Nagoya J. med. Sci. 34: 267-281, 1972

# $I^{131}$ TREATMENT OF HYPERTHYROIDISM

## ANALYSIS OF 369 CASES TREATED WITH AN INITIAL DOSE OF 15 MC OR LESS

HSUEH-FANG YANG

*Department of Internal Medicine, National Taiwan University Hospital*

### INTRODUCTION

Patients with hyperthyroidism can be treated by one of the following methods: (1) medical treatment with thiocarbamide, (2) surgical treatment with subtotal thyroidectomy, and (3) radiological treatment with radioactive iodine ($I^{131}$). Although each has certain advantages and disadvantages, radio-iodine has apparently been used much more frequently in recent years because of its simplicity, safety and economy.

The most important and difficult problem in $I^{131}$ treatment for hyperthyroidism is to determine the appropriate dose for each individual patient. Since the response of a patient to a selected dose varies widely, and a quantity which may restore normal thyroid function in one patient may prove entirely ineffective in another, or may even induce lasting myxedema in a seemingly comparable case.

The author started to use $I^{131}$ for the treatment of hyperthyroidism a tthe National Taiwan University Hospital since 1958. As a rule, the dose for administration was calculated based on the weight of the gland and 24 hour thyroidal $I^{131}$ uptake. The therapeutic dose was aimed to let 100 uc of $I^{131}$ to be retained in each gram of the gland. But when the calculated dose was too great, a limited dose was given.

During the period from September 1959 to December 1961, the level of this limitation was arbitrarily settled at 7 mc, and 348 cases were treated with an initial dose of 7 mc or less. The result after one dose administration was reported in this journal in 1964[1]. The one-dose cure rate was as follows: 1) 56.5% in the group of patients to whom calculated doses below 7 mc were given. 2) 34.6% in the group of patients to whom the limited dose of 7 mc was given although their calculated dose was larger. 3) 40.8% in overall patients.

This overall one-dose cure rate of 40.8% was considered too low, so that

楊 雪 舫

Received for publication January 1, 1972.

the limit of the initial dose was elevated Department of Internal Medicine, National Taiwan University Hospital to obtain a better one-dose cure rate.

During the period from January 1964 to December 1965, the limit of the initial dose was raised to 15 mc. When the calculated dose was below 15 mc. the individually calculated dose was given, but when the calculated dose exceeded 15 mc the limited dose of 15 mc was given as the initial dose. During this period 369 cases of diffuse, never operated, toxic goiter were treated.

The purpose of this communication is to report and discuss the result of 369 cases treated with an initial dose of 15 mc or less, and to compare with that of the previous report on 348 cases treated with an initial dose of 7 mc or less.

## MATERIALS AND METHODS

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 bases of the clinical findings, basal metabolic rate, and radioiodine studies such as 2 hour and 24 hour thyroidal $I^{131}$ uptake and 48 hour serum radioactivity.

Actually 421 cases of hyperthyroidism were treated with $I^{131}$ during this period, but 38 cases could not be followed-up, while 5 cases of toxic nodular goiter and 9 cases of post-operative recurrence were excluded from this study.

Sex incidence is shown in Table 1. There were 72 male patients and 297 female patients. The ratio of male to female was 1 : 4.

The age distribution shown in Table 2 ranged from 18 to 65 years of age. The greater majority of patients (83.7%) were between 21 and 50. Patients under 20 were only 12 cases (3.3%). In principle the author did not treat patients under 20 years of age with radioiodine unless they had severe exophthalmos or could not get

TABLE 1. Sex Incidence of All Patients Treated with $I^{131}$

| Sex | No. | % |
|---|---|---|
| Male | 72 | 19.5 |
| Female | 297 | 80.5 |
| Total | 369 | 100.0 |

TABLE 2. Age Distribution of All Patients Treated with $I^{131}$

| Age | No. | % |
|---|---|---|
| -20 | 12 | 3.3 |
| 21-30 | 86 | 23.3 |
| 31-40 | 131 | 35.5 |
| 41-50 | 92 | 24.9 |
| 51-60 | 41 | 11.1 |
| 61-70 | 7 | 1.9 |
| Total | 369 | 100.0 |

TABLE 3. Pretreatment with Antithyroid of All Patients Treated with $I^{131}$

| Pretreatment | No. | % |
|---|---|---|
| Pretreated | 290 | 78.6 |
| Not pretreated | 79 | 21.4 |
| Total | 369 | 100.0 |

permanent cure with medical treatment of more than one year.

As shown in Table 3, 290 cases (78.6%) had been previously treated with antithyroid drug for some extent, and 79 cases (21.4%) had never received any therapy. To avoid aggravation of thyrotoxicosis or thyroid crisis, $I^{131}$ was not given immediately to the patients unless their thyrotoxic symptoms were mild. Patients with severe or moderate thyrotoxicosis were treated with antithyroid drug first, and radioiodine was instituted after euthyroid state was obtained.

