

LATER RESULTS OF ^{131}I TREATMENT OF HYPERTHYROIDISM IN 73 CHILDREN AND ADOLESCENTS: 1967 FOLLOWUP

Paul Starr

White Memorial Medical Center, Los Angeles, California

Henry L. Jaffe

Cedars-Sinai Medical Center, Cedars of Lebanon Hospital Division, Los Angeles, California

Leon Oettinger, Jr.

The Children's Hospital, Los Angeles, California

The first report on the followup condition of 73 children and adolescents several years after receiving ^{131}I therapy for hyperthyroidism was presented to the American Thyroid Association in May, 1961 and subsequently published in 1964 (1).

CLINICAL MATERIAL

This group of 73 patients included 62 children and 11 adolescents. The clinical diagnosis, age, sex, condition of the thyroid gland and ^{131}I dose of these 73 children and adolescents are given in our original paper (1). Table 1 in this paper gives the same identification numbers as those used in Table 3 of the original paper. The ages of these children at the time of the 1967 followup evaluation range from 16 years (Case 27 who was treated at 28 months of age) to 35 years (Case 73 who was 18 years old when treated). The average age at the time of the 1967 followup evaluation was 28 years.

RESULTS IN 1967

Table 1 shows the identification number, sex, year of the first ^{131}I treatment, age when first treated by ^{131}I , total dose of ^{131}I , month and year of last examination, last PBI when available and/or T_3 ^{131}I resin uptake study, amount of thyroid replacement therapy, palpable thyroid nodules and history of pregnancy after treatment.

Table 2 shows the distribution by the year of treatment and by the first and second followup re-examination. Followup examinations were completed between 1965 and 1967 in 61 patients or 83% of the total group. Of these 61 cases, 42 patients were examined in 1967, 17 patients were examined in 1966 and two patients were examined in 1965. Nine additional cases were examined between 1961 and 1964, bringing the total followup between 1961 and 1967 to 98%. Only one case has not been

seen since 1958. Two of the patients in the entire group died after surgery in the same year as they received ^{131}I treatment.

Table 3 shows the number of years that had elapsed after ^{131}I therapy at the time of the last followup examination.

CLINICAL AND PATHOLOGICAL OBSERVATIONS

On reexamination in 1967 special attention was paid to the thyroid area and to cervical adenopathy. Seven of the 73 children had palpable thyroid tissue masses after initial isotope treatment. Four of these were subjected to thyroid surgery. No palpable nodules were found in the remaining 64 patients.

In 1964 Patient 4 (Table 1) had a 1.5×1.0 -cm mass in the right thyroid area: she has not been seen since; she was not on thyroid hormone medication and at that time her PBI was 4.8.

In Case 16 the initial dose of ^{131}I was given in January, 1952 when the patient was 12 years old. A right total and left subtotal thyroidectomy for nodular tissue was done in 1954. The tissue shows histologic features characteristic of radiation changes. The follicles are disrupted, and some of the colloid is globular. There is an increase in fibrous tissue. Many of the smaller vessels show fibrinoid degeneration but without evidence of acute vasculitis. There is heavy lymphocytic infiltration but no polymorphonuclear leukocytes. There are many atypical cells and Hurthle cells present. There is no evidence of malignancy. In 1961 hyperthyroidism associated with a "hot" nodule was recognized and a second dose of 10 mCi was administered in 1962. When the pa-

Received April 2, 1968; revision accepted March 12, 1969.

For reprints contact: Henry L. Jaffe, Radiation Therapy and Nuclear Medicine, Cedars-Sinai Medical Center, Cedars of Lebanon Hospital Division, 4833 Fountain Avenue, Los Angeles, Calif. 90029.

tient was examined in September, 1967, there was no palpable thyroid tissue; she was taking desiccated thyroid gr i but the PBI done for this survey was only 2.9 mcg%; she had had five pregnancies with three miscarriages, doubtless due to hypothyroidism.

