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# Testicular Function in Patients with Differentiated Thyroid Carcinoma Treated with Radioiodine

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The aim of the present study was to assess whether  $^{131}\text{I}$  therapy for differentiated thyroid carcinoma (DTC) can affect endocrine testicular function. **Methods:** Serum follicle-stimulating hormone (FSH) and testosterone (T) concentrations were measured in 103 patients periodically submitted for radioiodine therapy for residual or metastatic disease. Mean follow-up was  $93.7 \pm 54$  mo (range 10–243 mo). **Results:** Mean FSH values in  $^{131}\text{I}$ -treated patients tested after their last treatment were  $15.3 \pm 9.9$  mU/ml, significantly higher than those of 19 untreated patients ( $6.5 \pm 3.1$  mU/ml). Considering the mean  $+3$  s.d. FSH of untreated subjects as the upper limit of normal range, 36.8% of the patients had an abnormal increase in serum FSH. Longitudinal analysis performed in 21 patients showed that the behavior of FSH in response to  $^{131}\text{I}$  therapy was not universal. Six patients had no change or a slight increase in serum FSH after  $^{131}\text{I}$  administration; eleven patients had a transient increase above normal values 6–12 mo after  $^{131}\text{I}$  treatment, with return to normal levels in subsequent months. The administration of a second dose was followed by a similar increase in FSH levels. Finally, four patients, followed for a long period of time and treated with several  $^{131}\text{I}$  doses, showed a progressive increase in serum FSH, which eventually became permanent. Semen analysis, performed in a small subgroup of patients, showed a consistent reduction in the number of normokinetic sperm. No change was found in serum T levels between treated and untreated patients. **Conclusions:** Our results indicate that  $^{131}\text{I}$  therapy for thyroid carcinoma is associated with transient impairment of testicular germinal cell function. The damage may become permanent for high-radiation activities delivered year after year and might pose a significant risk of infertility.

**Key Words:** radioiodine therapy; thyroid cancer; testis; FSH; testosterone; infertility

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**R**adioiodine treatment is a well established therapy for metastatic differentiated thyroid carcinoma (DTC). Long-term results are usually satisfactory, especially in patients

with lymph node metastases or diffuse lung metastases not detectable by x-rays (1,2). Toxic effects of  $^{131}\text{I}$  therapy consist of leukemia, pulmonary fibrosis, acute or chronic sialadenitis and gastrointestinal symptoms (1). However, they are rare and usually appear after high cumulative doses. Since DTC can affect children and young subjects in their reproductive age, with an excellent expectancy normal life when appropriately treated, these subjects may be exposed to large doses of  $^{131}\text{I}$  in the course of their disease. Apart from a few case reports (3–5), little data are available regarding the gonadal effects or the fertility changes (6) due to radioiodine therapy in male patients with DTC. Damage of the germinal cells after  $^{131}\text{I}$  therapy has been reported by Handelsman and Turtle (7) in a small group of patients with DTC, followed up to 3.5 yr. This finding has been confirmed by us in a preliminary retrospective study (8). We now report the impact of  $^{131}\text{I}$  therapy on testicular endocrine function in a large series of male patients with a mean ( $\pm$  s.d.) follow-up of  $93.7 \pm 54$  mo.

## PATIENTS AND METHODS

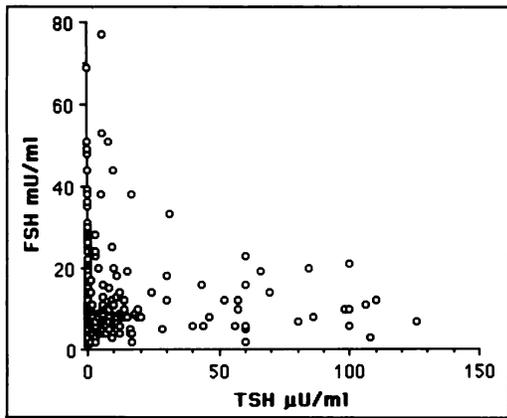
### Patients

We studied 103 male patients affected by DTC (92 papillary and 11 follicular) ranging in age between 17 and 60 yr at diagnosis. Mean ( $\pm$  s.d.) follow-up was  $93.7 \pm 54$  mo, with a range of 10–243 mo and a median of 94 mo. Eight patients with a previous history of infertility or testicular diseases were not included in this study.

