Incidence of hypothyroidism after radioiodine treatment of hyperthyroidism:

A report of the radioiodine therapy follow-up study

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甲状腺機能亢進症 ^{131}I 治療後の甲状腺機能低下症

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甲状腺機能亢進症の ^{131}I 治療後の甲状腺機能低下症の発生が日本においては果して欧米に比べて低率であるか否か，又然りとすればその原因は何処にあるかを検討するため，^{131}I の投与量を個

々の患者の甲状腺の ^{131}I 吸収線量を推定して決定投与された症例群について調査分析した．症例は1955—1967年における5施設の合計1119例であるが，それらの ^{131}I の初回投与量の平均は 5.6mCi, 6340rads で，これは別に調査した同期間における日本の大多数症例の平均初回投与量とほぼ等しい．治療成績は1回投与群（625例）と2回以上投与群(494例)，および全例について検討した．機能低下症発生率は life table method によつて計算したが，全例の5，10，12年後の率はそれぞれ 9.4，18，26%で，多くの欧米の報告に比べて低率であつた．年間の増加率は 2.3%づつである．機能低下症発生率は1回投与群の方に反覆投与群より一般にやや高く，又その5年後までの増加率もやや高い．

欧米諸国と日本の ^{131}I 治療症例群の機能低下症発生率を比較検討すると，初回投与における甲状腺吸収線量と初回投与後5年における機能低下症発生率との間に高い相関関係が見出された．即ち欧米の症例群でも初回投与量の少ない症例群では機能低下症の率は低い．日本における機能低下症の低率は初回投与量が平均して少ないことにあると推定される．

1回投与によつて機能低下となつた患者の甲状腺の吸収線量は7220±2810rads で3000rads 未満から 14000rads 以上までに分布している．1回投与で吸収線量6000～8000rads の症例群のみについて検討すると推定甲状腺重量の小さいものに機能低下症発生率が高いことが認められた．

There has been considerable discussions concerning the delayed and rising incidence of hypothyroidism among hyperthyroid patients treated with radioiodine has hitherto been considered lower in Japan than in the Western countries. Miyake and Torizuka[16] reported a rising incidence of hypothyroidism of much lower percentage and less increment, calculated from the collected results of radioiodine treatment at many clinics in Japan.

In connection with the question of whether the incidence of hypothyroidism is really low in Japan and, if this is so, what is its reason, factors possibly related to the development of hypothyroidism, besides radiation dose to thyroid, should be analyzed.

Materials and Methods

A total of 1119 hyperthyroid (Graves' disease) patients who were treated with ^{131}I at five clinics (Table 1 and 2) from 1955 to 1967 were retrospectively investigated. The total number of patients evaluated was about 65% of all patients treated at these clinics in this period. The sex ratio of female to male was 3.9: 1. The principles of dosage used at these clinics were not always uniform, but the dose of ^{131}I to these patients was determined from the estimated radiation absorbed dose delivered to the thyroid by measuring the uptake ratio and effective half life (EHL) of ^{131}I in the thyroid, as well as estimated thyroid weight for each patients. The radiation dose to the thyroid was recalculated from the above mentioned data of each patient by Anno, Sasaki and Takeshita using the formula described by Loevinger et al.[15], i.e. the total average dose to the gland (D) is calculated as follows

$$D \text{ rad} = 150UA\ T_{eff}/G$$

where G is the mass of the thyroid gland (g), A is the administered activity in mCi, U is the uptake in gland as a fraction of A in %, and T_{eff} is the effective half-life of ^{131}I in the gland, in days.

As shown in Table 1, the number of patients examined for this study was about one-seventh of all patients whose treatment records were forwarded to us from 58 institutions, and presumably about one-tenth of the whole patients (about 11,000) treated in Japan for the corresponding period.