In Case 24 the patient received 4 mCi of ^{131}I in 1953 at the age of 18. A second episode of hyperthyroidism occurred in 1961 and a subtotal thyroidectomy was done. The pathological changes were interpreted as being similar to those of Case 16 but less severe. There was no evidence of malignancy. She is now hypothyroid requiring 0.2–0.3 mg of Synthroid daily. She has had four children.

On examination of a healthy young man of 18 (Case 32), the thyroid was palpable as a firm roll of tissue across the trachea and in the area of each lobe. Without thyroid medication the PBI was 4.0 mcg%.

Case 39 has already been reviewed in our first paper. It was reported in detail by Karlan, Polloch and Snyder (2) in 1964. This is the case of a 12-year-old girl who received a total of 3.25 mCi of ^{131}I in two doses between July, 1955 and February, 1956. In 1953 surgical thyroidectomy revealed papillary and follicular adenocarcinoma. Winship commented as follows: "According to my figures the diagnosis of carcinoma was established two years and four months after her first dose of ^{131}I . I doubt that there is any relationship between the radiation and the cancer." When seen in 1967 there was no palpable thyroid tissue nor other evidence of recurrence. The serum PBI was 6.5 mcg%. The patient is receiving desiccated thyroid gr ii.

In Case 42 (a young woman) followup in 1966 revealed bilateral palpable symmetrical thyroid tissue. The PBI was normal, and the patient was not on thyroid hormone medication. She has had two children.

After two treatments with ^{131}I in 1954 and 1955, Case 43 was found to have enlargement of the thyroid without postradiation thyroid medication. A thyroidectomy was performed in 1963. Review of this surgical material indicates minimal fibrosis consistent with radiation changes but nothing characteristic of malignancy. Since 1963 she has been on desiccated thyroid gr iii and has one normal child. When examined in 1967, there was no palpable thyroid tissue.

OPHTHALMOPATHY

In only one case (35) of the entire series were orbital changes found. This patient who has not taken any thyroid medication since ^{131}I treatment 13 years ago has some orbital infiltration with Hertel measurements of 22 and 23 mm.

HYPOTHYROIDISM OCCURRING AFTER TREATMENT

Of the 15 children who were treated when they were 9 years old or younger, seven are on thyroid medication, presumably hypothyroid without it. Two of these children who are not receiving supplemental thyroid show PBI values of 3.7 and 4.0 mcg% respectively. Five may be assumed to be euthyroid. One child (Case 66) died after subtotal thyroidectomy performed after incomplete isotope therapy. Therefore nine of 14 are presumably hypothyroid.

Of the 33 children who were from 10 to 14 years of age at the time of treatment, 13 are on thyroid hormone medication and six have low PBI's—19 of 33 presumably hypothyroid.

Of the remaining 26 adolescents who were from 15 to 18 years of age at the time of treatment, 15 are on thyroid medication and seven have low PBI's—22 of 26 are presumably hypothyroid.

In summary, about 81% of these children is presumably hypothyroid at this time. With such a high incidence of hypothyroidism after this treatment, we recommend the beginning of maintenance thyroid medication immediately or shortly after the treatment is given to maintain a euthyroid state.

LENGTH OF FOLLOWUP AFTER TREATMENT

Twenty-three or about one-third of these children have been observed for from 15 to 18 years since treatment; 42 or more than half from 10 to 14 years; and six children from 6 to 9 years.

The younger children have been observed on an average of 14 years; the children from 10 to 14 years of age have been observed an average of $12\frac{3}{4}$ years; those from 15 to 18 years of age at the time of treatment have been observed an average of 13 years.

OFFSPRING

Of the 73 children in the original treatment series, 56 are female and 28 of these have 52 children. Six of the 17 males now have 17 children. No thyroid abnormalities are known in these 69 children. The females had 10 miscarriages in addition to their completed pregnancies. These may have been related to untreated hypothyroidism.

