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I^{131} TREATMENT FOR TOXIC DIFFUSE GOITER

ANALYSIS OF 1056 CURED CASES

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INTRODUCTION

The many advantages of radioiodine, I^{131}, have led to its more extensive use for the treatment of hyperthyroidism in recent years. These advantages include; no mortality, no vocal cord paralysis, no chronic tetany, no discomfort or scar, no loss of time and income, no hospitalization, fewer recurrences than in other forms of treatment and the least expensive form of treatment.

Twenty fiive years have elapsed since Hertz[1] and Hamilton[2] first used radioiodine to treat hyperthyroidism. During this time many reports have been published on the treatment of large numbers of hyperthyroid patients with radioiodine. A few disadvantages of I^{131} treatment were detected, but a great question still remains unanswered.

The disadvantages detected by many reporters were; a wide variation in the response of patients to a selected dose, so that no method has yet been devised to select a satisfactory uniform dose, high incidence of hypothyroidism after the treatment, delayed recovery, one year or longer, in some cases with repeated tretment with I^{131}, and complete resistance to I^{131} in a few cases.

The question that remains unanswered is whether cancer of the thyroid gland or leukemia occur after I^{131} treatment.

Although the author can not offer definite methods to correct the disadvantages of I^{131} treatment nor can give a definite answer to the question, but he has made this study of 1056 cases of toxic diffuse goiter cured with I^{131}, with the primary interest of shedding further light on the I^{131} treatment for hyperthyroidism.

METHODS AND MATERIALS

All patients were examined at the Thyroid Clinic of National Taiwan University Hospital, and the diagnosis of hyperthyroidism was established before therapy in each patient on the basis of the clinical findings, basal metabolic rate, and radioiodine studies such as 2 hour and 24 hour thyrodal I^{131}

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uptake and 48 hour serum activity.

From March 1958 to December 1966, 1496 patients with hyperthyroidism were treated with I^{131}. Fourty-eight patients were treated too recently to be included in this study. Three patients were judged resistant to I^{131} treatment after several doses of I^{131} and referred for thyroidectomy. Three hundred and seventy-three patients were lost for follow up after receiving one or more treatment doses of I^{131}. Sixteen cases of toxic nodular goiter were not included because the etiology of the disease and dose determination for I^{131} treatment for toxic nodular goiter were different from that of toxic diffuse goiter (Table 1).

TABLE 1. All Patients Treated with I^{131} (1958-1966)

Diffuse toxic goiter		
Cured cases	1,056	1,480
Resistant cases	3	
Lost for follow-up	373	
Under follow-up	48	
Toxic nodular goiter	16	
Total	1,496	

One thousand and fifty-six cases cured of hyperthyroidism with I^{131} treatment were followed for 1 to 8 years.

Sex incidence of the 1056 cured cases is show in Table 2. There were 195 male patients and 861 female patients. The ratio of male to female was 1 : 4.

TABLE 2. Sex Incidence of Patients Cured with I^{131}

Sex	Number	Per cent
Male	195	18.5%
Female	861	81.5
Total	1,056	100.0

The age distribution (Table 3) ranged from 14 to 65 years. The majority of patients (84.8%) were between 21 and 50 years of age. There were only 21 patients (2.0%) under 20. The authors did not treat patients under 20 years of age with I^{131} unless they had severe exophthalmos or could not be cured after one year of medical treatment.

TABLE 3. Age Distribution of Patients Cured with I^{131}

Age	Number	Per cent (%)
-20	21	2.0
21-30	212	20.1
31-40	394	37.3
41-50	289	27.4
51-60	120	11.4
61-70	20	1.9
Total	1,059	100.0

As shown in Table 4, 58 cases (5.5 %) were patients with recurrent hyperthyroidism after thyroidectomy. Six hundred and seventy-eight cases (64.2%) had been pretreated with antithyroid drugs, and 320 cases (30.3%) had received

no therapy. To avoid aggravation of thyrotoxicosis or thyroid crisis after I^{131} administration, I^{131} was not given immediately to the patients unless their thyrotoxic symptoms were mild. Patients with moderate or severe thyrotoxicosis were treated with antithyroid drugs for an average of 2 months, and radioiodine was instituted after the euthyroid state was obtained.

