JOURNAL OF NUCLEAR MEDICINE 5:796-801, 1964

An 18 Year Study of the Use of Beef Thyrotropin to Increase I^{131} Uptake in Metastatic Thyroid Cancer[1,2]

Richard S. Benua, M.D., Martin Sonenberg, M.D., Ph.D., Robert D. Leeper, M.D. and Rulon W. Rawson, M.D.

New York

Thyrotropin (TSH) has been used to stimulate the uptake of radioactive iodine by metastatic thyroid cancer since 1946 (1,2,3). The present report encompasses 28 courses of TSH given to 20 patients prior to 1951 and 54 courses in 28 patients since 1958. A report of success with this procedure (4) led us to re-investigate this method of stimulation and to further evaluate all the patients we have studied.

METHODS

Patients with histologically proven thyroid cancer received beef TSH[3] for one to 14 days. Intramuscular injection was used in all except 2 patients, who were treated intravenously. The intravenous route was used twice in 1948 because the initial lots of TSH caused pain at intramuscular sites. TSH was administered twice daily in most of the studies since 1958. The average total dose in a series of injections was 580 USP units prior to 1951, 78 units between 1958 and 1961, and 95 units since 1961. At the present time the usual regimen is 10 units intramuscularly every 12 hours for 5 days. All patients were previously thyroidectomized by surgery or radioiodine. Most were hypothyroid, and thyroid hormones were discontinued during TSH stimulation.

Tracers of I^{131} were usually administered both before and after a course of TSH. In the first part of the study an interval of 48 hours elapsed between the last injection of thyrotropin and the subsequent administration of the tracer, but since 1958, a 6 hour interval has been a standard procedure. For the purpose of analysis, no tracer given more than 60 days prior to the TSH has been used for comparison. In some cases therapeutic I^{131} directly followed the course of thyrotropin, but most often a pretherapy tracer and another course of TSH preceded treatment with radioiodine.

---

[1]From the Department of Medicine and Division of Clinical Investigation, Memorial Sloan-Kettering Cancer Center, New York.

[2]Supported in part by grants-in-aid from the American Cancer Society (P-81, T-71), the Damon Runyon Memorial Fund (DRG 377, DRG 442), the Atomic Energy Commission, under contract No. AT (30-1)-910 and the National Cancer Institute, U. S. Public Health Service (C-2052, CY 3809).

[3]Thyrotropar. Some was kindly furnished by Armour Laboratories, Kankakee, Illinois.

The counting rate at a given position over the tumor was measured at various times, most often 48 hours, after the tracer was administered. By using the same radiation detector and correcting for the size of the tracer dose, the relative tumor uptake in the area of greatest tumor concentration was compared before and after TSH. It has not been possible to compare tumor uptake after giving a therapy dose of I^{131} with that following a tracer dose of I^{131}. This was because the higher levels of radioactivity present following I^{131} therapy required the use of a less sensitive counter with a different collimater. Measurement of the amount of I^{131} excreted in the urine during the first 48 hours after the tracers permitted an estimation of the relative body retention before and after stimulation. In some patients there was subjective evidence from hand scanning that uptake had been stimulated, but in the present report only objective evidence of change in tumor uptake is reported.

RESULTS

A total of 82 courses of stimulation with TSH have been given to 48 patients with metastatic thyroid cancer. Four patients experienced side effects during their first course of TSH. The reactions were nausea, fever, pain at the site of injection or hives, and were seen only with the lots of TSH employed before 1949. Of 18 patients who received more than one series of injections of TSH, 2 developed hives during the second or third series.