As mentioned above, at first the expected dose which would remain in each gram of thyroid gland was settled as 100 uc., and according to their thyroid weight which was estimated by palpation, and 24 hour thyroidal $I^{131}$ uptake, the dose was calculated by the following formula for each case:

Calculated dose = 100 uc. × Thyroid

$$\text{Weight (Gm)} \times \frac{100}{\text{24 hr Uptake (\%)}}$$

When the calculated dose was below 15 mc, the calculated dose was given as the initial therapeutic dose, but when the calculated dose exceeded 15 mc the limited dose of 15 mc was given as the initial dose.

Thus, to 322 cases (87.3%) of the total of 369 cases the individually calculated dose below 15 mc was given as the initial dose, and to 47 cases (12.7%) the limited dose of 15 mc was given.

Response to therapy was judged by the regression of clinical symptoms and signs, and complete or almost complete disappearance of goiter three months after the initial treatment. If the patient still remained in hyperthyroid state, the second dose was scheduled according to the same regimen used in the initial treatment.

In this communication only the result after the initial treatment is discussed.

## RESULTS

### *A. Results of 322 Cases Treated with Calculated Dose Below 15 mc*

Among 322 cases treated with the individually calculated dose below 15 mc, 127 cases were cured with one dose, and 195 cases were judged incomplete three months after the administration of the initial dose. So that the one-dose cure rate in this group was 39.6%.

This one-dose cure rate was much lower than the one-dose cure rate of 56.6% in the group treated with the calcurated dose below 7 mc which was reported in the previous communication. This point wil be discussed later.

Relationships of sex, age, previous treatment, duration of the disease, weight of goiter, thyroidal $I^{131}$ uptake, and quantity of given dose to the result after one dose administration are shown in Tables 4 to 10.

1. Sex (Table 4). Among 61 male patients 25 cases (41.0%) were cured with one dose and among 261 female patients 102 cases (38.9%) were cured with one dose. There was no difference between both sexes concerning the prognosis after one-dose treatment.

TABLE 4. Sex Incidence and Cure Rate of Patients Treated with Calculated Dose Bolow 15 mc

| Sex | No. | Cured | Incomp.ete |
|---|---|---|---|
| Male | 61 | 25 (41.0%) | 36 (59.0%) |
| Female | 261 | 102 (38.9%) | 159 (61.1%) |
| Total | 322 | 127 (39.6%) | 195 (60.4%) |

2. Age. As shown in Table 5, there was no difference in the one-dose cure rate among patients aged 21 to 50 years, but it was lower in the group of patients aged below 20 and over 50. The one-dose cure rate of paitients aged 21 to 50 years was 42.6%, and that of patients aged below 20 and over 50 was 23.1% ($P$ 0.02).

TABLE 5. Age Distribution and Cure Rate of Patients Treated with Calculated Dose below 15 mc

| Age | No. | Cured | Incomplete |
|---|---|---|---|
| -20 | 9 | 2 (22.2%) | 7 (77.8%) |
| 21-30 | 72 | 28 (38.9%) | 44 (61.1%) |
| 31-40 | 115 | 47 (40.9%) | 68 (59.1%) |
| 41-50 | 83 | 40 (48.1%) | 43 (51.9%) |
| 51-60 | 36 | 9 (25.0%) | 27 (75.1%) |
| 61-70 | 7 | 1 (14.3%) | 6 (85.7%) |
| Total | 322 | 127 (39.6%) | 195 (60.4%) |

3. Previous treatment (Table 6). Among 247 patients previously treated with antithyroid drug 88 cases (35.6%) were cured with one dose and among previously non-treated 75 patients 39 cases (52.0%) were cured with one dose.

TABLE 6. Pretreatment with Antithyroid and Cure Rate of Patients Treated with Calculated Dose below 15 mc

| Pretreatment | No. | Cured | Incomplete |
|---|---|---|---|
| Pretreated | 247 | 88 (35.6%) | 159 (64.4%) |
| Not treated | 75 | 39 (52.0%) | 36 (48.0%) |
| Total | 322 | 127 (39.6%) | 195 (60.4%) |

The one-dose cure rate was significantly lower in the group of patients previously treated with antithyroid drug ($P$ 0.01).

4. Duration of the disease (Table 7). When the duration of the disease was shorter than one year the one-dose cure rate was more than 40%, but when the duration of the disease was longer than three years the one-dose cure rate was not so good. But among 8 patients whose duration of the disease was more than 10 years 4 cases (50%) were cured with one dose. This might mean that although the duration of the disease was quite long but the goiter was mild the prognosis after one dose treatment was not so bad.