TABLE 4. Previous Treatment of Patients Cured with I^{131}

Treatment	Number	Per cent (%)
Non-treated	320	30.3
Med. Treat.	678	64.2
Surg. Treat.	58	5.5
Total	1.056	100.0

For the dose selection of I^{131}, according to the weight of thyroid gland which was estimated by palpation, and 24 hour thyroidal I^{131} uptake, the dose was calculated by using the following formula to let 100 c. of I^{131} to be retained in each gram of the thyroid gland:

Calculated dose = 100 c. × Thyroid weight

$$(\text{Gm.}) \times \frac{100}{24 \text{ hour uptake}(\%)}$$

When the calculated dose was larger, a limited dose was given. From March 1958 to December 1963, the level of this limitation was arbitrarily settled at 7 mc.[3] In January 1964 this level was elevated to 15 mc. for the purpose of improving the one-dose cure rate, but the author reported the one-dose cure rate could not be improved[4], so in July 1966 the limit of the therapeutic dose was reduced to 7 mc.

Response to I^{131} therapy was judged by the regression of clinical signs and symptoms, and complete or almost complete disappearance of the goiter three months after each treatment. If the patient still remained in hyperthyroid state, the next dose was scheduled according to the initial regimen.

RESULTS

Among 1056 cured cases, 528 cases (50.0%) were cured with one dose, 363 cases (34.4%) were cured with two doses, 113 cases (10.7%) were cured with three doses, 33 cases (3.1%) were cured with four doses, 12 cases (1.1%) were cured with five doses, 5 cases (0.5%) were cured with six doses, one caes required seven doses and another case needed ten doses.

The total therapeutic dose in each case ranged from 2.4 mc. to 76.9 mc. The average total therapeutic dose was 12.94 mc., and the average number of treatment was 1.73 doses.

Relationships of sex, age, previous treatment, duration of the disease, weight of thyroid gland, and quantity of calculated dose to the number of treatments and the total dose for cure are shown in Tables 5 to 10.

1. Sex (Table 5). Average number of treatment of male patients was 1.66 doses, and average total dose for cure was 13.47 mc. The averages for cure in the female patients were 1.75 doses and 12.81 mc. of I^{131}. There was no difference between the sexes in the average number of doses and average total therapeutic dose (P 0.1).

TABLE 5. Sex Incidence and Number of Treatment of Patients Cured with I^{131}

Doses→ Sex ↓	I	II	III	IV	V	VI	VII	X	Av. No. of Rx.	Av. Total Dose
Male	105 (8.2)	66 (15.3)	15 (22.6)	5 (39.3)	3 (47.9)	1 (70.7)	0	0	1.66	13.47 mc.
Female	423 (7.3)	297 (14.4)	98 (21.8)	28 (30.4)	9 (41.2)	4 (43.7)	1 (52.0)	1 (76.9)	1.75	12.81 mc.
Total	528 (7.5)	363 (14.6)	113 (21.9)	33 (31.7)	12 (42.9)	5 (49.1)	1 (52.0)	1 (76.9)	1.73	12.94 mc.

2. Age. As shown in Table 6, patients under 20 years of age needed more doses (2.14 doses) and a larger total dose (16.98 mc.), but this was not statistically significant. Patients over 20 years of age required the same number and total quantity of doses.