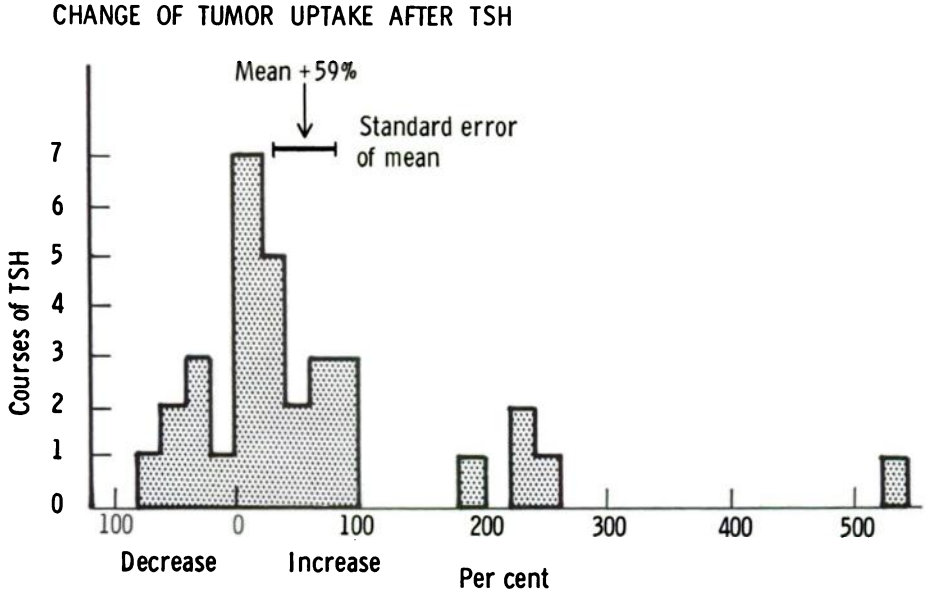

Fig. 1

Tracer doses of I^{131} were administered at the conclusion of 61 courses of thyrotropin in 45 patients. Tumor uptake increased 59 ± 21 per cent on the average in the 32 instances where paired data were available. Figure 1 shows that this average increase is accounted for, in the main, by increases of over 100 per cent in 5 studies. This degree of stimulation was obtained in 4 patients with follicular and one with papillary cancer. They received courses totalling 100 units in 3 instances, 120 units in one and 700 units in another instance. Body reten-