All patients were studied after total thyroidectomy at various intervals during their follow-up. Radioiodine therapy in our institution is routinely used for ablation of thyroid residues and for treatment of functioning (i.e., able to take up radioiodine) metastases. Iodine-131 is administered after a 45-day withdrawal of l-thyroxine (l-T4) and after a 15-day withdrawal of l-triiodothyronine. The usual  $^{131}\text{I}$  dose is 30–100 mCi for ablation of thyroid residues and 100–150 mCi for treatment of node or distant metastases. A total of 345 blood samples, stored in our bank sera, were available for the study: 247 had been collected on thyroid hormone suppressive therapy (6–12 mo after  $^{131}\text{I}$  treatment) and 98 during short-term hypothyroidism, before performing  $^{131}\text{I}$  whole-body scan. Although we tested all sera for subsequent analysis, we only report the results for sera drawn before any  $^{131}\text{I}$  treatment in 19 patients and after the last  $^{131}\text{I}$  treatment in 103 patients.

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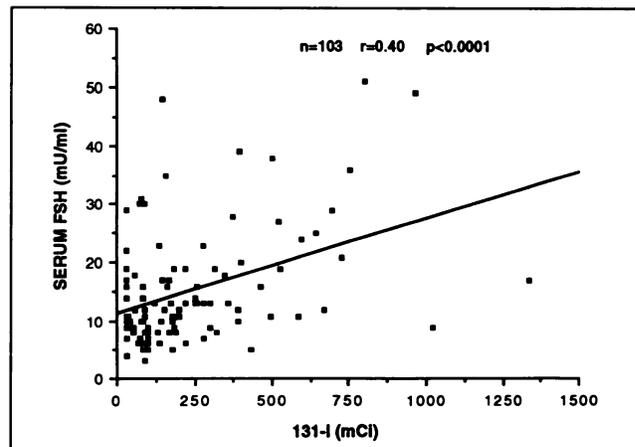
**FIGURE 1.** Absence of correlation ( $r = 0.07$ ) between serum TSH and FSH levels in all blood samples ( $n = 345$ ) available during l-thyroxine therapy or during short-term hypothyroidism in the 103 patients included in this study.

### Methods

FSH and T were measured in all blood samples using commercial kits (AIA PACK FSH, Tosoh Corporation, Tokyo, Japan; Coat-A-Count Total Testosterone, Diagnostic Products Corporation, Los Angeles, CA). Measurements were carried out in the same assay to avoid interassay variations. The results were analyzed according to the cumulative therapeutic  $^{131}\text{I}$  dose administered: 30–100 mCi (40 patients, 113 sera), 101–200 mCi (24 patients, 76 sera), 201–400 mCi (22 patients, 81 sera), 401–600 mCi (8 patients, 31 sera) and >600 mCi (9 patients, 25 sera). As controls, 19 patients were studied before any  $^{131}\text{I}$  treatment. Results were also analyzed in a longitudinal way in individual patients ( $n = 21$ ) with serial blood tests after repeated  $^{131}\text{I}$  administrations. Occasionally performed semen analysis was carried out according to the directions of WHO (9).

### RESULTS

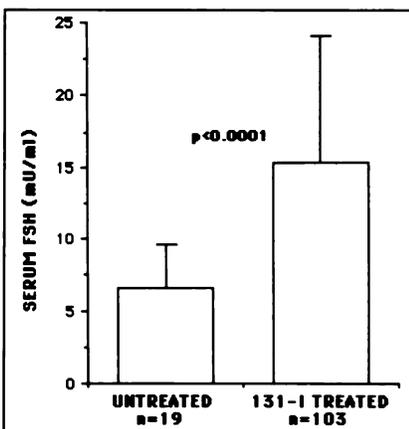
Mean ( $\pm$  s.d.) FSH values were not different in sera from euthyroid ( $13.2 \pm 9.7$  mU/ml) with respect to sera from hypothyroid patients ( $11.8 \pm 11.3$  mU/ml), and no correlation ( $r = 0.07$ ) was found between TSH and FSH values (Fig. 1). Thus the metabolic state of the patient was



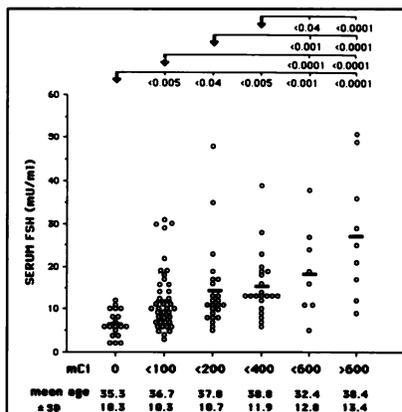
**FIGURE 3.** Correlation between serum FSH levels after the last  $^{131}\text{I}$  treatment and the corresponding total dose of  $^{131}\text{I}$  received by the patients ( $n = 103$ ).

