnished at a later date.


JOHN E. FLYNN
By direction

SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH

RESEARCH UNIT OF MEMORIAL CENTER
FOR CANCER AND ALLIED DISEASES

410 EAST 68TH STREET
NEW YORK 21, NEW YORK

March 11, 1955

Chief of Naval Research
Office of Naval Research
Washington 25, D. C.

Dear Sir:

We are submitting herewith a research proposal for support of the project entitled "Determination of the Effect of High Dosage Betatron Irradiation to the Pituitary and Hypothalamus in Man" in the amount of \$11,340 for the year beginning July 1, 1955. A Fixed Price Contract is requested with payments to be made quarterly. The principal investigator will be Dr. Min-Chiu Li, who will work under the supervision of Dr. O. H. Pearson, Associate and Head of the Metabolism Laboratory Section.

In spite of the reputation of Memorial Center and the Sloan-Kettering Institute in the cancer field, the Sloan-Kettering Institute engages in extensive research in basic fields of chemistry, biology, and physics. The availability of cancer patients for these basic studies is fortunately coincidental.

We believe that the results that may be obtained from this investigation will prove of interest and value to the Office of Naval Research and I recommend this application for your favorable consideration.

Sincerely yours,



C. P. Rhoads, M. D.
Director, Sloan-Kettering Institute

CPR:avr

RESEARCH PROPOSAL

TO THE

OFFICE OF NAVAL RESEARCH

DETERMINATION OF THE EFFECT OF
HIGH DOSAGE BETATRON IRRADIATION
TO THE PITUITARY AND HYPOTHALAMUS
IN MAN

Min-Chiu Li, M.D., Research Fellow,
Metabolism Laboratory Section, Division
of Clinical Investigation, Sloan-Kettering
Institute

Sloan-Kettering Institute for Cancer Research
410 East 68th Street, New York 21, New York

Amount Requested: \$11,340

For the period: July 1, 1955 - June 30, 1956

Date: March 11, 1955

Min Chiu Li

Min-Chiu Li, M.D.

O. H. Pearson

O. H. Pearson, M.D., Head,
Metabolism Laboratory Section

C. P. Rhoads

C. P. Rhoads, M.D., Director
Sloan-Kettering Institute

Determination of the Effect of High Dosage Betatron Irradiation
to the Pituitary and Hypothalamus in Man.

Dr. Min-Chiu Li

a. We are requesting consideration of a research proposal to determine the effect of high dosage betatron irradiation to the pituitary and hypothalamus in man.

b. Scientific Background

There is evidence from the literature that only high dosage such as 18,000 r or above irradiation to the pituitary will produce complete destruction and ablation of pituitary functions in animals. Large single doses of betatron radiation can produce damage of brain substance and marked cellular deterioration of the hypothalamus nuclei in primates. From our recent experience, high-dosage radiation to the pituitary and hypothalamus areas can cause severe optic atrophy and mental abnormalities. This study offers ample opportunity to evaluate radiation effects on brain substance.

The relationship of hypothalamic control of gastric secretion, development of peptic ulcers, and the relationship with parasympathetic and sympathetic control of the body and with temperature control and carbohydrate and fat metabolism have been reported by a number of authors in studies of damage to the hypothalamus due to various diseases. This study offers the opportunity to determine whether or not radiation damage to the hypothalamus will produce these alterations.

Our experiences with 65 cases of surgical hypophysectomy suggest that it is still a highly technical procedure. Thus, if irradiation will result in complete ablation of pituitary and end-organ function, the value and importance of this project is apparent.

c. Technical Description of the Proposed Work

(1) Objectives of the Project

Preliminary studies on betatron irradiation to the pituitary and hypothalamus of patients with neoplastic diseases at a dosage of 8,000 r for two weeks have indicated partial arrest of the function of the pituitary and the endocrine end-organs. Histological examination of these areas have shown marked degeneration of nuclei of the hypothalamus and of the pituitary parenchymal cells. A high dosage level, such as 12,000 r to 15,000 r given in a similar period, has induced further response. Whether or not such high dosage levels will result in brain damage will be determined. The studies outlined below are designed:

1. To determine whether betatron irradiation at a dosage of 12,000 r to 15,000 r will result in complete ablation of the pituitary and end-organ functions.

2. To determine histological radiation changes of the pituitary, hypothalamus and brain tissues.

(2) Scientific Methods to be Employed

A. Irradiation Procedure

Patients with advanced neoplastic diseases are hospitalized in the research and metabolic units of the James Ewing Hospital, Memorial Center, for studies. Our group has found that surgical hypophysectomy will result in remission of 65% of carcinoma of the breast and therefore radiation to the pituitary is being used in selected patients who refuse surgery. Because of subsequent prolonged follow-up pituitary and end-organ function studies, young patients with good nutrition, a life expectancy of more than six months, and intact gonadal, adrenal and thyroidal functions are preferred.