TABLE 6. Age Distribution and Number of Treatment of Patients Cured with I^{131}

Doses→ Age ↓	I	II	III	IV	V	VI	VII	X	Av. No. of Rx.	Av. Total Dose
-20	9 (8.0)	3 (15.7)	6 (22.2)	3 (34.9)	0	0	0	0	2.14	16.98 mc.
21-30	107 (7.6)	65 (14.4)	28 (22.8)	5 (26.2)	5 (49.6)	2 (39.0)	0	0	1.78	13.40 mc.
31-40	195 (7.9)	146 (14.2)	38 (21.7)	12 (32.7)	1 (30.3)	2 (62.7)	0	0	1.69	12.65 mc.
41-50	158 (7.2)	87 (15.1)	29 (21.2)	7 (33.0)	6 (39.3)	1 (41.5)	0	1 (76.9)	1.71	12.63 mc.
51-60	50 (6.7)	53 (14.4)	11 (21.8)	5 (32.5)	0	0	1 (52.0)	0	1.80	12.86 mc.
61-70	9 (7.5)	9 (15.0)	1 (13.7)	1 (26.5)	0	0	0	0	1.70	12.14 mc.
Total	528 (7.5)	363 (14.6)	113 (21.9)	33 (31.7)	12 (42.9)	5 (49.1)	1 (52.0)	1 (76.9)	1.73	12.94 mc.

3. Previous treatment (Table 7). Average total dose and number of treatments in each group was 15.62 mc. in 1.70 doses for non-pretreated patients, 13.29 mc. in 1.76 doses for patients pretreated with antithyroid drugs, and 10.53 mc. in 1.57 doses for patients with postoperative recurrence. There was

no difference between the patients pretreated with antithyroid drugs and the patients not pretreated as to the number and quantity of the therapeutic dose of I^{131} (P 0.1). The fact that the cases of postoperative recurrence required a smaller number and less quantity of the therapeutic dose of I^{131} might be due to the fact that the thyroid glands of these patients were smaller than those of the other groups.

TABLE 7. Previous Treatment and Number of Treatment of Patients Cured with I^{131}

Doses→ / Treatment ↓	I	II	III	IV	V	VI	VII	X	Bv. No of Rx.	Av. Total Dose
Non-treated	169 (7.4)	102 (14.9)	35 (21.3)	7 (28.4)	4 (29.3)	2 (55.6)	1 (52.0)	0	1.70	15.62 mc.
Medical Rx.	322 (7.6)	248 (14.6)	73 (22.0)	24 (33.1)	7 (46.8)	3 (44.5)	0	1 (76.9)	1.76	13.29 mc.
Surgical Rx.	37 (6.6)	13 (13.1)	5 (22.6)	2 (26.8)	1 (31.1)	0	0	0	1.57	10.53 mc.
Total	528 (7.5)	363 (14.6)	113 (21.9)	33 (31.7)	12 (42.9)	5 (49.1)	1 (52.0)	1 (76.9)	1.73	12.94 mc.

4. Duration of the disease. In a previous study[3] the author reported that the shorter the duration of the disease, the better the one-dose cure rate. But in the present study there was seen no relationship between the duration of the disease and number and quantity of therapeutic doses of I^{131} (Table 8).

TABLE 8. Duration of the Disease and Number of Treatment of Patients Cured with I^{131}

Doses→ / Duration ↓	I	II	III	IV	V	VI	VII	X	Av. No. of Rx.	Av. Total Dose
-6 ms.	197 (7.5)	119 (14.4)	31 (22.0)	12 (31.9)	3 (45.1)	2 (55.6)	0	0	1.66	12.35 mc.
6 ms.-1 yr.	138 (7.7)	115 (14.4)	35 (22.0)	9 (27.8)	5 (42.3)	0	0	0	1.77	13.09 mc.
1 yrs.-3 yrs.	120 (7.2)	70 (15.1)	29 (21.2)	4 (36.4)	0	3 (44.5)	0	0	1.69	12.46 mc.
3 yrs.-5 yrs.	31 (6.6)	31 (14.2)	11 (22.0)	5 (30.9)	3 (45.3)	0	1 (52.0)	1 (76.9)	2.14	15.72 mc.
5 yrs.-10 yrs.	29 (7.2)	24 (15.7)	9 (22.1)	2 (34.5)	1 (31.1)	0	0	0	1.74	13.17 mc.
10 ys.-	13 (8.0)	4 (13.9)	1 (21.0)	1 (35.3)	0	0	0	0	1.47	11.36 mc.
Total	528 (7.5)	363 (14.6)	113 (21.9)	33 (31.7)	12 (42.9)	5 (49.2)	1 (52.0)	1 (76.9)	1.73	12.94 mc.