not taken into account in the subsequent evaluation. As shown in Figure 2, mean ( $\pm$  s.d.) FSH values in 19 untreated patients were  $6.5 \pm 3.1$  mU/ml. Mean FSH values in 103 patients tested after their last  $^{131}\text{I}$  treatment (cumulative dose: median 167 mCi; range 30–1335 mCi) were  $15.3 \pm 9.9$  mU/ml, significantly higher ( $p < 0.0001$ ) with respect to untreated subjects. Furthermore, a positive correlation was found between FSH levels and the cumulative dose of  $^{131}\text{I}$  received by treated patients ( $r = 0.40$ ,  $p < 0.0001$ ) (Fig. 3).

As shown in Figure 4, when patients were grouped according to different total amounts of administered  $^{131}\text{I}$  a progressive, statistically significant increase in mean FSH concentrations was found. FSH levels were  $12.3 \pm 7.5$  mU/ml in patients treated with  $^{131}\text{I}$  doses of 30–100 mCi ( $n = 40$ );  $14.2 \pm 9.6$  mU/ml in those treated with 101–200 mCi ( $n = 24$ );  $15.4 \pm 7.4$  mU/ml in those treated with 201–400 mCi ( $n = 22$ );  $18.9 \pm 10.6$  mU/ml in those treated with 401–600 mCi ( $n = 8$ ); and  $27.7 \pm 15.1$  mU/ml in those treated with >600 mCi ( $n = 9$ ). As shown in Figure 4, mean age was not different among the various groups and could not account for the differences in mean FSH concentra-



**FIGURE 2.** Serum FSH values in untreated and  $^{131}\text{I}$  treated patients tested after their last  $^{131}\text{I}$  treatment. Vertical bars indicate the s.d. from the mean. The statistical difference between the two groups as assessed by Student's t-test is reported at the top.



**FIGURE 4.** Serum FSH levels in untreated and  $^{131}\text{I}$  treated patients according to the total dose of  $^{131}\text{I}$  (mCi) received. At the bottom of the figure, the mean ( $\pm$  s.d.) age for each group is reported. The horizontal bars in each column indicate the mean FSH. Statistics, by Student's t-test, are shown on the top.

**TABLE 1**  
Mean FSH Concentrations and Mean Iodine-131 Administered in Relation to the Site of Iodine-131 Uptake

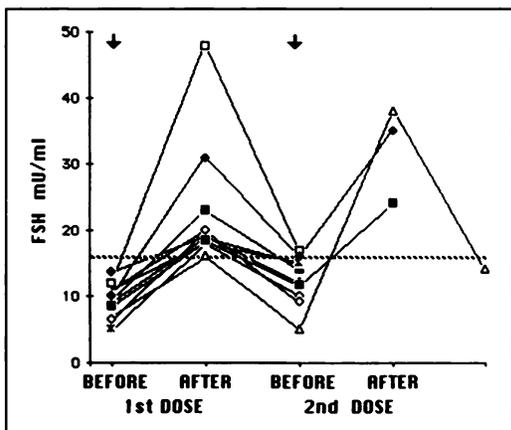
Uptake	FSH (mU/ml)	<sup>131</sup> I (mCi)
Thyroid bed (n = 62)	12.0 ± 7	130 ± 99
Lymph nodes (n = 28)	13.0 ± 8	251 ± 179*
Distant metastases (n = 13)	25.1 ± 16*	538 ± 360*

\*p < 0.0001 versus thyroid bed.

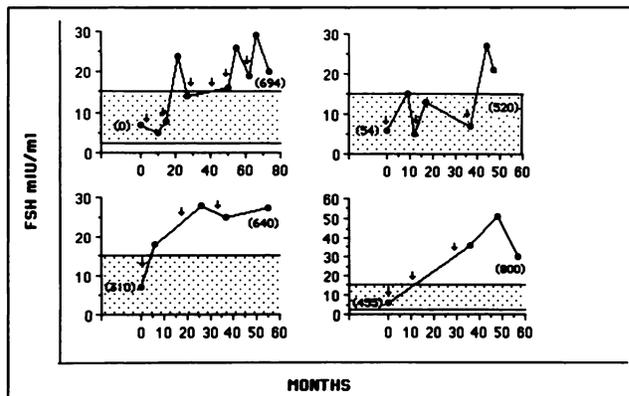
tions. Considering the mean + 3 s.d. FSH of untreated subjects (i.e., 15.8 mU/ml) as the upper limit of normal range, 36.8% of treated patients showed abnormally increased levels: 27.5% of the patients who received 30–100 mCi, 29.1% of those treated with 101–200 mCi, 36.3% with 201–400 mCi, 62.5% with 401–600 mCi and 77.7% with >600 mCi.