Table 1. Average factors in examination and treatment of paat 5 clinicstients

Clinic No.	No. of cases	Weight (g)	Thyroid Uptake (%)	EHL (days)	Absorbed dose of ^{131}I Initial (mCi)	Initial (rad)	Total (mCi)	Total (rad)	No. of doses
1	124	55	69	5.3	8.0	7433	12.6	10576	1.6
2	385	42	67	5.6	5.1	7037	8.3	8741	1.7
3	137	65	63	5.2	6.4	5102	8.4	6792	1.3
4	260	59	66	5.7	5.0	6100	8.4	9069	1.7
5	213	54	66	6.3	4.8	5827	6.3	7150	1.4
	Total								
Average	1119	53	66	5.7	5.6	6340	8.4	8370	1.6
58 clinics	7458*	48	61		5.6		7.5		

* Number of patients whose records of treatment were collected by Anno et al.

Clinic No.

1. Dept. Radiol., Chiba Univ.
2. Ohkubo Municip. Hosp., Tokyo
3. 1st Dept. Intern. Med., Kyoto Univ.
4. 2nd Dept. Intern. Med., Kyoto Univ.
5. Dept. Radiol., Tottori Univ.

Table 2. Number of cases in each age category

Age (yrs.)	58 clinics No. of cases treated	%	5 clinics No. of cases followed up	%
—19	266	3.5	24	2.2
20—29	1204	16.1	268	23.9
30—39	2228	30.0	383	34.2
40—49	2164	29.0	269	24.0
50—59	1379	18.5	145	13.0
60—	217	2.9	30	2.7
Total	7458	100.0	1119	100.0
	Female: male ratio = 4.1: 1			3.9: 1

In order to follow up the results, conditions of these patients were examined at each clinic in the period between January 1969 and December 1969. The diagnosis of hypothyroidism was made on the basis of three criteria: (1) Clinical signs and symptoms, (2) ^{131}I-triiodothyronin resin uptake, and (3) cholesterol level of blood serum. Results of the examination were collected for analysis by Anno, Sasaki, and Takeshita.

Average factors in the treatment of patients at each clinic are shown in Table 1. The initial dose of ^{131}I and radiation dose delivered to the thyroid of patient in the five clinics on the average were 5.6 mCi and 6340 rads.

Data of treatment at the 5 clinics were analyzed as a whole to obtain the general trend of treatment results in Japan. These 1,119 patients evaluated consisted of 625 patients treated with only one dose and 494 with two or more doses. As seen in Table 1, the average values of the thyroid weight, the uptake ratio, and initial dose of ^{131}I to the patients in the present series were similar to those of 7,458 patients treated at 58 institutions in Japan for corresponding period. The age distribution of the treated patients in both groups were similar (Table 2). Therefore, the results obtained in this study may be regarded roughly to represent the average trend of radioiodine treatment of hyperthyroidism in Japan.

Incidence of hypothyroidism was calculated by dividing the number of hypothyroid patients by the total number of patients evaluated for each year of the treatment. In addition, the annual cumulative incidence of hypothyroidism after the initial dose was calculated by the life table method, estimating the time of onset of hypothyroidism according to the records of patients. The patients whose thyroidal function was not recorded yearly in the chart, were regarded as euthyroid until they were recorded as hypothyroid. In 1972, patients of this series, except in one clinic, were again evaluated by the same method.

Results

As shown in Table 3 and 4-a, b, results of the treatment evaluated in 1969 were calculated, separately for one dose, repeat dose group, and the total number. There were no significant differences in percentage

Table 3. Results of treatment and average factors in dosage

	No. of		Weight	Thyroid Uptake	EHL	Initial dose		Total dose	
Results	cases	%	(g)	(%)	(days)	mCi	rads	mCi	rads
Euthyroid	899	80.3	51	67	5.7	5.6	6360±2430[a)]	8.3	8450±2510[a')]
Still hyperthyroid	65	5.8	68	64	6.0	6.5	5510±2230[b)]	9.6	6850±2570[b')]
Hypothyroid	126	11.3	48	63	5.5	5.4	6620±2870[c)]	8.0	8810±3580[c')]
Deceased	29	2.6	74	62	5.8	5.9	5970±3500	10.8	6890±3140
Total	1119	100.0	53	66	5.7	5.6	6340±2450	8.4	8370±2930
						a)−b)	$p<0.05$	a')−b')	$p<0.05$
						a)−c)	$p<0.30$	a')−c')	$p<0.25$