5. Weight of thyroid gland. As shown in Table 9, the larger the weight of the thyroid gland, the more the number of I^{131} treatments and the larger the total therapeutic dose.

TABLE 9. Weight of Thyroid Gland and Number of Treatment of Patients Cured with I^{131}

Doses→ Gm. ↓	I	II	III	IV	V	VI	VIII	X	Av. No. of Rx.	Av. Total Dose
- 40	205 (6.0)	74 (11.3)	16 (17.4)	2 (32.9)	0	0	0	0	1.38	8.14 mc.
41- 50	145 (7.1)	91 (13.8)	31 (19.5)	7 (25.5)	1 (31.1)	0	0	0	1.65	11.31 mc.
51- 60	99 (8.6)	97 (14.9)	20 (21.3)	6 (30.0)	3 (33.3)	1	0	0	1.76	13.44 mc.
61- 70	37 (9.2)	44 (16.0)	17 (23.4)	2 (27.7)	0	1 (41.5)	0	0	1.88	15.27 mc.
71- 80	34 (10.5)	26 (17.3)	11 (23.7)	6 (30.9)	5 (43.5)	0	1 (52.0)	1 (76.9)	2.20	19.01 mc.
81-100	8 (13.5)	17 (20.7)	9 (25.5)	4 (31.6)	2 (54.5)	1 (41.2)	0	0	2.46	23.54 mc.
101-	5 (14.2)	14 (22.8)	9 (27.7)	6 (41.4)	1 (51.5)	2 (62.7)	0	0	3.49	27.05 mc.
Total	528 (7.5)	363 (14.6)	113 (21.9)	33 (31.7)	12 (42.9)	5 (49.1)	1 (52.0)	1 (76.9)	1.73	12.94 mc.

6. Calculated dose of the first treatment (Table 10). The larger the calculated dose of the first treatment, the more the number and the quantity of therapeutic doses of I^{131} required for cure.

7. The cure rate after each treatment. The cure rate after each treatment in percentage is shown in Table 11, excluding the cases lost for follow-up. With one dose treatment 44.9% of the patients were cured, 79.6% of the patients were cured with one or two doses of I^{131}, 92.0% of the patients were cured with three doses or less, and 8% of the patients required more than three doses.

8. Complications of I^{131} treatment (Table 12). Infrequently, in an extremely toxic person sufficient damage may occur and cause excessive release of thyroglobulin into the blood stream, producing an exacerbation of the thyrotoxicosis and, rarely thyroid storm.

We prescribed antithyroid drugs to patients with severe or moderate thyrotoxicosis, and gave I^{131} without pretreatment to patients whose thyrotoxicosis was mild, so that we only had few cases of minor exacerbation of symptoms after I^{131} treatment. Only one case had severe exacerbation and necessitated hospialization.

TABLE 10. Calculated Dose of the First Treatment and Number of Treatment of Patients Cured wlth I^{131}

