Synthesis of Thyroglobulin in Thyroid Carcinoma Patients After Radioiodine Therapy

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Endogenously radioiodinated thyroglobulin (Tg) and the serum concentration of Tg have been measured in patients with metastatic thyroid carcinoma after therapeutic doses of radioiodine. Serial samples of blood were analyzed for both these parameters over a period of 10 to 22 days. The specific activity of Tg (cpm/ng) was calculated for each sample. Among the six patients studied, three showed constant specific activity. The specific activity of the other three fell, indicating the entering of newly synthesized Tg into the circulation. The respective amounts of Tg entering into the circulation in these three patients were 120, 852, and 20,935 ng/ml serum/day.

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IT IS NOW well known that serum thyroglobulin (Tg) can be used as a reliable biochemical marker for detection of presence of metastases of recurrence of disease in patients with differentiated thyroid carcinoma after surgical removal of primary tumor.[1–6] It is also has been shown that Tg is undetectable after successful ablation of thyroid cancer.[7,8] In addition, Tg levels are shown to be lower in patients who have undergone thyroid ablation as compared with patients with partial thyroidectomy or normal subjects. Very recently, Ashcraft and Van Herle have further pointed out that the Tg level, less than 1 ng/ml during thyroxine (T_4) therapy or 10 ng/ml off T_4 therapy, is suggestive of a successful therapy, and a routine scan could be avoided unless clinically indicated.[9] This avoids the potential risk of stimulation of thyroid cancer cells by thyroid stimuluating hormone and morbidity of induced hypothyroidism. In the current study, we made an attempt to study the specific activity of radioiodinated Tg in thyroid carcinoma patients after radioiodine therapy as a guideline for the effectiveness of radioiodine therapy.

Materials and Methods

Study Subjects

Six patients with thyroid carcinoma who had undergone thyroidectomy, but who had functioning metastases, were studied. Of the six patients, two (N, Rx) had already undergone radioiodine treatment in the past and one patient (P) had undergone deep x-ray therapy. Thyroxine therapy was started in all six patients on fifth day after radioiodine treatment.

The sera of these patients were found to be negative for the presence of antithyroglobulin and antimicrosomal antibody by tanned red cell agglutination technique using kits from Fugizoki Pharmaceutical Co., Ltd., Japan.

Of the six patients studied, three were followed up later when they came for the successive therapeutic treatments.

Measurement of radioiodinated serum Tg: Serial blood samples were obtained with an interval of 1 to 2 days after radioiodine treatment from these patients. The percent radioactivity associated with Tg/ml serum and the disappearance rate of radioiodinated serum Tg were measured according to the procedure described earlier.[10]

Measurement of Tg by radioimmunoassay (RIA): The amount of total circulating Tg referred as stable Tg, was measured by RIA as described by Van Herle *et al.*[7] Since the presence of ^{131}I in the serum interferes with the RIA procedure, all radioiodinated sera were stored at −20°C until decay of radioactivity.

Specific activity: The specific activity of Tg in each sample was calculated as follows:

$$\text{Specific activity (counts/50 sec/ng Tg)} = \frac{\text{Radioactive counts with Tg per ml serum}}{\text{Amount of Tg in ng per ml serum}}$$

Results

In all patients studied, the levels of radioiodinated and stable Tg rose initially, attained a maximum value be-

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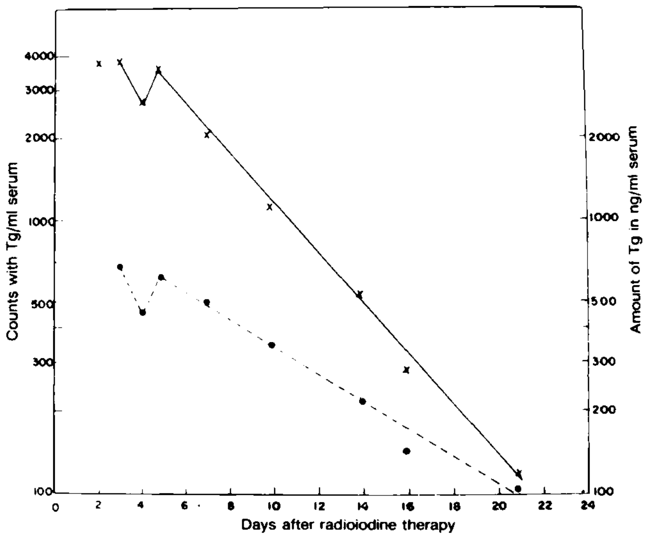

FIG. 1. Disappearance rate of radioiodinated Tg (×) as measured by column chromatography and stable Tg (O) as measured by radioimmunoassay.

tween 2 and 8 days, and then declined. The disappearance rate of stable Tg, however, differed in these patients (Figs. 1 and 2).