Table 4. Results of treatment and average factors in dosage

a) One-dose group

Results	No. of cases	%	Weight (g)	Uptake (%)	EHL (days)	Dose mCi	Dose rads
Euthyroid	506	81.0	51	57	5.9	5.8	6640±2470[a)]
Still hyperthyroid	38	6.1	59	60	6.5	6.5	6090±2230[b)]
Hypothyroid	68	10.9	47	66	5.8	5.6	7220±2810[c)]
Deceased	13	2.0	71	68	5.8	6.1	6880±1650
Total	625	100.0	52	67	5.9	5.8	6690±2510
						a)−b)	$p>0.20$
						a)−c)	$0.15<p<0.10$

b) Repeat-dose group

Results	No. of cases	%	Weight (g)	Uptake (%)	EHL (days)	Initial dose mCi	Initial dose rads	Total dose mCi	Total dose rads
Euthyroid	393	79.6	52	67	5.4	4.5	5840±2090	12.2	10220±3140[a)]
Still hyperthyroid	27	5.5	81	69	5.3	6.7	4650±2610	17.1	7950±2470[b)]
Hypothyroid	58	11.7	50	59	5.1	5.4	5260±3160	11.1	12410±5810[c)]
Deceased	16	3.2	79	57	5.8	5.7	3480±1680	19.7	6530±2680
Total	494	100.0	54	65	5.4	5.4	5660±2150	12.8	10250±3270
								a)−b)	$p<0.05$
								a)−c)	$p<0.05$

