

## **$I^{131}$ Therapy For Hyperthyroidism: A Plea for Less Conservatism in Complicated Cases<sup>1</sup>**

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Since the advent of radioiodine therapy for hyperthyroidism there has been concern for the small proportion of patients so treated who develop permanent hypothyroidism (1,2,3, & 4). Nevertheless the absence of other more serious complications associated with surgery or antithyroid drug therapy has led to the gradual acceptance of  $I^{131}$  as the treatment of choice for hyperthyroidism in the adult (5).

Some physicians employ small doses of  $I^{131}$ , preferring to retreat rather than risk hypothyroidism (6 & 7). We would agree with those who contend that such an approach serves only to delay achieving a remission in the hyperthyroidism and simply postpones the inevitable incidence of hypothyroidism (8). Furthermore inadequate doses of  $I^{131}$  may, by delaying the control of the hyperthyroidism, lead to disastrous consequences, especially in the elderly and the thyrocardiac. In the standard references treating the subject of  $I^{131}$  therapy surprisingly little attention is paid to the desirability of higher dose  $I^{131}$  therapy in these special instances (9,10,11 & 12). Yet the problem of Post- $I^{131}$  hypothyroidism is discussed in detail by these authors.

It is the purpose of this paper to emphasize the point that prolonged hyperthyroidism in the elderly and the thyrocardiac may result in significant morbidity and even mortality. Whereas hypothyroidism, anticipated and properly managed, is an insignificant problem.

### CASE REPORTS

Case I. The patient was a 72-year-old Negro woman seen first in July of 1962 with classical, severe hyperthyroidism. The thyroid was diffusely enlarged to three times normal size. The 24-hour radioiodine uptake was 70 per cent. Five mc of  $I^{131}$  was administered. This dose was selected on the premise that retreatment was preferable to hypothyroidism. In September of 1962 the patient was hospitalized in thyroid storm. Treatment included intravenous iodides, steroids, reserpine and full blocking doses of tapazole. Prompt improvement was obtained on this regimen. The patient was discharged after 2 weeks with instructions to remain on tapazole until she was deemed ready for treatment with  $I^{131}$ . One month after discharge the patient discontinued her medications since she considered herself well. She did not return for further follow-up examination until January of 1963 when she was again hospitalized in thyroid storm and expired in spite of the usual treatment.

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(Comment: Concern for the production of hypothyroidism lead to persistence in the hyperthyroidism which ultimately proved fatal. Had the risks of hyperthyroidism to this patient been more carefully evaluated, a substantially larger initial dose of I<sup>131</sup> might have been given and this fatality avoided. One might attribute this unsatisfactory result to poor patient cooperation but it is equally likely that failure to attain prompt control of the disease was the cause of the poor cooperation. At any rate, this case exemplifies the fact that the elderly may not tolerate prolonged hyperthyroidism and should not be exposed to this risk.)

Case II. The patient was a 79-year-old white woman who, while being treated by the psychiatric service of a general hospital for extreme anxiety with agitation, was discovered to have hyperthyroidism. The PBI was 9.9  $\mu\text{g}\%$  and the 24-hour radioiodine uptake was 37 per cent. The scan revealed an hyperfunctioning nodule 3x4 cm in diameter. No cardiac involvement was noted other than a sinus tachycardia of 112 per minute. On June 13, 1960, 20 mc of I<sup>131</sup> was administered. In August, the patient developed an acute bout of atrial flutter with variable block. Congestive heart failure promptly ensued. Hospitalization with rapid digitalization, diuretic and reserpine therapy quickly improved the patient. A 24-hour radioiodine uptake was 24 per cent. The PBI was 8.5  $\mu\text{g}\%$ . The scan again revealed all the function localized to the previously noted nodule. A 50 mc dose of I<sup>131</sup> was given 5 days after admission. Two months following this therapy the patient was in sinus rhythm. All medication with the exception of digitalis was withdrawn. When last seen in October the patient was euthyroid and, except for progressive senility, well.