The 23-million volt betatron machine of the Memorial Center is available for irradiation. Using a cone 3 cm. in diameter, 12,000 r to 15,000 r or higher will be delivered by a bitemporal route. The irradiation field will include the pituitary, the stalk and the hypothalamus. It will also include the tip of the temporal lobes of the cerebrum. It is expected that alteration of pituitary and end-organ functions will begin to occur at the end of six weeks to three months following the completion of irradiation.

B. Methods of Studying the Effects of Radiation

1. Alteration of Pituitary Function

Bioassay of urinary follicular stimulating hormone will be used as one of the indices of alteration of pituitary function. The development of diabetes insipidus will also be used as a criterion, as will clinical tests such as insulin sensitivity and glucose tolerance.

2. Alteration of End-Organ Function

a. Gonadal: In females, vaginal smears, urinary pregnandiol determination, occurrence of menses and endometrial biopsy will be used as criteria for alteration of gonadal function. In males, testicular biopsy and the size of the testes will be used.

b. Thyroid: Serum protein-bound iodine determination, radioactive iodine uptake studies, basal metabolic rate and clinical evidence of the development of myxedema will be used as indices of alteration of thyroid function.

c. Adrenal: Urinary 17-ketosteroids, formaldogenic steroid determination and accumulative water tolerance test will be used for the study. Clinical observations of the development of adrenal insufficiency is one of the important indices of alteration of adrenal function. It is expected that adrenal function will be the last to alter.

3. Observation of Systemic Reaction

Electroencephalogram and careful psychological and neurological examinations will be carried out to determine whether or not the brain substance is affected. Hematological studies will also be employed to detect

signs of any changes from irradiation. Gastric secretion, temperature control and autonomic nervous system derangement will be studied to determine whether or not radiation hypothalamic damage or irritation will influence these. Other systemic reactions, such as local skin reaction and radiation side-effects, will be evaluated.

4. Histological Studies on Pituitary, Hypothalamus and Brain Substance

Since these patients are in the terminal stages of disease, materials can usually be obtained from postmortem examination. Tissues will be fixed in special preservatives. Various differential staining techniques will be applied to study radiation changes in parenchymal cells of the pituitary and the stalk, the degree of damage to the hypothalamic nuclei and irradiation alteration of the pyramidal cells, glial cells, myeline sheath, nerve fibers and perivascular reaction of the cerebral cortical substances. Special attention will be focused on any possible anaplastic changes of glial cells following irradiation.

d. Facilities Available to this Project

There are available for these studies several laboratories, fully equipped, for betatron irradiation, physiological chemistries, histological and pathological examination of irradiated tissues, bioassays, urinary steroid determinations and metabolic balance studies.

Suitable patients for this project will be maintained in our special research ward in the James Ewing Hospital of the Memorial Center. This ward contains 30 beds, two or three of which are available for these studies.

e. Name and Background of Principal Investigator

Min-Chiu Li, M.D.

Born: Canton, China, Sept. 21, 1919

Education: Christian College of Mukden, China -- 1937-1939
Mukden Medical College " " M.D. 1940-1944
Univ. of So. Cal. Grad.Sch. of Med. M.Sc. 7/47-6/49

Licensed: China, 1944.

Member: Sigma Xi, American Association for the Advancement of Science

Teaching and Research Appointments:

Instructor in Bacteriology, Mukden Medical College, 1945-1947
Assist. Instructor in Medicine, Med. School, Univ. of Ill. 1950-1953
Clinical Research Fellow in Med., Univ. of Ill., 1952-1953
Research Fellow, Div. of Clin. Invest, Sloan-Kettering Inst. 3/1/53-pres.

Hospital and Laboratory Appointments:

Res. Phys. in Medicine, Deaconess Hosp., Montana, 7/49-6/50
Sr. Res. Physician in Medicine, Presbyterian Hosp., Chicago, 7/50-6/52.

Prizes and Awards:

Reformed Presbyterian Church medical scholarship, 1947-1949
Western Traudeau Society research fellowship, 1947-1948
American Cancer Society Clinical Research fellowship, 1952-1953

f. Pertinent Publications

Extensive studies have been carried out on the physiologic, metabolic, and hormonal alterations in adrenalectomized and hypophysectomized patients. The effect of hormone maintenance replacement therapy has also been studied. Our experiences suggest that hypophysectomized patients can lead a normal life with the use of readily available cortisone acetate, thyroid extract and pitressin.

Our preliminary studies of betatron radiation to the pituitary and hypothalamic region have been reviewed. Our data suggest that partial and transient suppression of gonadal and thyroidal function are present at the dosage level of 8,000 r given in two weeks. Dosage up to 12,000 r and 15,000 r, given over a similar period of time, has induced further suppression of pituitary and end-organ functions. Whether or not brain damage will result at these levels is to be studied. Our duration of follow-up studies of the latter group is too short to be conclusive.