Specific activity: The specific activity of radioiodinated Tg in these six patients is shown in Figure 3. Three patients who had parallel decline of both radioiodinated Tg and stable Tg, showed constant specific activity (represented by horizontal line in Figure 3), thus indicating a negligible amount of newly synthesized Tg entering the circulation. The remaining three patients who had a slower disappearance rate of stable Tg, showed a fall in specific activity,

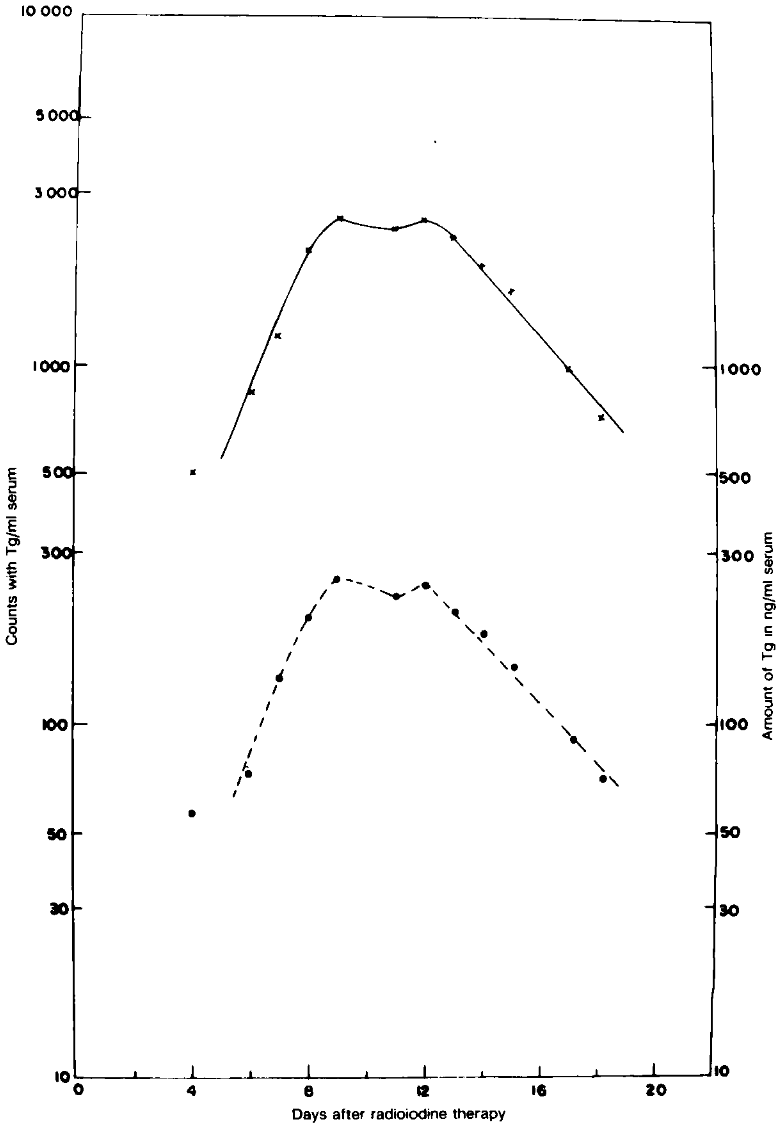

FIG. 2. Disappearance rate of radioiodinated Tg (×) as measured by column chromatography and stable Tg (O) as measured by radioimmunoassay.