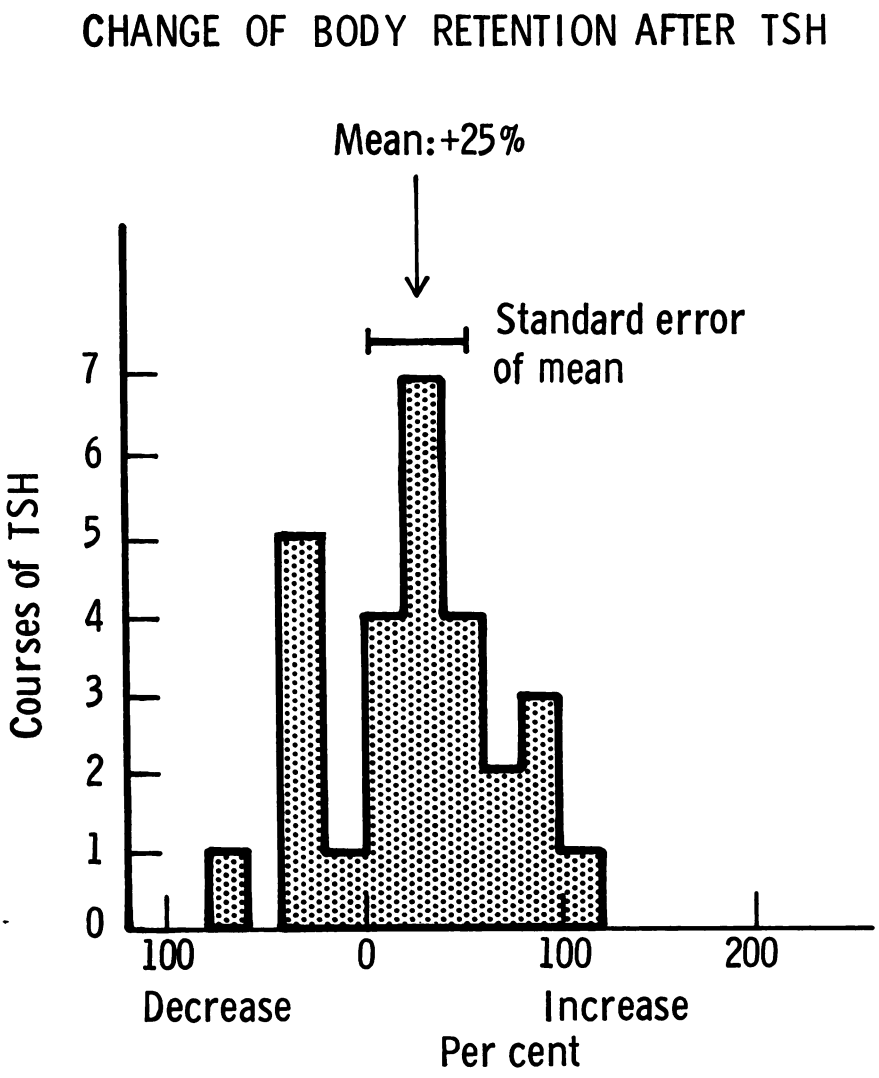

Fig. 2

tion of the tracer I^{131} at 48 hours averaged 25 ± 25 per cent higher after administration of TSH in 28 paired studies (Fig. 2).

The histologic types of thyroid cancer in patients in whom TSH was given are shown in Table I. The differences in tumor uptake or body retention by histologic type are not statistically significant in a series of this size.

Therapeutic amounts of radioactive iodine were administered at the conclusion of 21 courses of TSH. Body retention increased by an average of only 4 ± 19 per cent in the 13 instances where reliable collections of urine were available for both the therapy and a pre-TSH tracer.

DISCUSSION

Although no statistically significant change occurred in most patients receiving TSH, dramatic increases in tumor uptake of I^{131} were produced by 5 of 32 courses of thyrotropin. The ability of such a procedure to more than double tumor uptake in some patients with metastatic follicular or papillary thyroid cancer makes the attempts worthwhile. A similar increase has been reported in one of 15 patients by Sheline and Miller (5) and some increase in 5 of 11 patients treated by Rose and Kelsey (6). These studies contrast with the observations of others who conclude that this method of stimulating tumor uptake is successful in most cases (4).

TABLE

Histologic Type	*Number of Patients*	*Number of Courses of TSH*		
		Total	*With paired tumor uptakes following tracer I^{131}*	
			Total	*With increase in uptake > 100%*
Papillary	13	25	11	1
Follicular and Alveolar	23	42	15	4
Solid	9	12	5	0
Hürthle Cell	2	2	1	0
Anaplastic	1	1	0	0
Total	48	82	32	5

Body retention at 48 hours was not significantly affected by thyrotropin administered before tracer or treatment doses of I^{131}. Such data did not reflect the occasional dramatic stimulation of individual metastases observed with tracer I^{131}, but urine measurements over a longer interval might have shown an effect. The failure of body retention to increase when therapeutic radioiodine followed the TSH may also have resulted from a radiation effect on the tumor which we have described elsewhere (7).

The optimum schedule for using TSH to stimulate tumor uptake is not entirely clear. Our data would suggest that the dose of TSH necessary does not exceed 100 units over a 5 day period, since earlier experience with larger doses for longer periods was not more successful. If data for 30 minute uptake in normal thyroid after a single injection of TSH (8) can be applied in the thyroid cancer patient, the optimum interval between the last TSH and the I^{131} would probably be 18 hours.

Side effects have been minimal with isolated instances of pain or fever limited to the initial years of the study. As has been reported by others (9,10), repeated courses may cause allergic reactions, and careful observation must be maintained to avoid continuing in the face of such reactions. Stimulation of the rate of tumor growth, while theoretically possible, has not been evident during or immediately after these brief courses of thyrotropin.