1. Effect of hypophysectomy on neoplastic disease in man
Pearson, O.H., Ray, B.S., Harrold, C.C., West, C.D., Maclean, J.P. and Li, M.C.
J. Clin. Endoc. and Metab. 14: 828-829, July 1954.
2. Physiological effects of hypophysectomy in man.
West, C.D., Li, M.C., Maclean, J.P., Rall, J.E., and Pearson, O.H.
J. Clin. Endoc. and Metab. 14: 786, July 1954.
3. Medical management of bilateral adrenalectomy and hypophysectomy
Li, M.C., Maclean, J.P., Lipsett, M.B. and Pearson, O.H.
Arch. of Int. Med., 1955 (to be published)
4. Alteration of thyroid function following hypophysectomy
Li, M.C., Maclean, J.P., Lipsett, M.B. and Pearson, O.H.
(to be published)
5. Alteration of adrenal function following hypophysectomy
Li, M.C., Maclean, J.P., Lipsett, M.B. and Pearson, O.H.
(to be published)

Shimkin, et al., reported failure of suppression of end-organ functions or histological changes of pituitary following conventional kv machine irradiation over the normal human pituitary, delivering 8,000 to 10,000 r over a two-month period (1).

Lawrence reported that x-ray irradiation to the pituitary region of rats results in a) a temporary decrease of growth rate and b) a striking decrease in the number of acidophiles and a relative increase of basophiles, by histological examination of the irradiated hypophysis (2).

Arnold has reported that betatron irradiation to the primate's hypothalamus could induce histological damage of the paraventricular and supra-optic nuclei. His report suggests that pituitary function can be arrested from hypothalamic damage (3). He also observed acute radionecrosis of the brain substances occurred by single doses of 5,000 r betatron irradiation to the brains of primates (4).

1. Irradiation of normal human hypophysis in malignancy: report of three cases receiving 8,000 r to 10,000 r tumor dose to the pituitary gland. Kelly, K.H.; Feldsted, E.S.; Brown, R.F.; Ortega, R.; Bierman, H.R.; Low-Beer, B.V.A.; Shimkin, M.B.
J. Nat. Can. Inst. 11: 967, 1951.
2. Roentgen irradiation of the hypophysis
Lawrence, J., et al.
Radiology 29: 446, 1937.
3. Effect of x-ray irradiation on the hypothalamus
Arnold A.
J. Clin. Endoc. and Metab. 14: 859, 1954.
4. Changes in the central nervous system following irradiation with 23 Mev x-rays from the betatron.
Arnold, A., et al.
Radiology 62: 37, 1954.

Tobias, et al., reported that rapid destruction of the pituitary occurred only after the use of high doses of irradiation, 18,000 r, by deuteron particles to the pituitary of the rat (5).

5. Irradiation of the pituitary of the rat with high energy deuterons.
Tobias, C.A., et al.
Am. J. Roentgenol. 72: 1-21, 1954.

Title: Determination of the effect of high dosage betatron irradiation to the pituitary and hypothalamus in man.

g. This project is expected to continue for two years.

Budget for the period July 1, 1955 to June 30, 1956

<u>(1) Personnel</u>	<u>Requested from ONR</u>
Min-Chiu Li, M.D., Research Fellow (presently a Damon Runyon Fellow; fellowship terminates June 30, 1955)	\$6,000
<u>(2) Capital Equipment*</u>	
<u>(3) Expendable Equipment</u>	
Chemicals, glassware and general laboratory supplies	1,000
Laboratory determinations	3,500
<u>(4) Other Expense: None</u>	
subtotal	<u>\$10,500</u>
<u>(5) Overhead: (8% of subtotal)</u>	<u>840</u>
total	<u>\$11,340</u>

(6) Extent of Institutional participation

Overhead

\$1,053**

* In addition, the institution is providing the major capital equipment (betatron) plus technical assistance in its operation as well as suitable patient material from the hospital.

** This figure is arrived at by computing the institutional overhead (31.59% of payroll expense) and subtracting the overhead requested from the ONR (8% of the subtotal).

h. Other Research Projects of the Principal Investigator

Dr. Li is presently a professional assistant on Dr. Pearson's National Cancer Institute project, C-925, "A Study of endocrine factors which influence the growth of tumors in man," in the amount of \$31,186 for 1955. He also participates in work supported by AEC Contract AT(30-1)-910. Funds from this contract for the entire Metabolism Laboratory Section are \$10,173 for 1955. This is part of an institution-wide contract on "The Biological Effects of Radiation, with Related Biochemical and Physical Studies."

i. Other agencies to which this proposal will be submitted:

It is planned to submit this proposal to the Atomic Energy Commission.