TABLE 7. Duration of the Disease and Cure Rate of Patients Treated with Calculated Dose below 15 mc

| Duration | No. | Cured | Incomplete |
|---|---|---|---|
| -6 m. | 110 | 45 (41.0%) | 65 (59.0%) |
| 6 m.-1 r. | 110 | 47 (42.7%) | 63 (57.3%) |
| 1 yr.-3 yr. | 60 | 23 (38.3%) | 37 (61.7%) |
| 3 yr.-5 yr. | 21 | 4 (19.0%) | 17 (81.0%) |
| 5 yr.-10 yr. | 13 | 4 (30.8%) | 9 (69.2%) |
| 10 yr.- | 8 | 4 (50.0%) | 4 (50.0%) |
| Total | 322 | 127 (39.6%) | 195 (60.4%) |

5. Weight of thyroid gland. Although the calculated dose, according to the weight of their thyroid gland, was given to all cases, the prognosis after one dose treatment differed according to their thyroid weight. The one-dose cure rate of patients with goiter less than 50 grams was more than 50%, but as the weight of goiter increased the one-dose cure rate decreased steadily, as shown in Table 8.

TABLE 8. Weight of Thyroid Gland and Cure Rate of Patients Treated with Calculated Dose below 15 mc

| Grams | No. | Cured | Incomplete |
|---|---|---|---|
| 31-40 | 29 | 18 (58.1%) | 11 (41.9%) |
| 41-50 | 76 | 40 (52.6%) | 36 (47.4%) |
| 51-60 | 97 | 43 (44.3%) | 54 (55.7%) |
| 61-70 | 51 | 12 (23.5%) | 39 (76.5%) |
| 71-80 | 47 | 14 (29.8%) | 33 (70.2%) |
| 81-90 | 5 | 0 (0%) | 5 (100%) |
| 91-100 | 17 | 0 (0%) | 17 (100%) |
| Total | 322 | 127 (39.6%) | 195 (60.4%) |

6. Thyroid $I^{131}$ uptake. As shown in Table 9, there was no relationship between thyroid $I^{131}$ uptake and the one-dose cure rate.

TABLE 9. Thyroid $I^{131}$ Uptake and Cure Rate of Patients Treated with Calculated Dose below 15 mc

| Uptake (%) | No. | Cured | Incomplete |
|---|---|---|---|
| 41–50 | 15 | 6 (40.0%) | 9 (60.0%) |
| 51–60 | 37 | 20 (54.1%) | 17 (45.9%) |
| 61–70 | 87 | 35 (40.2%) | 52 (59.8%) |
| 71–80 | 121 | 43 (35.5%) | 78 (64.5%) |
| 81–90 | 50 | 17 (34.0%) | 33 (66.0%) |
| 91–100 | 12 | 6 (50.0%) | 6 (50.0%) |
| Total | 322 | 127 (39.6%) | 195 (60.4%) |

7. Given dose. Although the calculated dose, according to their thyroid weight and thyroid $I^{131}$ uptake, was given to all cases, the larger the given dose the lower was the cure rate. When the given dose was below 7 mc the cure rate was between 50% and 60%, but as the given dose increased the cure rate decreased steadily as shown in Table 10.

TABLE 10. Given Dose and Cure Rate of Patients Treated with Calculated Dose below 15 mc

| Given Dose (mc) | No. | Cured | Incomplete |
|---|---|---|---|
| 4.1– 5.0 | 10 | 6 (60.0%) | 4 (40.0%) |
| 5.1– 6.0 | 23 | 14 (60.9%) | 9 (39.1%) |
| 6.1– 7.0 | 46 | 24 (52.2%) | 22 (47.8%) |
| 7.1– 8.0 | 53 | 24 (45.3%) | 29 (54.6%) |
| 8.1– 9.0 | 54 | 20 (37.0%) | 34 (63.0%) |
| 9.1–10.0 | 40 | 14 (35.0%) | 26 (65.0%) |
| 10.1–11.0 | 24 | 8 (33.3%) | 16 (66.7%) |
| 11.1–12.0 | 33 | 10 (30.3%) | 23 (69.7%) |
| 12.1–13.0 | 12 | 3 (25.0%) | 9 (75.0%) |
| 13.1–14.0 | 12 | 3 (25.0%) | 9 (75.0%) |
| 14.1–15.0 | 15 | 1 ( 6.7%) | 14 (93.3%) |
| Total | 322 | 127 (39.6%) | 195 (60.4%) |

8. Comment. In this group 100 uc. of retained $I^{131}$ dose per gram of thyroid weight was given to each patient. Among 322 cases, 127 cases were cured with one dose and 195 cases needed an additional dose after three months' follow-up so that the one-dose cure rate was 39.6% in this group. This one-

dose cure rate of 39.6% was much lower than the 56.5% in the group of patients treated with calculated dose below 7 mc which was reported in the previous study.

