

FS-34
SFS 10.001
MASTER

ANNUAL PROGRESS REPORT

and

RENEWAL APPLICATION

710142

TID-6063

TITLE OF PROJECT: The Biologic Effects of Radiation on Thyroid Tissue

CONTRACT: AT(30-1) 667

FOR PERIOD: 16 May 1959 to 15 May 1960

ANNUAL RATE: Total budgeted Annual Rate of Expenditure for this Project
for 15 September 1959 through 14 September 1960 —
\$13,000.00

CONTRACTOR: Massachusetts General Hospital

PRINCIPAL INVESTIGATOR: Oliver Cope, M. D.
Associate Professor of Surgery, Harvard Medical School
Visiting Surgeon, Massachusetts General Hospital

Date: 17 June 1960

1067519

DOE/HQ

I. Progress Report Under Contract AT(30-1)667

The concern of this Contract is the possible deleterious effects of radiation therapy of the thyroid gland. The principal concern relates to the possible carcinogenic action of the radiation in the gland itself. We have also begun extending our interests to possible leukemia and genetic effects. The center of effort continues to be the observation of patients irradiated from 1941 through 1949. The program with experimental animals is minor.

A. Observations on Patients

1. The Patients and Number of Thyroids Examined

It is presumed from analogy of the effect of radiation on other tissues that there will be a long latent period, perhaps 20 years, between the radiation necrosis in the thyroid gland and the final appearance of any malignancy. The patients with the longest period of follow-up therefore are those of the most importance to this study and are being watched carefully. The statistics of the patients with hyperthyroidism treated by radioactive iodine together with the number of gland specimens under study at the Massachusetts General Hospital are as follows:

TABLE I

N u m b e r o f P a t i e n t s

<u>Period of Rx</u>	<u>Treated</u>	<u>Died with Autopsy</u>	<u>Died No Autopsy</u>	<u>Active Follow-Up</u>	<u>Seen 1959-1960</u>	<u>Goiter Biopsies</u>
1941 - 1943	22		1	13	4	11
1944 - 1946	65	5	2	45	15	8
1947 - 1949	170	7	20	120	76	8
1950 - 1954	650	18	43	512	146	13
1955 - 1959	<u>762</u>	<u>5</u>	<u>14</u>	<u>741</u>	<u>60</u>	<u>2</u>
Totals	1669	35	80	1431	301	42

1067520

1116

102

DOE/HO

2. Management of the Follow-Up

The follow-up of the patients has proven to be painstaking. The patients are dispersed all over the country. In spite of this, we have maintained a close contact with a surprising number. The actual follow-up is given in Table I above. We are determined to locate the missing patients or to find out if post-mortem examinations were made if the patients have died.

Mrs. Irene Nobrega is the medical statistician employed to accomplish the many aspects of the follow-up including location of the patients, appointments, post mortem material, etc. In addition she is cataloguing carefully the data of the patients. The clinical follow-up program of the patients remains under the direction of Dr. Earle Chapman. Dr. Maloof continues to help. Research Fellows also join in the program.

3. Results of the Follow-Up

a. Neoplasia in the Thyroid Gland

Last year we reported the case of an adenomatous thyroid gland in a young patient who had been irradiated 17 years earlier (1941) at the age of 9. Three or more of the lumps were certainly neoplastic. Our pathologists consider them benign and clinically thus far they have so behaved. Our judgment, however, is still open to question. In this past year we have not encountered another such suspicious gland among the 301 patients examined. (See Table I.)

We have accumulated a considerable number of thyroid specimens for study, a total of 77. (See Table II.) The majority of the specimens were obtained within 12 years after irradiation. We have only 5 specimens from 13 to 17 years post-irradiation, namely, 1 operated 17 years after irradiation, 1 operated 13 years after irradiation, and 3 biopsies 14 years after irradiation. More material particularly in the longer follow-up ranges are needed.