MORTALITY

As was reported, there were no deaths attributable to isotope therapy, but two children died following thyroid surgery (Cases 65 and 66, Table 1).

DISCUSSION

The papers by Crile (3), Kogut (4) and Sheline (5) together with this series bring to 158 the number of children and adolescents reported in this country who were treated with ^{131}I for hyperthy-

TABLE 1. INFORMATION ON PATIENTS TREATED BY ¹³¹I THERAPY

Patient	Sex	Year of first ¹³¹ I R _x	Age when R _x (yr)	Age at last exam (yr)	Total ¹³¹ I dose	Date last exam	Last PBI/T _s	Thyroid replacement therapy	Palpable thyroid nodules	History of pregnancy
1	M	1949	4	22	0.63	4-67	On active duty in Vietnam			
2	F	1949	13	31	0.83	8-67	6.4	0	0	2 normal; 1 miscarriage
3	F	1950	15	32	5.0	10-67	5.5	0	0	2 normal; 1 miscarriage
4	F	1950 1954*	8	25	2.2	9-64	4.8	0	1.5 × 1.0 cm in rt. thyroid area	0
5	F	1950	15	32	12.25	8-66	T _s 41%	gr i	0	1
6	F	1950 1952*	14	31	8.8	7-66	T _s 31.5%	gr ii	0	5
7	F	1950	7	24	0.92	8-67	5.2	0	0	0
8	F	1950	10	27	3.1	8-67	4.6	gr i	0	3
9	F	1951	8	24	2.0	1967	Phone contact†			Several
10	F	1951	9	25	2.0	6-66	3.7 T _s 0.75%	0	0	0
11	F	1951 1953*	14	30	7.0	12-66	5.1	0	0	2 normal; 2 miscarriages
12	F	1951	14	30	6.9	3-66	5.6	gr i	0	3
13	M	1952 1953*	15	30	12.0	1963	3.6	0	0	0
14	F	1952	14	30	9.1	9-67	3.6	0	0	1 normal; 1 miscarriage
15	F	1952 1953*	15	27	8.6	10-67	—	gr iii	0	5
16†	F	1952 1962*	12	27	12.21	9-67	2.9	gr i	0	2 normal; 3 incomplete
17	M	1952	18	33	14.0	9-66	3.1	gr i	0	7
18	F	1952	7	23	3.9	10-67	5.2	gr ii	0	0
19	F	1952	15	30	7.0	10-67	4.4	gr iii	0	4
20	M	1952 1953*	18	33	23.0	6-66	5.0	gr i ½	0	1
21	F	1954	15	30	29.2	1-65	4.1	gr ii	0	1
22	F	1952	5	20	0.7	12-66	5.0	gr ii	0	0
23	F	1953	13	27	1.0	6-67	4.5	0	0	0
24†	F	1953	18	32	4.0	9-67	3.8	gr i	0	4
25	F	1953	12	26	0.31	8-67	—	0	0	2
26	M	1952	12	27	21.0	10-67	4.9	gr iii	0	0
27	F	1953	28 mo.	16	4.0	6-67	—	gr iv	0	0
28	F	1953	15	29	6.9	3-67	—	gr iv	0	2 normal; 1 miscarriage
29	F	1953	16	30	7.17	7-63	—	0	0	0
30	F	1953	17	31	7.0	3-67	8.6	Syn. 0.4	0	0
31	F	1954	11	24	1.5	5-67	6.2	gr iii	0	2
32	M	1954	5	18	1.5	7-67	4.0	—	Palpable	0
33	F	1954	11	25	2.0	3-67	6.5	0	0	0
34	F	1954	12	25	1.5	11-61	—	—	—	—
35	M	1954	14	28	1.75	11-67	4.5	0	Palpable ?	0
36	F	1954	13	26	4.0	7-67	5.0	Syn. 0.4	0	1 with cleft palate
37	F	1954	14	27	4.9	2-62	—	0	—	0
38	M	1954	16	29	14.0	4-67	5.8	Syn. 0.2	0	5
39†	F	1955 1956*	12	24	3.25	7-67	6.5	gr ii	0	0
40	M	1955	16	28	5.0	11-67	5.2	gr ii	0	2
41	F	1955	9	21	1.0	5-67	5.4	0	0	0
42†	F	1955	11	23	6.4	4-66	7.6	0	Nodule on both sides	2
43†	F	1954 1955*	10	23	2.25	8-67	5.7	gr iii	0	1

* Year of ¹³¹I retreatment.† Thyroidectomy after ¹³¹I R_x.