(Comment: The initial 20 mc dose was considered high, and given in the hope of assuring success with a single treatment in this elderly patient. The marked radioresistance of the autonomous hyperfunctioning nodule (13) was not appreciated.)

Case III. The patient is a 44-year-old Negro woman who presented in frank congestive failure. A diagnosis of rheumatic heart disease with mitral insufficiency was made. Because of a diffuse goiter twice normal in size, tremor, weight loss and heat intolerance a complicating hyperthyroidism was suspected. The 24-hour radioiodine uptake was 55 per cent. Radioiodine therapy was contemplated. Our usual dose for such a patient would be 7 mc. Because of the associated heart disease, 14 mc was given. Within 6 weeks the patient was clinically well. By 10 weeks signs of early hypothyroidism were detected and treatment was instituted with desiccated thyroid 1 grain daily. This was increased to 2 grains daily in 3 weeks and continued at that level. The patient has remained well with no additional medication for over 6 months.

(Comment: Although lifelong thyroid replacement may prove necessary this patient returned to full activity only 2 months after facing a life-threatening medical problem. A prolonged period of disability which ultimately might have terminated with the same need for thyroid medication was avoided.)

Case IV. The patient was a 59-year-old white woman complaining of nervousness and palpitation. A sinus tachycardia of 120 per minute was present and bouts of paroxysmal atrial tachycardia were confirmed. A 4 cm thyroid nodule was detected on the right side of the neck. The 24 hour radioiodine uptake was

57 per cent. Figure I is the scintigram which reveals an autonomous hyperfunctioning nodule completely suppressing function of the extra nodular thyroid tissue. 40 mc of  $I^{131}$  was administered. Reserpine 0.25 mg. q.i.d. was given for 2 weeks then t.i.d. for 2 weeks, then b.i.d. for 2 weeks and then discontinued. By 6

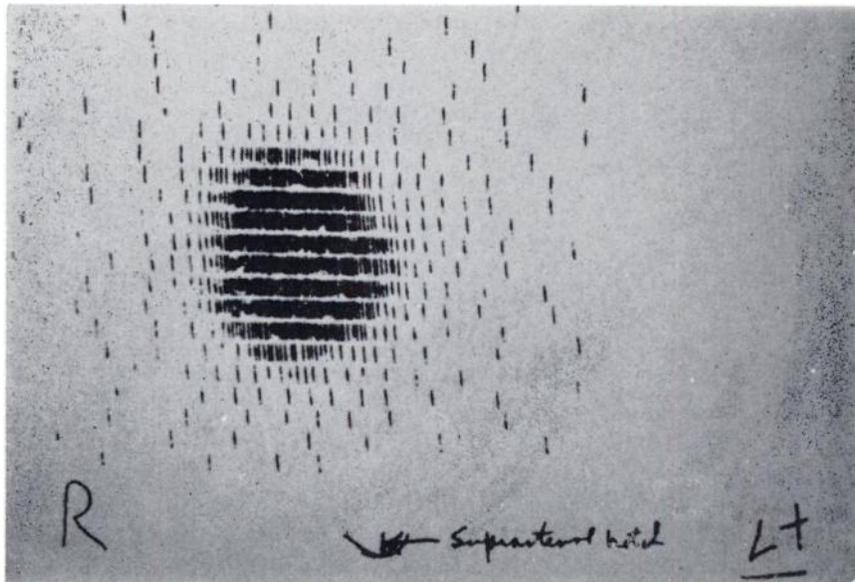


Fig. 1. Case IV  $I^{131}$  scintigram prior to  $I^{131}$  therapy revealing an autonomous hyperfunctioning nodule.