TABLE II

Number of Post-Therapy Thyroid Specimens

	<u>130</u>	<u>131</u>
Open Surgical Biopsies	4	5
Needle Biopsies	3	3
Operations	12	15
Autopsies	<u>5</u>	<u>30</u>
Total	24	53
Grand Total		77

b. Other Effects of Irradiation

1. Possible Leukemia Effect

Our patients with long follow-up offer an excellent opportunity for exploration of the possible leukemia effect of radiation therapy. A start has been made and the program is described below in the Application for Renewal.

2. Possible Genetic Effect

It has been suggested that radioactive iodine therapy of hyperthyroidism may result in a deleterious genetic effect. Again, our long-standing group of patients offers an excellent opportunity to examine this question. We have been sorting out the married women who have borne children since the therapy to the thyroid. This aspect of the program is dealt with in the Application for Renewal.

c. Malignancy of Organs Other than the Thyroid in Treated Patients

Since possible malignant degeneration in the thyroid is a principal objective of this Contract, it has been suggested that it would be wise to see whether there was a predilection of our patients to malignant degeneration, a possible "presensitization". With this idea in mind a study is being made of the occurrence of carcinoma

1067522

116 04
DOE/HQ

organs other than the thyroid gland. Fifty-four patients have been found to have had a cancer in another organ. In some, the cancer antedated the hyperthyroidism and in others it appeared after the treatment of their hyperthyroidism. The patients, the cancer, the date treated, the date of the thyroid therapy and the outcome thus far is given in Appendix A. The data are only a start and no conclusions can be drawn.

d. Radioactive Iodine Fall Out and Pathology Department Activities

Since June of 1959, Dr. Vickery and the Department of Pathology monitored over 600 thyroids from routine autopsies for radioactivity. Aliquots of thyroid were assayed in a well-type scintillation counter for low level radioactivity in the region of the main iodine gamma peak. Two per cent of this total showed significant elevations above background and one-half of this number (roughly 1 per cent of the total 600) were from patients known to have had tracer doses of I^{131} or, in a few instances, radioactive I^{131} for brain scans. A final estimate of considerably less than 1 per cent would take into account those patients whose hospital histories do not record previous isotope administrations.

The Department of Pathology continues to follow patients who have had therapeutic doses of I^{131} and who have subsequently come to thyroid surgery or to post-mortem examination. During the past year we have had the opportunity to see the thyroids of 5 patients at autopsy and 3 from surgery who had received radioactive iodine either for toxic goiter or for coronary-artery disease.

In cooperation with members of the Thyroid Clinic, correlative studies on patients receiving tracer doses of radioactive iodine preoperatively have been performed in the Pathology Department. Techniques utilized have included gross autoradiographic methods, microautoradiographic preparations and assays of radioactivity of selected goiter areas. These observations have been made on both benign nodular goiters and thyroid cancers. Appropriate comparisons of these data with clinical diagnostic criteria and scanning maps of the neck for radioactivity are also performed.

1067523

DOE/HQ

116

25

B. Observations in Experimental Animals

Only one small study has been supported by this Contract. There are theoretical reasons to suppose that Vitamin B₁₂ might have an hyperplastic effect on the thyroid gland. Such an effect would have a deleterious action particularly if working in conjunction with another hyperplastic influence or upon a previously irradiated gland. A single series of rats were treated with a large dose of Vitamin B₁₂ over a six months' period. No significant change was noted in their glands compared with those of the litter-mate controls.

C. Personnel

There has been no change in the key personnel. Dr. Oliver Cope continues as the Principal Investigator. Dr. Earle M. Chapman and Dr. Farahe Maloof supervise the follow-up of patients. The medical, surgical, pathological and radio-biological participants are: Dr. Jacob Lerman, Dr. Edward Hamlin, Dr. George Nardi, Dr. Austin Vickery, and Dr. Gordon L. Brownell, respectively. Dr. Melvin Lederman has been a Research Fellow in the Thyroid Clinic.

II. Request for Renewal of Contract AT(30-1)667

A. Proposed Studies

For this coming year we propose three principal studies, namely, neoplasia in the thyroid gland, possible leukemia effects, and possible genetic effects. All are possible complications of radioactive iodine therapy of hyperthyroidism.