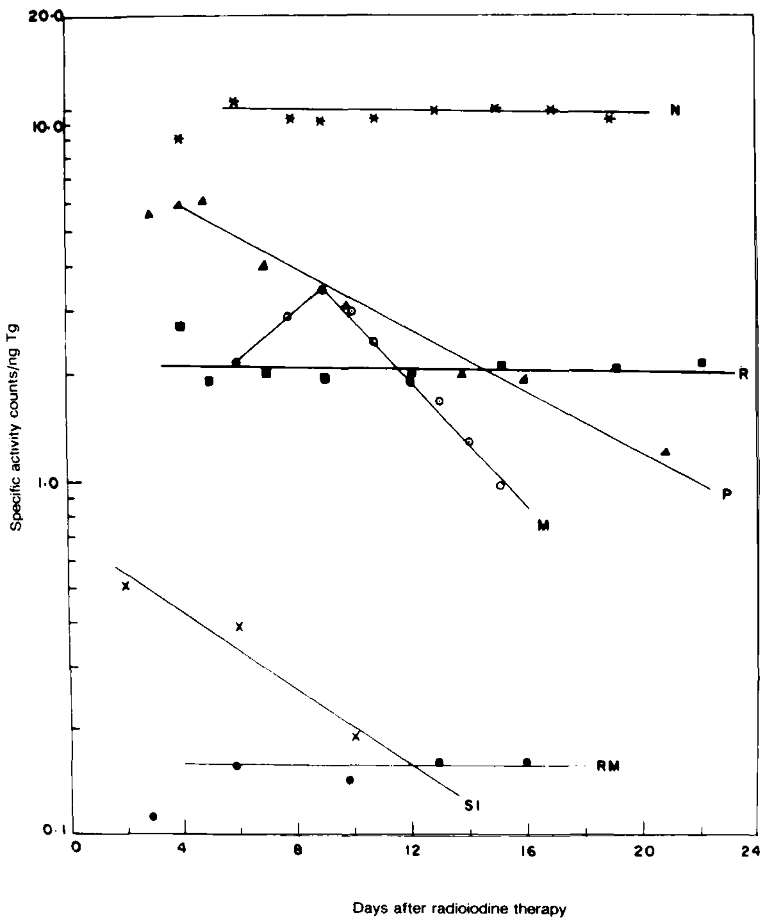

FIG. 3. Specific activity of radioiodinated Tg after radioiodine therapy (six patients). Three patients (N, R and RM) show constant specific activity and remaining three patients (P, M and SI) show decline in specific activity.

indicating possibly the newly synthesised Tg entering the circulation.

Discussion

The data presented here show that there is a parallel rise in stable and radioiodinated Tg in circulation, in all of the six patients studied, after radioiodine treatment. The increase in the level of stable and radioiodinated Tg between 2 and 8 days, indicate that the effect of radioiodine is seen within a short period. This is in contrast to the delayed effect of radioiodine observed for controlling thyroid activity of Graves' disease.[11] The purpose of radioiodine for the treatment of Graves' disease and thyroid cancer is different, *i.e.*, a large amount of radiation dose is given in thyroid cancer patients, with 80 to 250 mCi ^{131}I, for total destruction of functioning thyroid tissue, while comparatively small amount of radiation dose is given in Graves' disease, with 3 to 10 mCi ^{131}I, for partial destruction of thyroid.

Thyroxine therapy was started on the fifth day after radioiodine treatment in all patients studied. The circulating Tg level showed a decline in some patients even prior to Tg therapy, whereas in some other patients, the Tg level continued to show an increasing trend even after T_4 therapy, indicating at this stage that the radiation dose to the tumor has a primary role on the level of circulating Tg.

Although the stable and radioiodinated Tg showed a parallel rise after radioiodine treatment; they were not parallel during the declining phase in all the patients studied, *i.e.*, the disappearance rate of stable Tg was longer than that of radioiodinated Tg in three of the six patients. Theoretically, one would expect both radioiodinated and stable Tg to have similar kinetics resulting into a constant specific activity if complete ablation of tumor had been achieved with radioiodine. The decline in specific activity thus indicates the presence of functioning tumor, which releases the Tg and thus lowers the specific activity. The amount of Tg entering the circulation might have direct relation with the mass of functioning tumor present. It is pertinent to note that a direct correlation between circulating Tg and amount of tumor mass is not yet established.