However, among 79 patients treated with the calculated dose below 7 mc in the present series, 44 cases (55.7%) were cured with one dose. Thus the one-dose cure rate for the group of patients treated with an initial dose below 7 mc was quite consistent in both series. But, when the calculated dose became greater than 7 mc, even though the same method of calculation using thyroid weight and thyroid uptake was adopted, the cure rate became lower.

On the other hand, the smaller the size of goiter, the better was the one-dose cure rate, as shown in Table 8. But the smaller the size of goiter, the calculated dose, namely the given dose, was smaller so that discussion concerning this point would belong to the above mentioned category of discussion concerning the dose administered.

As shown in Table 6, the one-dose cure rate of patients pretreated with antithyroid drug was signicantly lower than that of non-pretreated patients. But, in the present series, only patients with mild thyrotoxicosis were treated with $I^{131}$ without antithyroid pretreatment so that it could not be simply concluded that pretreatment with antithyroid had some influence on the prognosis of $I^{131}$ treatment.

*B. Results of 47 Cases Treated with the Fixed Dose of 15 mc*

Among 369 cases of non-operated diffuse toxic goiter, there were only 47 cases (12.7%) whose calculated dose was greater than 15 mc, and the fixed dose of 15 mc was given as the initial dose.

Among 47 cases thus treated, only 8 cases (17.0%) were cured with one dose, and 39 cases needed a second treatment after three months' follow-up.

Relationships of sex, age, previous treatment, duration of the disease, weight of goiter, thyroidal $I^{131}$ uptake, and the quantity of given dose to the results after administration of one dose are shown in Tables 11 to 17.

1. Sex (Table 11). Among 11 male patients one case (9.0%) was cured with one dose and among 36 female patients 7 cases (19.4%) were cured with one dose. But there was no difference statistically ($P$ 0.1).

TABLE 11. Sex Incidence and Cure Rate of Patients Treated with the Fixed Dose of 15 mc

| Sex | No. | Cured | Incomplete |
|---|---|---|---|
| Male | 11 | 1 ( 9.0%) | 10 (91.0%) |
| Female | 36 | 7 (19.4%) | 29 (80.6%) |
| Total | 47 | 8 (17.0%) | 39 (83.0%) |

2. Age (Table 12). Because the number of cases belonging to each group was so small, difference in relationship between age and the one-dose cure rate could not be determined.

TABLE 12. Age Distribution and Cure Rate of Patients Treated with the Fixed Dose of 15 mc

| Age | No. | Cured | Incomplete |
|---|---|---|---|
| -20 | 3 | 0 (0%) | 3 (100%) |
| 21-30 | 14 | 4 (28.6%) | 10 (71.4%) |
| 31-40 | 16 | 3 (18.8%) | 13 (81.2%) |
| 41-50 | 9 | 0 (0%) | 9 (100%) |
| 51-60 | 5 | 1 (20.0%) | 4 (80.0%) |
| Total | 47 | 8 (17.0%) | 39 (83.0%) |

3. Previous treatment (Table 13). The one-dose cure rate of patients pretreated with antithyroid (16.3%) was lower than that of non-pretreated patients (25.0%). But, because the number of cases was too small this difference had little significance statistically.

TABLE 13. Pretreatment with Antithyroid and Cure Rate of Patients Treated with the Fixed Dose of 15 mc

| Pretreatment | No. | Cured | Incomplete |
|---|---|---|---|
| Pretreated | 43 | 7 (16.3%) | 36 (83.7%) |
| Not treated | 4 | 1 (25.0%) | 3 (75.0%) |
| Total | 47 | 8 (17.0%) | 39 (83.0%) |

4. Duration of the disease. As shown in Table 14, there was no case of one-dose cure among patients whose duration of the disease exceeded three

TABLE 14. Duration of the Disease and Cure Rate of Patients Treated with the Fixed Dose of 15 mc

| Duration | No. | Cured | Incomplete |
|---|---|---|---|
| -6 m. | 14 | 3 (21.4%) | 11 (78.6%) |
| 6 m.-1 yr. | 8 | 3 (37.5%) | 5 (62.5%) |
| 1 yr.-3 yr. | 17 | 2 (11.8%) | 15 (88.2%) |
| 3 yr.-5 yr. | 5 | 0 (0%) | 5 (100%) |
| 5 yr.-10 yr. | 3 | 0 (0%) | 3 (100%) |
| Total | 47 | 8 (17.0%) | 36 (83.0%) |

years. It can be said that large goiter with long duration might be more resistant to $I^{131}$ treatment.

5. Weight of thyroid gland. As shown in Table 15, among 47 patients 32 cases (68.1%) had goiter weighing more than 100 grams, and the one-dose cure rate in them was quite low.