1. Post-Irradiation Neoplasia in the Thyroid Gland.

A continuation of the follow-up of the thyroid gland of patients whose hyperthyroidism has been treated with radioactive iodine is the principal objective of this Contract. We hope that support will be continuing until the issue of possible permanent degeneration is settled.

DOE/HQ

1067524

116

26

Nineteen years have elapsed since the first patient with hyperthyroidism was treated with radioactive iodine at the Massachusetts General Hospital. By analogy with skin cancer following irradiation it has been anticipated that a 20 year latent period might exist between the irradiation of the thyroid and any malignant degeneration. The crucial years are therefore now immediately before us.

As patients are being called in for follow-up, it is hoped that it will be possible this coming year to carry out open surgical biopsies of the thyroid gland on patients selected from the earliest irradiated. This plan was described in last year's Application for Renewal but to date has not proved feasible. Appropriate patients have not been encountered in the follow-up. These proposed biopsies are apart from the thyroid specimens obtained from patients with suspicious nodules who will need surgical exploration for the patient's own protection.

Should a suspicious tumor be encountered in subsequent operations, or biopsies, it is proposed to carry out animal transplantation. An item for animals is therefore also included in the Proposed Budget.

2. Possible Leukemia Effects of Irradiation

The follow-up studies for several years have included a complete blood examination. It is proposed to continue this aspect in the search for possible leukemia. We also hope to run a control survey concurrently on patients with hyperthyroidism who have been treated by surgery or drug therapy and thus add to the information available on this important subject. Much of the work is in the management of the follow-up and relatively less additional time and expense is required for this aspect of the blood work.

3. Possible Genetic Effects of Irradiation

It has been suggested that the radioactive iodine given for therapy of hyperthyroidism may, while circulating in the blood stream, adversely affect the gonads and their derivatives.

1067525 There are 60 women who have been treated in our Thyroid Clinic who have borne 90 children since the therapy of their thyroid. (See Table III.)

TABLE III

PREGNANCIES AFTER RaI

<u>Number of Patients</u>	<u>Treatment</u>	<u>Period</u>	<u>Number of Patients</u>	<u>Follow-up</u>
9	I ¹³⁰	1941-1946	7	12 - 16 years
			2	lost to follow-up
31	I ¹³¹	1947-1951	8	10 - 12 years
			18	5 - 9 years
			5	2 - 4 years
<u>20</u>	I ¹³¹	1954-1960	20	1 - 6 years
60*				

*Bore 90 children

It is Dr. Chapman's design to inveigle the parents of these children to bring the children in for examination. This he points out will have to be done in such a way not to alarm the parents or children. The general approach is to be an informal one. As this proposed part of the follow-up program is undertaken, it may bring rewarding and let us hope reassuring information.

4. Other Malignancies

We plan to continue to tabulate the occurrence of malignancies in tissues other than the thyroid. It has been stated that a patient who has had a malignancy of one organ is more likely to have a cancer in a second organ than is a person in the population at large who has not previously had a cancer. Thus, it is deemed wise that the occurrence of other malignancies in our patients be tabulated as a part of the investigation of possible malignant degeneration in the thyroid gland resulting from radioactive iodine irradiation.

5. Radioactive Iodine Fall Out in the Human Being

Dr. Vickery plans to continue his study of fall out radioactive iodine in the thyroids of the human being obtained at autopsy. This study is supported from funds from another source but is considered so closely related to this project that it is mentioned in this plan of intent.

The support given by the Atomic Energy Commission has made it possible to organize this continuing follow-up and it is frevently hoped that it will be possible to continue the support and the project.