As shown in Table 1, mean FSH levels in 62 patients treated for thyroid residue were 12.0 ± 7 mU/ml, no different when compared to the mean FSH of 28 patients treated for node metastases (13.0 ± 8 mU/ml), but significantly lower (p < 0.0001) than the mean FSH (25.1 ± 16 mU/ml) of 13 patients treated for distant metastases (lung in all but one). This last group received the highest cumulative mean dose of <sup>131</sup>I (538 ± 360 mCi).

Results of longitudinal analysis of FSH performed in 21 patients who received <sup>131</sup>I doses ranging from 30 to 800 mCi in 30–100 mo of follow-up were not univocal. Six patients treated for thyroid residues or cervical nodes had no FSH change or slight increase (always comprised in the normal range) after <sup>131</sup>I administration (data not shown). Eleven patients (Fig. 5) who were primarily treated for cervical nodes had a transient increase in FSH values above the normal range 6–12 mo after the first <sup>131</sup>I treat-



**FIGURE 5.** Changes in serum FSH concentrations before and after (6–12 mo) the first and the second <sup>131</sup>I dose in 11 patients show only transient increases in serum FSH concentrations. Arrows indicate the administration of <sup>131</sup>I therapy. The broken horizontal line indicates the upper limit of normal FSH range.

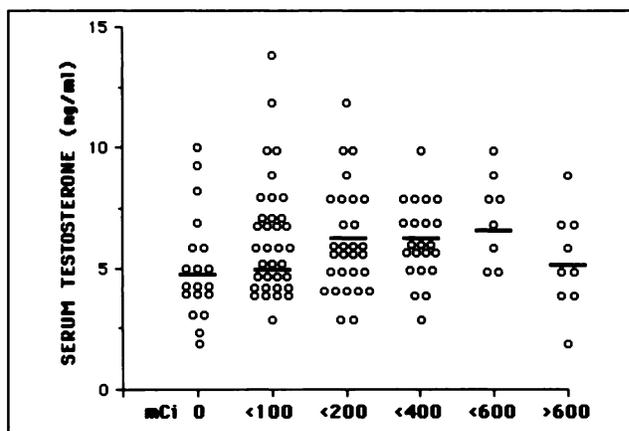


**FIGURE 6.** Longitudinal analysis of serum FSH in four patients with permanent testicular damage after several treatments with high doses of <sup>131</sup>I. Numbers in parentheses at the beginning and end of each curve indicate the total amount of <sup>131</sup>I received before the first and the last blood test, respectively. Each arrow indicates one single <sup>131</sup>I treatment (usually 100–150 mCi). The shaded area represents the normal FSH range.

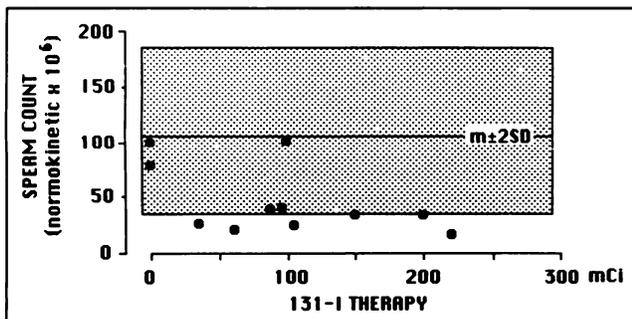
ment, but returned to normal levels after 6–10 mo. The administration of a second dose was again followed by a similar increase in FSH levels. As shown in Figure 6, four patients who were followed for a long period of time and were treated with several <sup>131</sup>I treatments for lung (n = 3) or lymph node (n = 1) metastases had an additive increase of FSH levels after each <sup>131</sup>I administration. FSH values at the end of follow-up were constantly above the normal range, thus indicating permanent damage of the germinal epithelium in these patients.

Mean serum T in untreated patients was 4.9 ± 2.3 ng/ml, not significantly different with respect to treated patients (Fig. 7). Furthermore, no correlation (r = 0.01) was found between serum T and the cumulative dose of <sup>131</sup>I received by the patient.

Sperm analysis, performed in 11 euthyroid patients,



**FIGURE 7.** Serum T levels in untreated and in <sup>131</sup>I treated patients according to the total <sup>131</sup>I dose received. Horizontal bars indicate mean T level in each group.