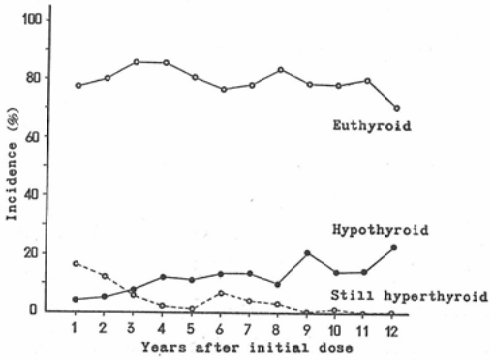


Fig. 1 Results of treatment
(a) All cases

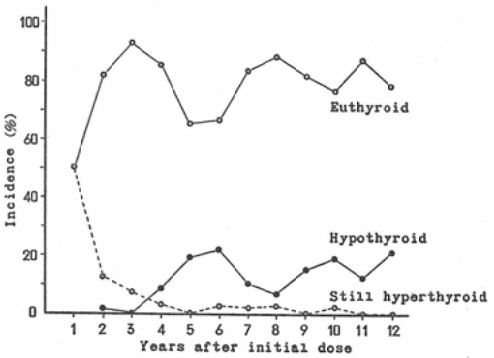


Fig. 1(b) Repeat-dose group

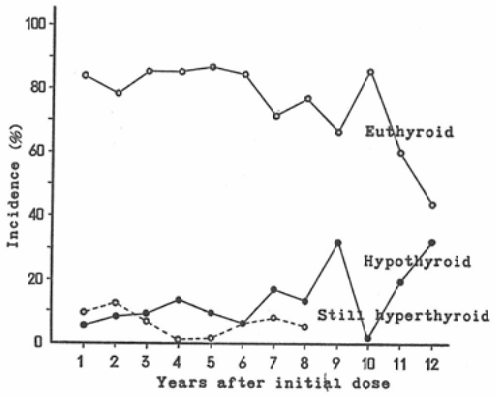


Fig. 1(c) One-dose group

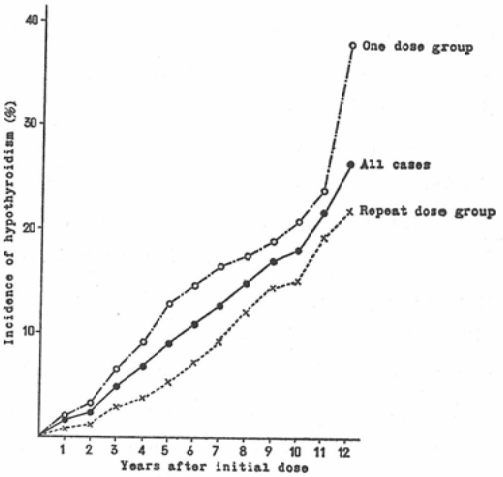
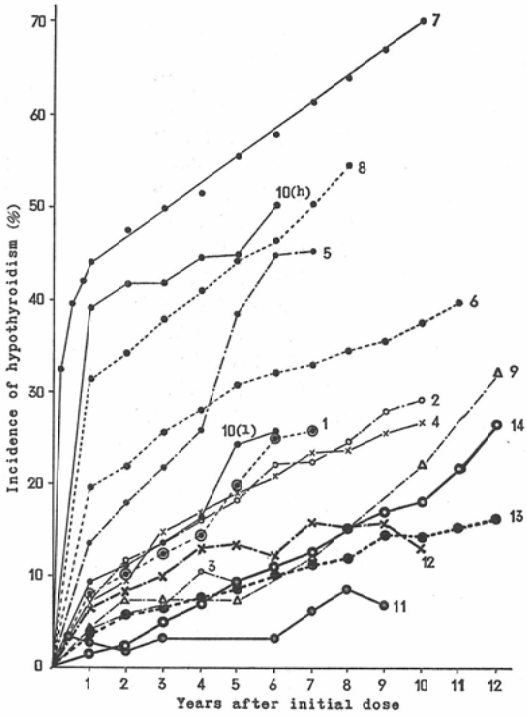


Fig. 2 Hypothyroidism after ^{131}I treatment (Life table method)



Numbers represent those in the first column of Table 5

Fig. 3 Incidence of hypothyroidism after ^{131}I treatment

distribution of the patients hypothyroid, euthyroid, and still hyperthyroid among these groups. Average radiation dose delivered to the thyroid of the patients, who became hypothyroid was the largest and amounted to 12410 ± 5810 rads in the repeat-dose group, about 1.7 times larger than that in the one-dose group (7220 ± 2810 rads).

Results of treatment of patients for each year are graphically shown in percentage in Fig. 1-a,-b,-c. Percentage of hypothyroid patients increased with the years elapsed after treatment and it was 4.3, 7.1, 11.9, 14.5 and 23.9%, respectively, for 1, 3, 5, 10, 12 years after initial treatment. On the other hand 50% of patients in the repeat-dose group were still hyperthyroid 1 year after the initial dose and 10% of those in the one-dose group were so. About 5% of the treated patients were still hyperthyroid 6 or 7 years after the initial treatment. The incidence of hypothyroidism calculated by the life table method is graphically shown in Fig. 2. The incidence of hypothyroidism thus calculated in the total cases was 12, 18 and 26%, 5, 10 and 12 years after the treatment and accordingly increased at an average rate of 2.3% per year. Percentages of hypothyroidism 1–3 years after treatment calculated by the life table method were less trustworthy, because thyroidal function of not a few of the patients were not recorded for 1–3