Doses→ Mc. ↓	I	II	III	IV	V	VI	VII	X	Av. No. of Rx.	Av. Total Dose
- 5.0	48 (4.4)	31 (10.1)	5 (14.8)	0	0	0	0	0	1.49	7.15 mc.
5.1 - 6.0	73 (5.6)	29 (11.9)	5 (19.3)	0	0	0	0	0	1.38	7.94 mc.
6.1- 7.0	99 (7.3)	43 (13.1)	19 (18.8)	1 (26.9)	0	0	0	0	1.52	9.95 mc.
7.1- 8.0	93 (7.4)	65 (13.4)	17 (20.9)	5 (29.8)	1 (39.9)	0	0	0	1.65	11.60 mc.
8.1- 9.0	51 (7.7)	49 (15.4)	14 (16.2)	4 (29.0)	3 (17.1)	1 (41.5)	0	0	1.87	14.85 mc.
9.1-10.0	54 (8.3)	40 (14.6)	9 (22.6)	4 (49.5)	1 (36.6)	1	0	0	1.72	13.33 mc.
10.1-11.0	23 (8.9)	19 (15.7)	8 (22.6)	0	0	0	0	0	1.70	13.48 mc.
11.1-12.0	31 (9.8)	20 (17.2)	2 (22.0)	4 (31.6)	3 (37.9)	0	0	0	1.80	15.54 mc.
12.1-13.0	13 (9.3)	17 (16.4)	5 (23.6)	1 (24.4)	0	0	0	0	1.83	15.08 mc.
13.1-14.0	10 (10.8)	10 (17.2)	2 (32.0)	4 (31.2)	1 (54.4)	0	0	0	2.11	19.37 mc.
14.1-15.0	16 (12.3)	9 (18.4)	8 (23.2)	1 (26.5)	2 (54.5)	0	0	0	2.00	19.01 mc.
15.1-20.0	11 (11.8)	25 (19.4)	12 (23.4)	4 (32.3)	0	1 (41.2)	1 (52.0)	1 (76.9)	2.47	21.74 mc.
20.1-25.0	3 (12.0)	5 (24.4)	6 (25.4)	5 (41.1)	1 (51.5)	0	0	0	2.80	28.74 mc.
25.1-30.0	2 (14.0)	1 (21.9)	0	0	0	1 (55.4)	0	0	2.50	26.33 mc.
30.1-35.0	0	0	1 (32.0)	0	0	1 (70.0)	0	0	4.50	51.00 mc.
35.1-40.0	1 (13.0)	0	0	0	0	0	0	0	1.00	13.00 mc.
Total	528 (7.5)	363 (14.6)	113 (21.9)	33 (31.7)	12 (42.9)	5 (49.1)	1 (52.0)	1 (76.9)	1.73	12.94 mc.

Seven patients developed pretibial myxedema after improvement of thyrotoxicosis with I^{131} treatment, but this complication could also be induced by other methods of treatment.

At present no case of cancer of the thyroid gland or leukemia has occured

TABLE 11. Cure Rate After Each Treatment

No. of Treatment	I	II	III	IV	V	VI	VII	X
No. treated	1,432	649	214	73	28	11	3	2
Cured	528	363	113	33	12	5	1	1
Lost for follow-up	255	72	28	10	5	3	0	0
Failed	649	214	73	30*	11	3	2	1**
Cure rate	44.9%	62.9%	60.8%	52.4%	52.2%	62.5%	33.3%	50.0%

Cured with one dose 44.9%
Cured with two doses or less 79.6%
Cured with three doses or less.....92.0%
* Two cases were referred for thyroidectomy
** This case was referred for thyroidectomy

among patients treated with I^{131} during this period.

9. Hypothyroidism after I^{131} treatment. Among 1056 cases cured of hyper thyoidism with I^{131} treatment, 83 cases (7.9%) developed hypothyroidism later. The total therapeutic dose of I^{131} which induced hypothyroidism ranged from 3.7 mc. to 60.3 mc., and the average of the total dose was 12.5 mc., which was not significantly different from the total therapeutic dose of all cured cases (Table 13). As shown in Table 14, among 195 male patients cured with I^{131} treatment 20 cases (10.3%) developed hypothyroidism, and among 861 female patients cured with I^{131} treatment 63 cases (7.3%) developed hypothyroidism. There was no difference in the incidence of hypothyroidism between the sexes (P 0.1). As shown in Table 15, there was no difference in the incidence of hypothyroidism between patients of different age groups. As shown in Table 16, the incidence of hypothyroidism after I^{131} treatment was not significantly different in patients medically

TABLE 12. Complications and Toxic Effect of I^{131}

1. Thyroid crisis	0
2. Exacerbation of thyrotoxicosis necessitated hospitalization	1
3. Radiation thyroiditis	0
4. Assravation of exophthalmos	0
5. Pretibial myxedema	7
6. Hypothyroidism	83
7. Thyroid cancer	0
8. Leukemia	0

TABLE 13. Hypothyroidism after I^{131} Treatment

No. of Rx.	I	II	III	IV	V	VI	Total
No. of cases	46/528	29/363	4/113	0/33	3/12	1/5	83/1056
Incidence	8.7%	8.0%	2.5%	0%	25.0%	20.0%	7.9%
Av. Dose	7.4 mc.	14.5 mc.	24.0 mc.		46.8 mc.	41.2 mc.	12.5 mc.