TABLE 15. Weight of Thyroid Gland and Cure Rate of Patients Treated with the Fixed Dose of 15 mc

| Grams | No. | Cured | Incomplete |
|---|---|---|---|
| 61–70 | 3 | 2 (66.7%) | 1 (33.3%) |
| 71–80 | 3 | 1 (33.3%) | 2 (66.7%) |
| 81–90 | 0 | 0 | 0 |
| 91–100 | 9 | 3 (33.3%) | 6 (66.7%) |
| 100– | 32 | 2 ( 6.3%) | 30 (93.7%) |
| Total | 47 | 8 (17.0%) | 39 (83.0%) |

6. Thyroid $I^{131}$ uptake. As shown in Table 16, there was no relationship between thyroid $I^{131}$ uptake and the one-dose cure rate.

TABLE 16. Thyroid $I^{131}$ Uptake and Cure Rate of Patients Treated with the Fixed Dose of 15 mc

| Uptake (%) | No. | Cured | Incomplete |
|---|---|---|---|
| 41–50 | 11 | 4 (36.4%) | 7 (63.6%) |
| 51–60 | 11 | 0 (0%) | 11 (100%) |
| 61–70 | 22 | 3 (13.6%) | 19 (86.4%) |
| 71–80 | 3 | 1 (33.3%) | 2 (66.7%) |
| Total | 47 | 8 (17.0%) | 39 (83.0%) |

TABLE 17. Calculated Dose and Cure Rate of Patients Treated with the Fixed Dose of 15 mc

| Calculated dose (mc) | No. | Cured | Incomplete |
|---|---|---|---|
| 15.1–20.0 | 25 | 7 (28.0%) | 18 (72.0%) |
| 20.1–25.0 | 32 | 0 (0%) | 12 (100%) |
| 25.1–30.0 | 7 | 1 (14.3%) | 6 (85.7%) |
| 30.1–35.0 | 2 | 0 (0%) | 2 (100%) |
| 35.1– | 1 | 0 (0%) | 1 (100%) |
| Total | 47 | 8 (17.0%) | 39 (83.0%) |

7. The calculated dose in each case (Table 17). Calculated dose in each case ranged from 15.2 to 46.2 mc. Among 25 cases whose calculated dose was between 15 mc and 20 mc, 7 cases (28.0%) were cured with one dose, but of the remaining 22 cases whose calculated dose exceeded 20 mc, only one case (4.5%) was cured with one dose.

8. Comment. Among 369 cases of diffuse toxic goiter, there were only 47 cases (12.7%) in which the calculated dose exceeded 15 mc, so that it can be said that in diffuse toxic goiter, the calculated dose for 100 uc. of retained dose per gram of thyroid gland does not often exceed 15 mc.

As shown in Table 17, in 25 cases whose calculated dose fell between 15 and 20 mc, the one-dose cure rate was 28.0%, but in 22 cases whose calculated dose exceeded 20 mc only one case was cured so that it could be said that when the calculated dose exceeded 20 mc there was little chance of cure with one dose administration of 15 mc.

As shown in Table 14, the one-dose cure rate of 8 patients whose disease had existed for more than three years was 0%, and as shown in Table 15, the one-dose cure rate of patients with large goiter was low. From this point of view it could be said that in patients whose disease had existed long and whose goiter was quite large, the prognosis after $I^{131}$ therapy was poor.

## DISCUSSION

The most important and most difficult problem in $I^{131}$ treatment for hyperthyroidism is the determination of the optimal dose for a given case. There is no satisfactory criterion for estimating the dosage.

The following list, summarizing the various methods of dosage determination, shows the wide range of criteria:

1. Equivalent roentgens calculated from the thyroid uptake and effective hal-life (E.H.L.) of the tracer dose.
2. Equivalent roentgens based upon the tracer dose, on the assumption that the E.H.L. is six days.
3. Microcuries per gram retained by the thyroid gland based upon the uptake of the tracer dose.
4. Microcuries per estimated gram of thyroid.
5. Minimum effective dose, with repetition as indicated.

It can be said that the first to the fourth criteria in this list would achieve one-dose cure in most cases, and the fifth criterion designs to achieve cure of the patient by multiple doses.

Theoretically the first criterion looks most scientific, as one should be able to predict the proper dose most accurately by estimating the weight of the gland, determining the uptake and effective half-life of the tracer dose, and then calculating the dosage in equivalent roentgen by the simple formula

of Marinelli and Quimby[2]. But this procedure requires much time and labor and it is doubtful whether there is sufficient increased dependability of result to justify the extra work. Concerning the uptake and E.H.L., Miller and Sheline[3], Seed and Jaffe[4] have found that there were discrepancies between tracer dose and treatment dose not only as a result of technical error but also as a result of metabolic alteration, so that they lost faith in the method.