Table 5. Hypothyroidism and dose of ^{131}I

	Author	Initial dose	Total dose
1)	Beling, Einhorn[2] (1961), Sweden	6000–10000 reps	
2)	Green, Wilson[11] (1964), England	7000 rads 5.0±2.0 mCi	
3)	Smith, Wilson[21] (1967), England	3500 rads 2.8±1.6 mCi	
4)	Tubiana et al.[22] (1966), France	8000–10000 rads	
5)	Cassidy[5] (1964), U.S.A.	6.7 mCi	11.9 mCi
6)	Dunn, Chapman[7] (1964), U.S.A.	10800 rads* 7.4±2.4 mCi	
7)	Nofal et al.[17] (1966), U.S.A.	16700 rads 10–11 mCi	10–20 mCi
8)	Burke, Silverstein[4] (1969), U.S.A.	Eu. 6.7±3.7 mCi Hypo. 6.5±2.3 mCi	8.9±7.2 mCi
9)	Glennon et al.[9] (1972), U.S.A.	2.7 mCi	
10-h)	Cevallos et al.[6]	(high dose) 9986 rads (7.4 mCi)	
10-l)	(1974), U.S.A.	(low dose) 5578 rads (3.6 mCi)	
11)	Miyake, Torizuka[16] (1966), Japan		7.6–8.8 mCi
12)	Saito et al.[19] (1971), Japan	7200 rads* 7.5 mCi	
13)	Hara, Kitabatake[13] (1973), Japan	110–115 μCi/g 6315 rads*	
14)	Present series[20] (1972), Japan	6340±2450 rads 5.6±2.7 mCi	8370±2930 rads 8.4±4.0 mCi

* Estimated by Anno

years after treatment their charts and regarded as euthyroid until they were recorded as hypothyroid. The cumulative incidence of hypothyroidism was separately calculated in the one-dose group and repeat-dose group as shown in Fig. 2. The incidence of hypothyroidism in one-dose group was 12 and 22%, 5 and 10 years after the treatment. The rate of hypothyroidism was generally a little higher and the increment to the end of 5th year was steeper in the one-dose group than in the repeat-dose group. Percentage incidence and increment of hypothyroidism among the patients of this series, except in one clinic evaluated in 1972, were similar to those made in 1969.

Comparison of incidence of hypothyroidism among the data from Western countries and Japan

Rising incidence of hypothyroidism reported by several authors regarding years after the treatment is illustrated in Fig. 3. Curve 14 in Fig. 3 shows the incidence in the present series. It is noteworthy that both the incidence of hypothyroidism and the average radiation dose delivered to the thyroid were all low in the present series and two other series from Japan (Table 5).

Fig. 4 shows a fairly good correlation between the incidence of hypothyroidism 5 years after the initial treatment and the average initial dose in rads delivered to the thyroid of the several series from the Western countries and Japan, although both in the lower- and higher-dosage groups reported by Cevallos et al.[6] showed exceptionally high incidence of hypothyroidism in relation to radiation dose. This suggests low incidence of hypothyroidism in Japan mainly due to the lower initial radiation dose delivered to the thyroid.

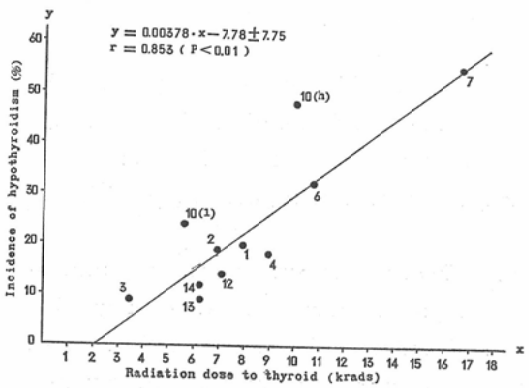


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Fig. 4 Correlation of percentage in incidence of hypothyroidism (5 years after treatment) and radiation dose to thyroid (initial dose)

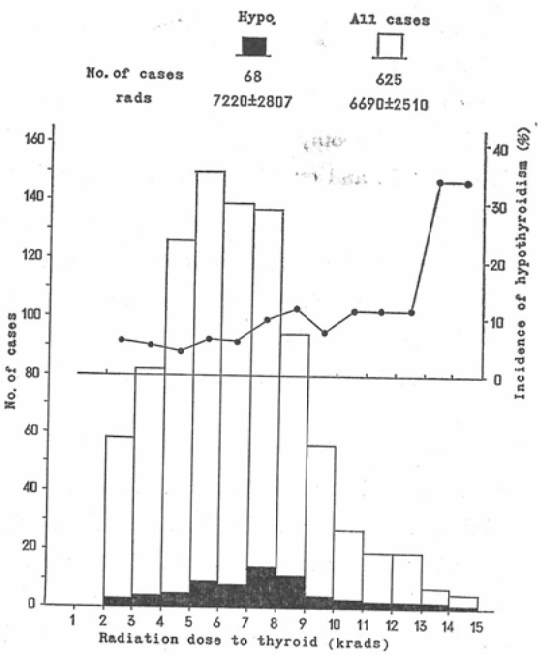

Fig. 5 Incidence of hypothyroidism (One-dose group)