Range of total dose 3.7 mc.-60.3 mc.

pretreated, not pretreated, and previously thyroidectomized (P 0.1). As shown in Table 17, there was no relationship between the incidece of hypothyroidism and the duration of the disease. Table 18 shows the incidence of hypothyroidism to be higher in patients whose goiter weighed less than 40 grams (P 0.05).

10. I^{131} teatment in resistant cases. There were three cases which were resistant to I^{131} treatment, and thyroidectomy was performed after several

TABLE 14. Sex Incidence and Hypotthroidism

Sex	No.	Per cent
Male	20/195	10.3%
Female	63/861	7.3
Total	83/1056	7.9

TABLE 15. Age Distribution and Hypothyroidism

Age	No.	Per cent
-20	0/ 21	0%
21-30	10/212	4.7
31-40	31/394	7.9
41-50	31/289	10.7
51-60	9/210	4.3
61-70	2/ 20	10.0
Total	83/1056	7.9

TABLE 16. Previous Treatment and Hypothyroidism

Treatment	No.	Per cent
Non-treated	30/320	9.4%
Medical Rx.	46/678	6.6
Surgical Rx.	8/ 58	13.8
Total	83/1056	7.9

TABLE 17. Duration of the Disease and Hypotthyroidism

Duration	No.	Per cent
-6 ms.	26/364	7.1%
6 ms.-1 yr.	27/302	8.9
1 yr.-3 yrs.	14/226	6.2
3 yrs.-5 yrs.	8/ 83	9.6
5 yrs.-10 yrs.	7/ 62	11.3
10 yrs.-	1/ 19	5.3
Total	83/1056	7.9

TABLE 18. Weight of Thyroid Gland and Hypothyroidism

Gm.	No.	Per cent
- 40	32/292	11.0%
41- 50	18/275	6.5
51- 60	18/226	8.0
61- 70	3/101	3.0
71- 80	4/ 84	4.8
81-100	5/ 41	12.2
101-	3/ 37	8.1
Total	83/1056	7.9

TABLE 19. Thyroidectomy after unsuccessful treatment with I^{131}

Case	Sex	Age	Duration of the disease	Thyroid weight	No. of treatment	Total dose of I^{131}
1	Male	34	3 yrs.	120 gm.	Ⅳ	42.0 mc.
2	Male	38	4	80	Ⅹ	107.3
3	Female	54	3	120	Ⅳ	60.0

doses of I^{131} had been administered (Table 19). The first case was a male aged 34, whose duration of thyrotoxicosis was 3 years with the goiter estimated to weigh 120 grams. He was treated with I^{131} four times, a total of 42.0 mc., but there was no improvement in thyrotoxic signs and no reduction in the size of goiter, so he was referred for thyroidectomy. The second case was a 38 years old male whose duration of thyrotoxicosis was 4 years and whose goiter was estimated to weigh 80 grams. He received I^{131} treatment ten times, total dose 107.3 mc., and since there was no improvement in thyrotoxicosis or reduction in the size of goiter, thyroidectomy was advised. The third case was a 54 years old female, whose duration of the disease was 3 years, and her goiter was estimated to weigh about 120 grams. She received I^{131} treatment four times, total dose 60.0 mc., without improvement in thyrotoxicosis or reduction in the size of goiter, and thyroidectomy was advised.

DISCUSSION

The introduction of radioactive iodine into clinical therapeutics in 1943[1)2)] revolutionalized the treament of hyperthyroidism, and it is now employed as the primary form of treatment.