**FIGURE 8.** Number of normokinetic sperm/ejaculate in two untreated and in nine  $^{131}\text{I}$  treated patients who underwent semen analysis. The shaded area indicates the normal range in our laboratory.

showed minor to evident reduction of sperm motility in eight patients (Fig. 8).

Eleven patients fathered one child each after radioiodine treatment (mean dose  $269 \pm 148$  mCi). None had persistent elevation of FSH levels and no abnormality was present in their offspring.

## DISCUSSION

Spermatogonia are the most sensitive testicular cells to external irradiation and cytotoxic drugs (10,11). After  $^{131}\text{I}$  administration, the sources of radiation to the testes are blood, bladder and gut, plus an additional component from  $^{131}\text{I}$  concentrated by metastatic lesions close to the testes (mainly pelvic metastases). The estimated absorbed radiation dose by the testes after oral administration of  $^{131}\text{I}$  in euthyroid adults is 0.085 rad/mCi (5,12). Since patients with metastatic thyroid cancer are treated with  $^{131}\text{I}$  when they are hypothyroid, they have a decreased clearance of iodide, resulting in a more prolonged exposure to radiation. In this condition, the estimated radiation dose to the testis is higher (0.5–1.5 rad/mCi) (1). Thus, the cumulative radiation to the testes after a standard dose of 100 mCi is roughly 50–150 rad per treatment. Similar or even lower doses have been associated to azoospermia in experimental animals (13,14). Based on this data, our finding of an increased serum FSH concentration, the best marker of germinal cell failure, in one-third of the patients treated with  $^{131}\text{I}$  is not surprising. Although the damage to the germinal epithelium was already apparent after exposure to relatively low radiation activities derived from one single treatment, it was magnified in patients exposed to high activities resulting from the cumulative effect of repeated treatments over the years. This behavior is also confirmed by the strong correlation between serum FSH and total millicuries of  $^{131}\text{I}$  received by the patients and by the increasing proportion of patients with abnormal FSH tests in the subgroups treated with larger  $^{131}\text{I}$  doses. In our series, distant metastases were associated with higher mean FSH levels. This finding may be attributed to the higher cumulative doses of radioiodine delivered to these patients rather than to the metastatic site.

Longitudinal studies performed in 21 patients were par-

ticularly informative: each single  $^{131}\text{I}$  treatment was frequently associated with elevation of FSH levels with respect to the pretreatment value, with possible recovery in some cases. However, when repeated  $^{131}\text{I}$  treatments were administered, they were almost invariably followed by permanent elevation of serum FSH concentrations. This finding indicates that the germinal cell damage may be transient with low-dose irradiation, such as those used for treatment of thyroid residues or cervical nodes, but becomes permanent with high cumulative doses, as in patients treated for distant metastases.

We had the opportunity to perform semen analysis in a few of our patients. Although we had no pretreatment assessment in these patients, our finding of decreased sperm motility support the germinal cell damage suggested by the increased serum FSH concentrations. Both the results of serum FSH and those on sperm analysis confirm and extend previous observations of Hendelsman and Turtle (7) in a cohort of 12 men studied at a median of 12 mo after their last treatment with  $^{131}\text{I}$  for metastatic thyroid cancer. Testicular atrophy with absent spermatogenesis has been reported by Trunnell et al. (5) in three men treated with cumulative  $^{131}\text{I}$  doses of 459–820 mCi and external radiation. Two of them had large pelvic metastases able to concentrate  $^{131}\text{I}$ . Also in our series, one patient had been treated for pelvic bone metastases and he was the one with the highest elevation of serum FSH levels. This may indicate that radiation by  $^{131}\text{I}$  accumulated in metastases close to the testes is a very important additional source of radiation for the gonads.

## CONCLUSION

Our data indicate that the male gonad may be damaged after  $^{131}\text{I}$  therapy for differentiated thyroid carcinoma, particularly at high levels of delivered activity. The damage is limited to the germinal epithelium and may become irreversible. Since many subjects with differentiated thyroid cancer are young and may be willing to have children, special efforts should be made to reduce at least some of the radiation sources to the testes. As suggested by Maxon III and Smith (1), this may be achieved by keeping the patients well hydrated with frequent urination and by ensuring one or two bowel movements per day during the first 2–4 days after treatment. For patients particularly at risk for  $^{131}\text{I}$ -induced testicular damage, a long-term storage of semen obtained before  $^{131}\text{I}$  therapy should be considered.

## ACKNOWLEDGMENT

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