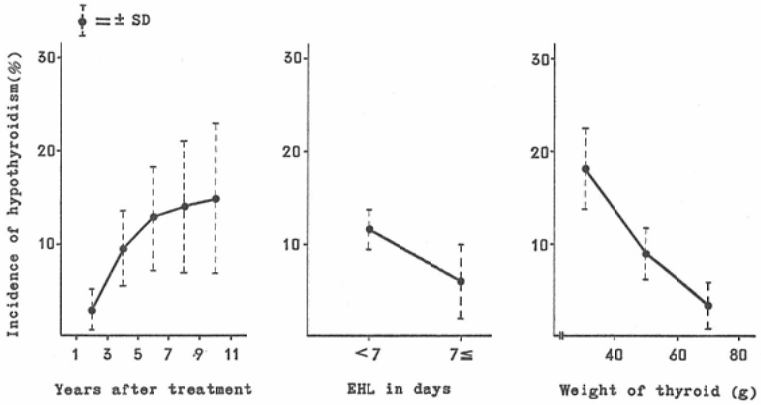

Fig. 6 Factors influencing the incidence of hypothyroidism (207 cases treated with single dose of ^{131}I between 6000 and 8000 rads)

Analysis of Hypothyroid Patients

Of 126 patients who became hypothyroid, 68 (54%) received a single dose, 30% of them were treated with two doses, and 16% were with three or more doses.

The radiation dose to the thyroid of the patients who became hypothyroid after one dose was 7220 ± 2810 rads and distributed in a wide range of less than 3000 rads to more than 14000 rads as shown in Fig. 5, and that in about 30% of them was less than 6000 rads. Radiation doses in hypothyroid cases treated with two or more doses revealed similarly wide variation as in the one-dose group. Therefore, some factors seem possible for the development of post-treatment hypothyroidism, besides radiation dose to the thyroid.

As shown in Fig. 6, despite similar radiation dose to the thyroid in a range of 6000 to 8000 rads, incidence of hypothyroidism was higher in the patients with longer time elapsed after treatment, with shorter EHL, and especially with less thyroid enlargement.

Discussion

Rising incidence of hypothyroidism with the passage of time after ^{131}I has been recognized in the present series, which might be regarded as a representative of cases treated with ^{131}I of the dose usually used in Japan. Fairly good correlation was found to exist between the incidence of hypothyroidism 5 years after the initial dose and radiation dose to the thyroid among several series from Japan and the Western countries.

Becker et al.[1] obtained in the Cooperative Thyrotoxicosis Therapy Follow-up Study from 26 medical centers (including one in England) a similar result to that in the present study; the incidence of hypothyroidism in patients treated with a single dose of ^{131}I was at a rate directly related to the dose of ^{131}I delivered to the thyroid gland expressed in the retained radioactivity in μCi of ^{131}I/g of thyroid. These suggest that relatively low incidence of hypothyroidism after radioiodine treatment in Japan be mainly due to the lower initial dose of ^{131}I to the thyroid gland.

According to Becker et al.[1] the probability of becoming hypothyroid by five years after the treatment was 0.22 for patients receiving below 50 μCi/g to the thyroid, which appears to deliver about 4500

rads to the gland according to our estimation, assuming 6 days for the effective half life of ^{131}I in the thyroid. Cevallos et al.[6] reported that the incidence of hypothyroidism at six years was 24% in the low-dose group (3.6 mCi, 5578 rads) and 48% in the high-dose group. Blahd and Hays[8] found a similar incidence of hypothyroidism to that in the above-mentioned series in males treated with an individually calculated dose of ^{131}I (initial dose was 5.56 $\pm$ 2.96 mCi, 5000–6000 rads). Radiation dose delivered to the thyroid in the half-dose series of Smith and Wilson[21] with a comparable incidence of hypothyroidism to the present series was 3500 rads, and it should be noted that the average thyroid weight in the former series was definitely smaller (38 g) than that in the latter.