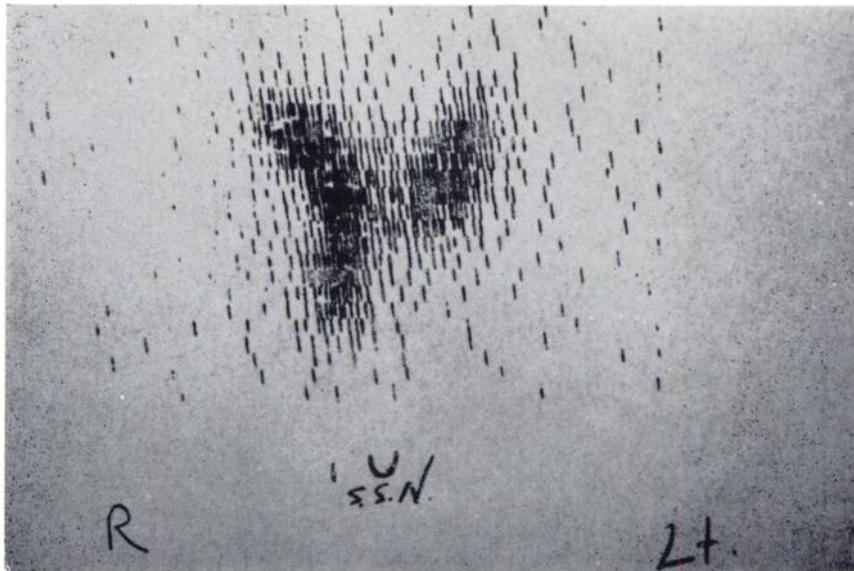


Fig. 2. Case IV  $I^{131}$  scintigram after  $I^{131}$  therapy revealing restored function in previously suppressed normal thyroid tissue.

weeks the patient was well. Fig. 2 is the scintigram 3 months after the  $I^{131}$  therapy. Note that the previously suppressed areas of the gland now function well. The 24-hour radioiodine uptake was 22 per cent.

(Comment: The large dose of 40 mc was given in consideration of the radio-resistant nature of these lesions (13). There was no fear for hypothyroidism, since the suppressed thyroid tissue could confidently be expected to function after the hyperfunctioning nodule was eliminated. The fact that the beta radiation of  $I^{131}$ , the radiation primarily responsible for the therapeutic effects of  $I^{131}$ , travels only a few mm in tissue protects adjacent suppressed thyroid from radiation damage.)

#### DISCUSSION

Unwarranted concern for post  $I^{131}$  hypothyroidism may lead to a disastrous prolongation of the hyperthyroid state. Treatment is a simple matter when anticipated and therapy is properly instituted prior to the development of a marked hypothyroid state. Regular administration of exogenous thyroid constitutes no hazard and only minimal inconvenience and expense to the patient. One must, of course, inform the patient of the necessity for lifelong administration of the thyroid, for untreated hypothyroidism would certainly be undesirable. The physician must also observe carefully for early clinical evidence of hypothyroidism to assure that treatment is promptly instituted. This is not to imply that the higher doses of  $I^{131}$  recommended in these special instances will uniformly produce permanent hypothyroidism. On the contrary, although the higher the dose of  $I^{131}$  administered, other things being equal, the greater the likelihood of hypothyroidism, nevertheless an occasional patient will still require additional  $I^{131}$  to control the hyperthyroidism. Even these few patients should experience considerable improvement.

In contrast hyperthyroidism inadequately treated may lead to severe impairment of myocardial function with intractable failure and/or arrhythmias. The effects of prolonged hyperthyroidism per se can lead to marked debility and even death.

It has been our experience as well as that of Skillern *et al* (13) that the autonomous hyperfunctioning nodule is a relatively radioresistant lesion. Fortunately adjacent and contralateral normal thyroid tissue is suppressed by the hyperfunctioning nodule and thus does not concentrate  $I^{131}$ . Since the principal therapeutic effects of radioiodine result from beta radiation, which travels only a few millimeters in tissue, function in the normal thyroid tissue is preserved and hypothyroidism is no concern.

The report of Eller *et al* (9) that patients with toxic nodular goiter do not require larger doses of  $I^{131}$  to achieve a successful result does not contradict the above position. These authors made no attempt to differentiate patients with diffuse hyperfunction and incidental nodules (a common disorder) from those with autonomously hyperfunctioning lesions (an uncommon disorder) as defined by Miller and Hamburger (14) and others (15), and to which the remarks of Skillern (13) were addressed. We agree that the former group will be treated successfully with nearly conventional doses of  $I^{131}$ . It is the autonomous hyperfunctioning nodules which require a significantly larger dose.