TABLE 1 (Continued)

Patient	Sex	Year of first ¹³¹ I Rx	Age when Rx (yr)	Age at last exam (yr)	Total ¹³¹ I dose	Date last exam	Last PBI/T _s	Thyroid replacement therapy	Palpable thyroid nodules	History of pregnancy
44	F	1955 1956*	12	24	5.6	6-65	2.0	gr iv	0	2
45	F	1955	12	24	6.5	2-66	T _s 27%	0	0	0
46	F	1955	15	27	1.5	1958	—	—	—	—
47	M	1955	6	18	2.77	6-67	—	gr iv	0	0
48	M	1955	16	28	4.0	6-67	2.9	gr ii	0	0
49	F	1955	6	18	1.5	10-66	9.6	0	0	0
50	M	1956	14	25	2.0		Patient is well—Telephone contact 11-67			
51	M	1956	13	24	5.89	4-66	4.6	0	0	2
52	M	1956	15	26	6.3	10-67	6.2	0	0	0
53	M	1956	12	23	7.0	11-67	T _s 33.6%	0	0	0
54	F	1956	8	19	4.2	8-66	T _s 39.6%	gr ii	0	0
55	M	1957	13	24	1.5	7-67	7.1	0	0	0
							T _s 28%			
56	F	1957	17	27	7.0	8-67	5.9	gr ii	0	0
57	F	1957	16	22	3.0	7-63	6.4	—	—	—
58	F	1957	14	24	14.6	5-67	5.2	0	0	0
59	F	1957	14	24	5.9	3-67	4.4	0	0	0
60	F	1957	12	22	5.9	7-66	5.9	gr v	0	0
61	M	1957	12	23	4.5	3-61	6.2	0	0	0
62	F	1957	10	20	5.6	9-66	3.5	0	0	0
63	F	1957	14	24	5.0	8-67	—	Syn. 0.1	0	0
64	F	1958	13	22	7.3	9-66	3.3	gr ii	0	0
65	F	1951	17	Expired 1951	3.0	—				
66	F	1953	8	Expired 1953	0.75	—				
67	F	1957	16	26	7.6	2-66	4.6 T _s 25%	gr ii-iii, & 5 mcg Cytomel	0	2
68	F	1958	17	26	9.5	7-67	5.5	0	0	1
69	M	1960	18	25	15.0	9-67	—	0	0	0
70	F	1961	8	14	1.5	10-67	6.2	Syn. 0.2	0	0
71	F	1958	16	25	5.0	4-67	3.7	Comp. W 60 mg 17S2-14	0	Twins
72	F	1954	11	24	6.0	9-67	10.0	gr iv, Enovid	0	1
73	F	1950	18	35	8.0	6-63	1.0	—	—	—

* Year of ¹³¹I retreatment.

roidism and who have been followed for several years. In our opinion thyroid nodules reported by Sheline (5) are probably of the nature of compensatory hypertrophy due to TSH action in untreated post-treatment hypothyroidism and not a neoplastic reaction to radiation.

The high incidence of hypothyroidism which we assume from the fact of thyroid hormone medication, suggests that maintenance dose of sodium levothyroxine should be started early and continued indefinitely.

This need is not peculiar to this form of therapy for hyperthyroidism since the occurrence of hypothyroidism after surgery is such that it requires prophylactic and permanent replacement medication (6)

and even antithyroid drug treatment requires prolonged thyroid hormone administration (7).