Why is the incidence of hypothyroidism in relation to radiation dose to the thyroid higher in the above-mentioned series than in the series from Japan? This may be partially due to the difference in criteria of hypothyroidism among the authors of these reports and difficulty of the exact estimation of radiation dose to the thyroid. Though radiation dose to the thyroid is, of course, the most important factor in the development of hypothyroidism after radioiodine treatment, several factors seem to be related to the development of hypothyroidism. Radiation doses to the thyroid of patients, who developed hypothyroidism in our series are distributed in a wide range of less than 3000 rads to more than 14000 rads. A similar wide distribution is seen in the data by Jackson[14].

As factors possibly related to the development of hypothyroidism in addition to radiation dose, size of the thyroid, nodule in the gland, prior treatment, autoimmune process[8], age, sex of the patient, and so on, should be taken into consideration. In the present study it was recognized that the incidence of hypothyroidism was evidently higher in the patients with less thyroid enlargement, despite similar radiation dose per unit gram of the thyroid of patients in the one-dose group.

In relation to the discrepancy of incidence of hypothyroidism between series from Japan and Western countries, the influence of race seems to be of interest. According to Becker et al.[1], the incidence of hypothyroidism in the white (both male and female) is very significantly higher than in non-whites. Blahd and Hays[8] reported that most Negro patients required multiple doses, whereas other racial groups needed fewer retreatment and suggested the value of tailoring the initial thyroid radiation dose to severity of the patient's disease, as well as to his sex and race.

To reduce the incidence of hypothyroidism after radioiodine treatment, the initial thyroid radiation dose should be lowered. Even with a dose of 3500 rads used in the series of Smith and Wilson[21] or lower doses by several groups in U.S.A., several percent of the treated patients became hypothyroid and scores of percent of them remained still hyperthyroid 1 year after the treatment. Therefore, the dosage of ^{131}I should be individualized so as to deliver greater radiation dose for larger thyroids and smaller for less thyroid enlargement, and supplemented with thiouracil derivatives or potassium iodide as needed.

Summary

To investigate whether the incidence of hypothyroidism after ^{131}I treatment of patients with hyperthyroidism is lower in Japan than in the Western countries, the results of treatment were retrospectively analyzed for patients to whom ^{131}I had been administered, individually estimating radiation dose to the thyroid. A total of 1119 patients treated at five clinics from 1955 to 1967 were evaluated in 1969. The average initial dose of ^{131}I in the present series was 5.6 m Ci and 6340 rads to the thyroid, and this was

an average dose used in Japan for the corresponding period.

The results of treatment were analyzed by the one-dose group (625 cases) and the repeat-dose group (494 cases), as well as for total cases. The incidence of hypothyroidism was calculated by the life table method and, of the total cases, the incidence was 9.4, 18, and 26%, 5, 10, and 12 years after the initial treatment. The rate of hypothyroidism was generally a little higher and the increment by the end of 5 years was steeper in the one-dose group than in the repeat-dose group.

In reviewing the results from the Western countries and Japan including the present series, fairly good correlation was found between radiation dose to the thyroid in the initial dose and the incidence of hypothyroidism 5 years after the initial dose. The lower incidence of hypothyroidism in Japan appeared mainly due to lower radiation dose to the thyroid in the initial treatment.

Radiation doses to the thyroid glands of patients who became hypothyroid in the one-dose group were 7220 $\pm$ 2810 rads and distributed from less than 3000 rads to more than 14000 rads.

Of the patients in the one-dose group, whose thyroid received a definite dose ranging from 6000 to 8000 rads, those with less thyroid enlargement were more apt to develop hypothyroidism.

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