The second and the third criteria in the list are identical, because the dose of $I^{131}$ is selected based upon the uptake of the tracer dose and the estimated weight of the thyroid gland, although in the second criterion the dose selection is based on the assumption that the E.H.L. is six days. The only difference is that the dose is expressed in equivalent roentgen in the second criterion and microcurie in the third criterion.

The fourth crierion in the list is also almost similar to the second and the third criteria. Although the dose is selected by only per estimated gram of thyroid tissue, it is still based upon the assumption that the 24 hour uptake of $I^{131}$ by toxic diffuse goiter is in the neighborhood of 70%.

Although there is a wide range of criteria to select the dose of $I^{131}$, yet all of them accomplish an amazingly similar therapeutic result. The one-dose cure rate reported by many workers is around 60%[5)~20)].

Principally the author adopted the third criterion of the above mentioned list. The author has given 100 uc. of retained dose per gram of thyroid tissue, but when the calculated dose was too large the author gave only some limited dose. The author did not give a larger dose because several reasons discouraged us from giving large dose of radioiodine: 1. the patient who needs a large dose usually has a larger goiter, and if the thyroid gland is more than 70 grams, its estimation may become more incorrect (error may reach 100% or more[14)]). 2. if the thyroid gland of this patient is unusually sensitive to radiation, the incidence of developing myxedema will be high from this large dose. 3. it is much easier to give one or more additional doses than to treat a myxedematous state that may result from larger dose. Thus it may be a safer policy to give some limited dose to the patient whose calculated dose is too large. The problem is at what level should we set the limited dose.

During the experimental period from September 1959 to December 1961, the author set the limit of dose at the level of 7 mc. During this period, 348 cases of hyperthyroidism were treated with $I^{131}$, and the following results were obtained: 1) The one-dose cure rate of patients, to whom calculated dose below 7 mc was given, was 56.5%. 2) The one-dose cure rate of patients, to whom limited dose of 7 mc was given, was 34.6%. 3) The one-dose cure rate of all patients was 40.8%.

During the period from January 1964 to December 1965, the limit of the initial dose of $I^{131}$ was elevated to 15 mc, and 369 cases of hyperthyroidism were treated with an initial dose of 15 mc or less. The results obtained were

as follows; 1) The one-dose cure rate of patients, to whom the calculated dose below 15 mc was given, was 39.6%. 2) The one-dose cure rate of patients, to whom the limited dose of 15 mc was given, was 17.0%. 3) The one-dose cure rate of all patients was 36.6%.

Comparing the results of these two serial studies, one can find the surprising but real phenomena that no improvement did occur in the overall one-dose cure rate by elevating the limit of the initial dose from 7 mc to 15 mc, and the one-dose cure rate of patients who received the calculated dose was even lower in the present series.

But, as shown in Table 18, comparing the results of the two series in detail, we can find the following facts: 1) To patients whose calculated dose was less than 7 mc, the individually calculated dose was given in both series, and the one-dose cure rate was quite identical (56.5% and 55.7%). 2) To patients whose calculated dose was between 7.1 mc and 15 mc, the fixed dose of 7 mc was given in the previous series and the individually calculated dose between 7.1 mc and 15 mc was given in the present series, but the one-dose cure rate was almost the same (38.5% and 34.2%). 3) To patients whose calculated dose was over 15 mc, the fixed dose of only 7 mc was given in the previous series and the larger fixed dose of 15 mc was given in the present series, and the one-dose cure rate was still nearly the same (10.3% and 17.0%) ($P$ 0.1).

From these facts the author would like to conclude that when the calculated dose of $I^{131}$, based on thyroid weight and thyroid uptake, exceeds 7 mc the therapeutic effect is the same whether we give 7 mc or more.

Why, although giving the calculated dose based upon the same principle, the effect is better when the calculated dose is less than 7 mc, and worse when the calculated dose is more than 7 mc, the precise reason is obscure. It might be due to difference of metabolism of radioiodine by the thyroid gland such as uptake, and turn over between smaller and large dose of radioiodine.

According to this conclusion the author intends to reduce the limit of the initial dose of $I^{131}$ to the range of 7 mc, and treat patients with hyperthyroidism with the regimen used in the previous series, namely: 1) when the calculated dose is less than 7 mc, the calculated dose is to be given. 2) when the calculated dose exceeds 7 mc, the limited dose of 7 mc is to the given. 3) an additional dose is to be given three months later if indicated.

Miyake *et al.*[21] and DeGowin *et al.*[19] recommended giving a smaller dose than the calculated dose to patients with large goiter from the experience that large goiter sometimes responded to smaller dose very well. This fact was also experienced in author's studies. But the author recommends the same policy to give a smaller dose than the calculated dose to patients with large goiter for another reason, that is, large goiter which does not respond to the limited dose also does not respond to larger dose.