During the early period of radioiodine therapy, attempts were made to standardize the radiation deliverd to the thyroid gland by varying the dose of radioiodine according to the size of the gland, the uptake of I^{131}, and its subsequent release[5)~20)]. Although there was a wide range of criteria for selection of the dose of I^{131}, all accomplished similar therapeutic results. Also it has been apparent that such calculations do not provide uniform results, probably due largely to variations in individual sensitivity. Hence most clinics have employed an arbitrary dose of 140 to 160 c. per gram of estimated glandular weight.

The authors employed an arbitrary dose of 100 c. to be retained in each gram of estimated glandular weight. Since the 24 hour I^{131} uptake by hyperthyroid patients is in the neighbourhood of 70%, this dose is equivalent to 140 mc. per gram of estimated gland weight. But when the calculated dose was too much a limited dose of 7 mc. was given, and during some periods of the study this limit was raised to 15 mc. With this regimen, the authors treated 1480 cases of diffuse toxic goiter from March 1958 to December 1966. The one-dose cure rate was 44.9%, and 79.9% of the patiants were cured with one or two doses of I^{131}, and 92.0% of the patients were cured with three doses or less of I^{131}. It can be said that for most patients with hyperthyroidism I^{131} treatment is a beneficcial therapy. The total dose of I^{131} for each case ranged from 2.4 mc. to 76.9 mc. This wide range shows the great difficulty in selecting the appropriate dose for each patient.

One of the disadvantages of I^{131} treatment is the risk of hypothyroidism aftter the treatment. In this study, although the follow-up period was not long enough, the incidence of hypothyroidism was 7.9%. Until the early 1960's, most reports indicated that the incidence of postradioiodine hypothyroidism was approximately 7 to 12 per cent, the majority occurring during the first year or two after treatment. Although an occasional patient developed hypothyroidism later, this was considered an uncommon occurrence. In 1961, however, there appeared several reports that completely altered this view. The incidence of hypothyroidism is not only higher during the first year or two after treatment than thought, but continues to increase at a rate of approximately 2 to 3 per cent per year thereafter[21]. The findings to date provide no evidence that this trend will cease. Thus the incidence of postradioiodine hypothyroidism at the end of 10 years is approximately 30 per cent[22], although values as high as 70 per cent have been reported[3].

Hypothyroidism is innocuous enough in an intelligent and reliable patient who remains under medical supervision and who consistently takes his replacement medication. The treatment program is easily established and is inexpensive. The difficulties arise among patients who through perversity discontinue their replacement medication or in whom myxedema gradually and almost imperceptibly develops. Profound myxedema, especially in the elderly, is a dangerous disorder with a high mortality if complicated by congesive heart failure or infection of the lung or urinary tract[24].

To reduce the incidence of postradioiodine hypothyroidism, the authors suggest two principles: 1) do not use radioiodine treatment on patients with a small goiter and mild thyrotoxicosis. 2) postpone the last treatment with radioiodine as long as possible. As shown in Table 18, the incidence of postradioiodine hypothyroidism was higher in the group of patients with a goiter smaller than 40 grams. After long term (one to two years) treatment with the antithyroid drugs about half the patients have permanent remission[25]. If the goiter of a patient is small, thyrotoxocosisis mild, and administration of desiccated thyroid is combined, the prognosis after long term treatment with the antithyroid drugs is better[26]. Recently Smith and Wilson[27] recommend giving one-half the conventional dose (70 mc. per gram of thyroid gland) followed by a fully effective dose of an antithyroid agent for 2 years.

As shown in Table 13, the incidence of hypothyroidism was also high in patients who received more than 5 doses of I^{131}. This suggests hypothyroidism might be induced by an impetuous last treatment. Therefore, the author believes the second principle of reducing the incidence of postradiodine hypothyroidism is to postpone the last I^{131} administration until the late effect of radioiodine appears, namely, if patients still have mild thyrotoxicosis or a small goiter after administration of one or two doses of radioiodine, these patients should be treated with antithyroid drugs instead of additional doses

of radioiodine.