If maintenance thyroxine is prescribed early and controlled by serial PBI determination, post-treatment ophthalmopathy, compensatory hypertrophy and hypothyroidism will be prevented and normal growth, development and fertility assured.

No carcinogenesis has been definitely shown in our group of patients which can be directly attributed to the ¹³¹I therapy of hyperthyroidism. The interval of 2 years and 4 months between the radiation therapy and the discovery of cancer following surgery in our Case 39 seems to be so short that there is a strong suspicion that the thyroid cancer was present when the patient was radiated.

TABLE 2. NUMBER OF PATIENTS REEXAMINED BY CALENDAR YEARS 1949-1967

	Year																	Total patients			
	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65		66	67	
Initial ¹³¹ I Rx	2	7	5	10	8	11	10	5	10	3		1	1								73
1st reexam up to 1963 exam				1*		1*				1	1	5	16	20	22						67
2nd reexam up to 1967				1*		1*				1			2	2	4	1	2	17	42		73

* Expired.

TABLE 3. LENGTH OF FOLLOWUP AFTER ¹³¹I TREATMENT AT TIME OF LAST EXAMINATION

Number of years after Rx	18	17	16	15	14	13	12	11	10	9	7	6	SD*	Total
Number of patients	2	7	6	8	9	8	11	7	7	3	1	2	2	73

* Expired after surgery same year of ¹³¹I Rx.

A 98% followup study through 1967 included the majority of the patients who were examined 10-18 years after ¹³¹I treatment for hyperthyroidism in a series of 73 children and adolescents. Seven children had palpable nodular thyroid tissue a few years after the isotope treatment; four of these were subjected to subtotal thyroidectomy and the histological findings are reported.

Of the 56 female patients in this group, 28 of them had 52 normal children and six of the 17 male patients have had 17 normal children.

To judge by the number of patients now treated with thyroid hormone medication, hypothyroidism developed in the majority of these children. Maintenance thyroid hormone therapy, preferably sodium levothyroxine, is suggested in all children following ¹³¹I treatment without waiting for this permanent deficiency to develop.

ACKNOWLEDGMENT

Supported by the American Cancer Society, Grant E#-152, with the assistance of Mrs. Betty Joseph. We are grateful to Theodore Winship of the Childhood Thyroid Cancer Registry, Washington Hospital Center, Department

of Pathology, Washington, D.C., for examination of surgical pathologic material from several of these children. All interpretations of pathological findings are those of Dr. Winship.

REFERENCES

1. STARR, P., JAFFE, H. L. AND OETTINGER, L., JR.: Late results of ¹³¹I treatment of hyperthyroidism in seventy-three children and adolescents. *J. Nucl. Med.* 5:81, 1964.
2. KARLAN, M. D., POLLOCH, W. F. AND SNYDER, W. H., JR.: Carcinoma of the thyroid following treatment of hyperthyroidism with radioactive iodine. *Calif. Med.* 101:196, 1964.
3. CRILE, G., JR. AND SCHUMACHER, O. P.: Radioactive iodine treatment of Graves' Disease, results in 32 children under 16 years of age. *Am. J. Diseases Children* 110:501, 1965.
4. KOGUT, M. D., *et al*: Treatment of hyperthyroidism in children: analysis of forty-five patients. *New Engl. J. Med.* 272:217, 1965.
5. SHELINE, G. E., *et al*: Thyroid nodules occurring late after treatment of thyrotoxicosis with radioiodine. *J. Clin. Endocrinol.* 22:8, 1962.
6. NOFAL, M. M., BEIERWALTES, W. H. AND PATUO, M. E.: Treatment of hyperthyroidism with sodium iodide ¹³¹I. *J. Am. Med. Assoc.* 197:605, 1966.
7. HOWARD, J. E.: Treatment of thyrotoxicosis. *J. Am. Med. Assoc.* 202:706, 1967.