TABLE 18. Comparison of the One-dose Cure Rate in Previous Series and Present Series

| Calculated dose | Previous series (treated with the initial dose of 7 mc or less) | | | | Present series (treated with the initial dose of 15 mc or less) | | | |
|---|---|---|---|---|---|---|---|---|
| mc | No. | Cured | Incompl. | Unclear# | No. | Cured | Incomplete | |
| -5.0 | 38 | 23(60.5%) | 15 | 0 | 10 | 6(60.0%) | 4 | |
| 5.1-6.0 | 28 | 15(55.6%) (56.5%) | 12 | 1 | 23 | 14(60.9%) (55.7%) | 9 | |
| 6.1-7.0 | 22 | 10(50.0%) | 10 | 2 | 46 | 24(52.2%) | 22 | |
| 7.1-8.0 | 82 | 42(54.5%) | 35 | 5 | 54 | 24(45.3%) | 29 | |
| 8.1-9.0 | 31 | 11(36.7%) | 19 | 1 | 54 | 20(37.0%) | 34 | |
| 9.1-10.0 | 37 | 11(33.3%) | 22 | 4 | 40 | 14(35.0%) | 26 | |
| 10.1-11.0 | 20 | 5(29.4%) | 12 | 3 | 24 | 8(33.0%) | 16 | |
| 11.1-12.0 | 25 | 5(23.8%) (38.5%) | 16 | 4 | 33 | 10(30.3%) (34.2%) | 23 | |
| 12.1-13.0 | 15 | 4(26.7%) | 11 | 0 | 12 | 3(25.0%) | 9 | |
| 13.1-14.0 | 8 | 2(25.0%) | 6 | 0 | 12 | 3(25.0%) | 9 | |
| 14.1-15.0 | 9 | 0(0%) | 7 | 2 | 15 | 1( 6.7%) | 14 | |
| 15.1-20.0 | 17 | 1( 6.3%) | 15 | 1 | 25 | 7(28.0%) | 18 | |
| 20.1-25.0 | 9 | 0( 0%) | 9 | 0 | 12 | 0( 0%) | 12 | |
| 25.1-30.0 | 2 | 0( 0%) (10.3%) | 2 | 0 | 7 | 1(14.3%) (17.0%) | 6 | |
| 30.1- | 5 | 2(40.0%) | 3 | 0 | 3 | 0( 0%) | 3 | |
| Total | 348 | 131(40.8%) | 194 | 23 | 369 | 135(36.6%) | 234 | |

# Cases lost for follow-up were excluded from calculation of cure rate.

Of course it is an ernest desire of patients, and also of doctors, to achieve permanent cure by one dose of radioiodine, because it means much saving in time and economy, and shortening of the period of illness. But at present it is unable to satisfy this desire for all patients, especially for those with large goiter, at least by means of increment of therapeutic dose of radioiodine.

Another problem to be discussed is the effect of pretreatment with antithyroid on the result of $I^{131}$ therapy. In the present series, the one-dose cure rate of patients pretreated with antithyroid was significantly lower than that of patients previously untreated. Werner[22], and Crooks[23], stated that pretreatment with antithyroid might induce relative radio-resistance of the thyroid gland.

But, it should be mentioned that in the present series only patients with mild thyrotoxicosis were treated immediately with $I^{131}$ without pretreatment with antithyroid. To determine the precise effect of antithyroid pretreatment on the results of $I^{131}$ therapy, we should select two groups of patients in the same range of severity of disease, weight of goiter, and quantity of calculated dose.

Occasionally an aggravation of thyrotoxicosis did occur after therapy with $I^{131}$, and even death due to thyroid storm after receiving therapeutic dose of

$I^{131}$ has been reported[11]. Actually the great majority of patients with thyrotoxicosis are ambulatory and are treated as outpatients, so that omission of pretreatment with antithyroid is not advisable for the purpose of preventing aggravation of thyrotoxicosis after $I^{131}$ treatment.

## CONCLUSION

From January 1964 to December 1965, 369 cases of diffuse toxic goiter were treated with $I^{131}$ of the initial dose of 15 mc or less. The dose of $I^{131}$ was calculated according to thyroid weight and thyroid uptake to let 100 uc. of $I^{131}$ retain in each gram of thyroid tissue. When the calculated dose was below 15 mc that calculated dose was given and when the calculated dose exceeded 15 mc the limited dose of 15 mc was given as the initial dose. Among 369 cases, 322 cases were treated with calculated dose of below 15 mc and 47 cases were treated with the fixed dose of 15 mc.

Among 322 cases treated with the calculated dose below 15 mc, 79 cases were treated with the dose less than 7 mc, and 243 cases were treated with the dose more than 7 mc. Although the calculated dose based upon the same principle was given, the one-dose cure rate of patients treated with the dose over 7 mc (34.2%) was definitely lower than that of patients treated with the dose below 7 mc (55.7%).