We have attempted to calculate the amount of Tg entering in circulation in the patients who show a decline in specific activity. As the level of stable Tg is not at a steady state, *i.e.*, the stable Tg is declining as a function of time but at a much slower rate than that of radioiodinated Tg, the rate of disappearance of stable and radioiodinated Tg were plotted on linear graph paper (Fig. 4) for the purpose of calculation Tg synthesis. If the disappearance rate of both stable and radioiodinated Tg were similar, the two curves could be superimpose; however, when there is a difference in disappearance rate or addition of Tg into circulation, the curves could be different. The first possibility could be ruled out, as the disappearing Tgs (stable and radioiodinated) are one and the same basically. Therefore, the area between the two curves is considered due to the addition of newly synthesised Tg. Thus, the net synthesis of Tg was calculated directly by measuring the area which gives ng/ml/days which then divided by the number of days for which the area was calculated gave the amount of Tg added per ml serum per day. The amounts of Tg entering the circulation in the three patients (P, M, SI) who showed a decline in specific activity were 120, 852, and 20,935 ng/ml serum/day; respectively.

The predictions made by the specific activity studies were further verified when three of the six patients came for subsequent follow-up. The Patient R who had shown constant specific activity was followed for a period of 6 months while the patient was on T_4, by collecting blood sample each month. The Tg level was 35 ng/ml and this remained almost constant in the 6-month period. The patient came for successive treatment after 14 months and thyroxine therapy was withdrawn prior to therapy, and the Tg level was 204 ng/ml. The Tg level could have gone up because of withdrawal of T_4 as it is clearly known that Tg level is dependent on thyroid stimulating hormone.[12] Following therapy the Tg level, came down to 25 ng/ml and the patient was on T_4.

The second patient, RM, who also showed constant specific activity had a Tg level of 43,000 ng at the time of the first treatment. The patient came for successive treatment after ten months and Tg level was 270 ng/ml. The level of Tg could have been lower than 270 ng/ml if the measurement was made prior to stopping T_4.

The third patient, M, who did not show constant specific activity had a Tg level of 2200 ng/ml at the time first treatment. The patient came for successive treatment six months after therapy and the Tg level was 1140 ng/ml. This is in accordance with the observed decline in specific activity.

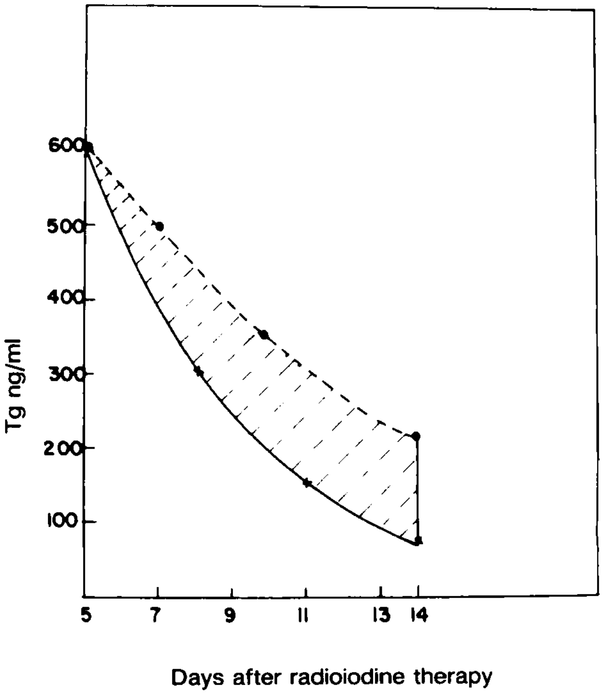

FIG. 4. Synthesis of Tg after radioiodine therapy. Amount of Tg entering the circulation between 5th and 14th day is shown by a shaded area between the two curves, radioiodinated Tg (×) and stable Tg (O).

As far as the new synthesis of Tg is concerned, it is adequate if serial determination of stable Tg in circulation is made. However, it would be difficult to assess the number of samples to be collected, as it is not possible to set up the assay for Tg immediately after the collection of sample because of the presence of radioiodine in serum. It is, therefore, desirable to determine the disappearance of radioiodinated Tg as a guideline for collecting the number of samples.

In conclusion, the specific activity determination may therefore serve as a guideline of effectiveness of therapy. The data on six patients is limited; nonetheless one can classify the patients into two groups on the basis of specific activity: patient should be called at the earliest possible day for the next therapy, and the patient may be kept safely on thyroxine for a prolonged period of time with a regular checking of circulating Tg.

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