APPENDIX A

CANCER AFTER RaI¹³¹ THERAPY

<u>Name</u>	<u>Sex</u>	<u>Age</u>	<u>Rx Date</u>	<u>Cancer</u>	<u>Date</u>	<u>Follow-Up</u>
B	F	66	12/10/53	Renal cell	9/29/56	4/28/58 Well
Bu	F	65	6/19/54	Breast	3/17/55	5/27/58 Well
C	M	66	11/21/53	Ca Kidney	12/19/58	5/11/59 Died
D	F	47	12/16/49	Sigmoid	3/25/53	6/1/53 Died
G	F	56	11/21/56	Skin	3/ 1/57	
H	F	79	4/ 7/56	Breast	9/11/57	
K	F	53	5/ 5/50	Pancreas		6/19/56 Died
Ke	F	54	12/ 5/46	Rectum	7/20/49	7/30/49 Died
L	F	71	4/ 1/49	Breast	4/11/53	11/ 2/59 Well
Ly	M	58	7/20/50	Malignant Lymphoma	9/19/57	1/ 6/59 Well
Mc	F	71	8/11/52	Antrum	10/ 3/52	9/29/54 Died
Mr	F	32	12/22/54	Papillary adenocarcinoma	5/23/55	
Mt	F	65	10/16/53	Breast	4/21/56	5/19/56 Died sud- denly
My	M	80	4/21/53	Pancreas		8/19/53 Died
P:	F	39	1/28/49	Papillary adenocarcinoma	4/29/50	4/ 7/59 Well
	F	54	6/ 7/47	Lung	10/19/51	11/19/51 Died
S	M	72	11/30/51	Stomach	6/ 6/52	2/ 5/53 Died
Se	F	69	2/22/51	Stomach	8/22/51	/52 Died
Sy	F	54	4/19/47	Breast	5/27/52	9/24/57 Died in failure
T	M	60	9/25/52	Stomach		5/24/57 Died
W	F	74	12/15/49	Breast	2/28/56	4/12/56 Died
Wr	F	65	11/20/46	Breast	6/22/51	6/16/59 Died
Wh	F	54	12/17/49	Breast	9/10/57	11/19/59 Well
Wi	F	57	8/26/46	Cervix	/51	

CANCER BEFORE RaI¹³¹

<u>Name</u>	<u>Sex</u>	<u>Ca Date</u>	<u>Cancer</u>	<u>Rx Date</u>	<u>Age</u>	<u>Follow-Up</u>
A	F	1940	Colostomy	9/ 8/56	62	4/10/58 Well
		1952	Colostomy			
		1953	Lung			
Ar	F	1941	Cervix	7/30/54	67	10/20/57 Well
At	F	1951	Breast	4/ 8/54	59	11/ 8/58 Well
B	F	1954	Colon	6/ 4/55	64	1/ 9/59
C	F	1952	Eyelid	8/13/52	56	2/24/59 Well
Ca	F	1954	Uterus	8/30/57	42	8/ 4/58 Well
Co	M	1934	Soft palate	2/ 1/51	41	
Cn	M	1955	Prostate	2/11/55	76	4/20/55 Died
D	F	1947	Colostomy	10/20/55	52	4/22/58 Well
E	F	1947	Breast	6/24/53	54	10/ 2/58 Well
G	F	1939	Breast	8/ 3/56	46	9/ 3/57 Well
H	F	1949	Sigmoid	6/ 5/54	64	4/ 8/57 Well
I	F	1927	Breast	3/17/48	61	9/ 1/59 Well
L	F	1942	Cervix	6/17/54	59	6/21/57 Well
Le	F	1956	Cervix	1/10/58	39	4/30/58 Well
L	F		Uterus	3/ 2/51	78	
M	F	1947	Breast	6/ 1/51	66	
Ma	F	1936	Rectum	4/22/55	59	6/27/57 Well
Me	F	1951	Uterus	10/ 6/55	50	
Mu	F	1952	Skin	1/29/60	59	
P	F	1954	Colostomy	9/10/55	57	12/ 4/57 Well
Pu	F	1944	Scalp	9/17/53	60	4/14/56 Died -- Cerebral hemorrhage
S	F	1956	Cervix	11/17/57	44	9/17/58 Well
T	F	1940	Colon	12/16/54	79	12/26/55 Died -- Subarachnoid hemor- rhage
Th	M	1953	Rectum	7/28/53	65	5/19/55 Died
Tu	F	1952	Breast	2/27/53	48	4/26/57 Well
U	F	1948	Ovary	1/25/52	50	5/ 7/57 Well
W	F		Cervix	1/31/58	35	
Wi	F	1951	Breast	5/ 4/56	74	
Wr	F					