The one-dose cure rate obtained in this series was the same as that obtained in the author's previous series. In the previous series, from September 1959 to December 1961, the author treated 348 cases of diffuse toxic goiter with $I^{131}$ of the initial dose of 7 mc or less. In the previous series, when the calculated dose was less than 7 mc the calculated dose was given, and when the calculated dose exceeded 7 mc the limited dose of 7 mc was given and the following one-dose cure rate was obtained: 1) 56.5% in patients treated with the calculated dose below 7 mc. 2) 34.6% in patients treated with the fixed dose of 7 mc. 3) 40.8% in all patients.

Comparing the one-dose cure rate in these two serial studies, the author obtained the following conclusions: 1) Giving the dose of $I^{131}$ to let 100 uc. retain in each gram of thyroid tissue, when the calculated dose below 7 mc is given, 56% of patients will be cured with one dose. 2) But, when the calculated dose exceeds 7 mc the one-dose cure rate will be the same whether we give 7 mc or more. Namely, maximum effective dose of $I^{131}$ for diffuse toxic goiter may be in the neighborhood of 7 mc.

From these conclusions the author suggests that the regimen of $I^{131}$ treatment for diffuse toxic goiter to be as follows: 1) When the calculated dose is less than 7 mc, give the calculated dose. 2) When the calculated dose is more than 7 mc, give the limited dose of 7 mc as the initial dose. 3) Give an additional dose three months later if indicated.

## REFERENCES


1) Yang, H. F., *J. Formosan Med. Assoc.*, **63**, 234, 1964.
2) Marinelli, L. D., Qumby, E. H., and Hine, G. J., *Am. J. Roentgenol.*, **59**, 260, 1948.
3) Miller, E. R. and Sheline, G. E., *Radiology*, **57**, 260, 1951.
4) Seed, L. and Jaffe, B., *J. Clin. Endocrinol.*, **13**, 107, 1953.
5) Freedberg, A. S., Kurland, G. S., Chamovitz, D. L., and Ureles, A. L., *J. Clin. Endocrinol.*, **12**, 86, 1952.
6) Scott, W. G., Seaman, W. B., Macbryde, C., Gottlieb, L., Daughaday, W. H., and Sweeney, B. J., *Am. J. Roentgenol.*, **66**, 171, 1951.
7) McCullagh, E. P. and Richards, C. E., *Arch. Int. Med.*, **87**, 4, 1951.
8) Blomfield, G. W., Jones, J. C., MacGregor, A. G., Miller, H., and Wayne, E. J., *Brit. M. J.*, **2**, 373, 1951.
9) Miller, E. R., Dailey, M. E., Soley, M. H., Foremen, H., Holmes, A. U., Alexander, G. L., and Sheline, G. E., *Radiology*, **57**, 227, 1951.
10) Shipley, R. A., Storassli, J. P., Friedell, and Potts, A. M., *Am. J. Roentgenol.*, **64**, 576, 1950.
11) Feitelberg, S., Kaunitz, P. S., Silver, S., Simon, N., Wasserman, L. S., and Ylhalem, S. B., *Arch. Int. Med.*, **85**, 471, 1950.
12) Gordon, E. S. and Albright, E. C., *J.A.M.A.*, **143**, 1129, 1950.
13) Moe, R. H., Adams, F. E., Rule, J. H., Moore, M. C., Kearns, J. E., Jr., and Clark, D. E., *J. Clin. Endocrinol.*, **10**, 1022, 1950.
14) William, R. H., Towery, B. T., and Jaffe, H., *Am. J. Med.*, **7**, 702, 1949.
15) Chapman, E. M. and Evans, R. D., *Med. Climics North Am.*, **33**, 1211, 1949.
16) Johnson, J. B., Ireland, C., Thomas, R. F., and Bass, A., *Am. J. Med.*, **6**, 504, 1949.
17) Seed, L. and Jaffe, B., *J. Clin. Endocrinol.*, **13**, 107, 1953.
18) Bauer, E. K. and Blahd, W. H., *Arch. Int. Med.*, **99**, 194, 1957.
19) Dogowin, E. L., Hodges, R. E., Hamilton, H. E., and Evans, T. C., *Arch. Int. Med.*, **104**, 959, 1959.
20) Segal, R. L., Silver, L., Yohalem S. B., and Feitelberg, S., *Am. J. Med.*, **31**, 354, 1961.
21) Miyake, T., Shizume, L., Kumabara, Y., Tokuyama, I., Kumaoka, S., Torizuka, K., and Yamashita, H., *Folia Endocrinologica Japonica*, **39**, 805, 1963.
22) Werner, S. C. Coelho, B. and Quimby, E. H., *Bull. N.Y. Acad. Med.*, **33**, 783, 1957.
23) Crooks, J., Buchanan, W. W., Wayne, E. J., and MacDonald, E., *Brit. Med. J.*, **1**, 151, 1960.