Thyrotropin stimulation is a rapid means of increasing tumor uptake, and thus is more acceptable to the patient than long courses of antithyroid drugs. The latter may be more effective, however, giving increases in up to ⅔ of the patients treated (11). Both methods of stimulation should only be used after normal thyroid is removed surgically or destroyed by radioiodine. Current practice is to try TSH before antithyroid drugs and again later if antithyroid agents fail to stimulate uptake in the tumor.

SUMMARY AND CONCLUSIONS

Eighty-two courses of treatment with beef thyrotropin have been used in 48 patients to increase the collection of radioactive iodine in metastatic thyroid cancer. The usual regime was 10 units twice daily for 5 days. Highly significant increases in tumor uptake were noted in 5 to 32 studies in which pre and post-TSH data were available. In these 5 instances, uptake more than doubled, but the average increase was 59 per cent for the 32 studies. This response could not be correlated with the dose of thyrotropin over the range employed or the histologic type of the tumor. Whole body retention of the radioactive iodine was 25 per cent higher after TSH, but this change was not statistically significant. Allergic manifestations occurred in 2 of 18 patients receiving more than one course of injections. In no instance did the thyrotropin appear to stimulate tumor growth. Thyrotropin stimulation should be attempted when thyroidectomy and antithyroid agents fail to yield sufficient tumor uptake to permit therapy.

REFERENCES

1. SEIDLIN, S. M., MARENLLI, L. D., AND OSHRY, E.: Radioactive Iodine Therapy, Effect on Functioning Metastases of Adenocarcinoma of the Thyroid. *J.A.M.A.*, **132**:838, 1946.
2. RAWSON, R. W., MARINELLI, L. D., SKANSE, B. N., TRUNNELL, J., AND FLUHARTY, R. G.: Effect of Total Thyroidectomy on Function of Metastatic Thyroid Cancer. *J. Clin. Endocrinol.*, **8**:826, 1948.
3. SEIDLIN, S. M., OSHRY, E., AND YALOW, A. A.: Spontaneous and Experimentally Induced Uptake of Radioactive Iodine in Metastases from Thyroid Carcinoma, Preliminary Report. *J. Clin. Endocrinol.*, **8**:423, 1948.
4. CATZ, B., PETIT, D. W., SCHWARTZ, H., DAVIS, F., MCCAMMON, C., AND STARR, P.: Treatment of Cancer of Thyroid Postoperatively with Suppressive Thyroid Medication, Radioactive Iodine, and Thyroid-Stimulating Hormone. *Cancer*, **12**:371, 1959.
5. SHELINE, G. E., AND MILLER, E. R.: Studies with Radioiodine, Evaluation of Radioiodine Treatment of Carcinoma of the Thyroid Based on the Experience at the University of California from 1938 to 1954. *Radiology*, **69**:527, 1957.
6. ROSE, R. G., AND KELSEY, M. P.: Radioactive Iodine in the Diagnosis and Treatment of Thyroid Cancer. *Cancer*, **16**:896, 1963.
7. BENUA, R. S., CICALE, N. R., SONENBERG, M., AND RAWSON, R. W.: Relation of Radioiodine Dosimetry to Results and Complications in the Treatment of Metastatic Thyroid Cancer. *Am. J. Roentgenol.*, 87:171, 1962.
8. EINHORN, J., AND LARSSON, L.-G.: Studies on the Effect of Thyrotropic Hormone on Human Thyroid Function. *J. Clin. Endocrinol. & Metab.*, **19**:28, 1959.
9. MACK, R. E., WELLS, H. J., AND OGBORN, R. E.: Management of Carcinoma of the Thyroid. *J.A.M.A.*, **163**:15, 1957.
10. BLAHD, W. H., NORDYKE, R. A., AND BAUER, F. K.: Radioactive Iodine (I^{131}) in the Postoperative Treatment of Thyroid Cancer. *Cancer*, **13**:745, 1960.
11. RALL, J. E., MILLER, W. N., FOSTER, C. G., PEACOCK, W. C., AND RAWSON, R. W.: The Use of Thiouracil in the Treatment of Metastatic Carcinoma of the Thyroid with Radioiodine. *J. Clin. Endocrinol.* **11**:1273, 1951.