Another disadvantage of I^{131} treatment is that some patients are refractory to the treatment. Instances of resistance have been noted by Werner *et al.*[28], Seed and Jaffe[29], and Bartels and Corn[30]. In this study as shown in Table 10, 92 per cent of patients with hyperthyroidism could be cured with three doses or less than three doses of I^{131}, but 8 per cent of the patients required more than three doses of I^{131}. Three patients showed complete registance to I^{131} treatment. In the patient who required the multiple doses, it took more than one year to attain an euthyroid state. Although during the treatment period hyperthyroidism could be controlled satisfactorily with an antithyroid drug, such prolongation of the therapeutic period is undesirable. Although Hamwi and Goldberg[31] reported radiodine therapy was a satisfactory means of preparing patients for thyroidectomy, it is unwise to give multiple doses of radioiodine to resistant patients before thyroidectomy. To avoid meaningless prolongation of the therapeutic period in patients with moderate or complete resistance to radioiodine therapy, the author recommends two points: 1) patients with an unusually large goiter should have a thyroidectomy instead of radioiodine therapy. 2) patients who do not show a definite decrease in the size of goiter or definite improvement in symptoms after 3 doses of radioiodine therapy should be referred for thyroidectomy.

In the early days of radioiodine therapy, the main concern was that the irradiation might induce malignant disease, but the evidence to date suggests this hazard is negligible. The irradiation dose to the bone marrow is low, and the subsequent incidence of leukemia is not significantly greter than that in the general population[32]~[34]. Thyroid neoplasma may follow irradiation of the thyroid in infancy and childhood, and cases have been reported after the use of I^{131} for the treatment of thyrotoxicosis in children[35][36]. Two cases of thyroid carcinoma have been reported after I^{131} therapy of thyrotoxicosis in adults, but in both instances the carcinoma was probably present when the radioiodine was administered[27]~[38].

Accentuation of hyperthyroidism by radioiodine has been reported and even deaths during thyroid storm were ascribed directly to exacerbation of the hyperthyroidism[39][40]. The author employed antithyroid treatment prior to administration of I^{131} in patients with moderate or severe thyrotoxocosis, so that no case developed thyroid crisis after I^{131} treatment. Only one case developed exacerbation of thyrotoxicosis and cardiac decompensation after I^{131} treatment and necessitated hospitalization. Werner *et al.*[28] and Crooks *et al.*[40] stated that pretreatment with antithyroid drugs might induce relative radioresistance of the thyroid gland, but as shown in Table 7, there was no influence by the pretreatment to total dose and number of treatment. The majority of patients with thyrotoxicosis are ambulatory and are treated as out-patients. Pretreatment with antithyroid drugs for patients with severe

thyrotoxicosis is advisable to prevent an aggravation of thyrotoxicosis after I^{131} administration. It is also advisable to give antithyroid drugs after I^{131} administration to these patients until the effect of I^{131} becomes evident or until the administration of additional dose of I^{131} for the purpose of preventing cardiac decompensation.

CONCLUSION

One thousand fifty six cases of diffuse toxic goiter cured by I^{131} treatment at our thyroid clinic from March 1958 to December 1966 were analyzed. A single dose cured 45 per cent of the patients, and 92 per cent were cured with three doses or less. Eight per cent of patients were moderately resistant to radioiodine and required more than three doses of I^{131} to attain the euthyroid state. During the period ot study three cases of hyperthyroidism showed complete resistance to radioiodine and were referred for thyroidectomy after administration of several doses of I^{131}.

Incidence of postradiodine hypothyroidism was 7.9 per cent in this study, but we believe it will rise with the passage of time.

To prevent postradioiodine hypothyroidism, further studies are required to determine the optimal dose of I^{131}. At present we propose two principles: 1) long term medical treatment with antithyroid drugs for patients with mild thyrotoxicosis or a small goiter, instead of I^{131} treatment. 2) cautious administration of an additional dose of I^{131} when previous treatment with I^{131} looks inadequate.

To avoid meaningless prolongation of the therapeutic period in cases resistant to radioiodine, do not give I^{131} to patients with unusually large goiters and refer patients for thyroidectomy if the effect of I^{131} is not apparent after 3 doses of I^{131} treatment.

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