Our criteria for consideration of larger dose  $I^{131}$  therapy are as follows:

1. The thyrocardiac. In this group we include those patients who have experienced congestive heart failure or cardiac arrhythmias (other than sinus tachycardia) while hyperthyroid.

2. The elderly patient or the patient with concomitant disease in whom one might anticipate prolonged hyperthyroidism would carry an extra hazard.

The patient with an autonomous hyperfunctioning nodule who fulfills the above criteria is particularly suited to high dose I<sup>131</sup> therapy since hypothyroidism will not occur.

In our clinic double the usual dose of I<sup>131</sup> is given patients who qualify for extra dose therapy.

The following considerations are weighed in the calculation of the dose of I<sup>131</sup> for the *usual* hyperthyroid patient.

1. Size of the gland. The larger the gland the larger the dose.

2. Physical characteristics of the gland on palpation. Multinodular glands are treated with slightly more I<sup>131</sup> than diffuse glands even though function is diffuse in both cases. In patients with proved autonomous hyperfunctioning nodules (14) we administer a dose adequate to deliver 15-20 mc I<sup>131</sup> to the nodule. This will usually require 30-50 mc.

3. Age of the patient. Younger patients are given a slightly lower dose since permanent hypothyroidism would require treatment for a proportionately longer time.

4. Severity of the hyperthyroidism. More severely hyperthyroid patients are given more I<sup>131</sup> since the disease carries a greater risk than the possibility of hypothyroidism.

(Note: We no longer believe that the 24 hour radioiodine uptake is a factor of major significance in the calculation of the dose in I<sup>131</sup> therapy. In the past we had administered higher doses to those with lower uptakes and vice versa. With this approach we observed a higher incidence of Post I<sup>131</sup> hypothyroidism in the patients with the lower uptakes and a higher incidence of the necessity for re-treatment in the patients with higher uptakes. The uptake alone does not give information about the duration of retention of the therapeutic dose, and the latter would bear more directly upon the radiation delivered. A possible explanation of our observations might be that patients with higher uptakes have more rapid turnover, hence the effects of uptake and turnover would cancel one another. This is an area in which further investigation would be informative.)

On the basis of the above considerations the usual dose of I<sup>131</sup> employed in patients with diffuse hyperfunction of the thyroid is from 5 to 12 mc, with an average dose of 8 mc. These doses are similar to those proposed by most authorities (8,9,16). Patients with diffuse hyperthyroidism satisfying our criteria for a larger I<sup>131</sup> dose are given double this estimated dose.

Silver *et al* have recently stressed the desirability of producing a prompt remission in the hyperthyroidism of patients with associated heart disease (16). Their average dose for cardiacs as 11.5 mc compared to 7 mc for the entire series of hyperthyroids. However, close inspection of their data reveals that 54 per cent of their cardiacs received 8 mc or less, and 70 per cent received 11 mc or less. Thus only 48 per cent of these patients were treated successfully with a single dose of I<sup>131</sup>. In excess of 25 per cent required 3 or more doses. These results are not too different from those with their uncomplicated patients.

Hence even where an awareness of the problem exists apparently there remains a reluctance to depart significantly from the hallowed path of conservatism.

#### SUMMARY AND CONCLUSIONS

1. Where a prolonged hyperthyroid state would constitute a special hazard, consideration should be given to therapy with large doses of  $I^{131}$ . A dose twice that usually employed is suggested for diffuse hyperthyroidism. In patients with autonomous hyperfunctioning nodules a dose adequate to deliver 15 - 20 mc  $I^{131}$  to the nodule is employed.

2. Post  $I^{131}$  hypothyroidism, if anticipated and promptly treated, is a relatively minor therapeutic problem, causing only insignificant inconvenience and expense to the patient.

3. Prolonged hyperthyroidism may be lethal in the elderly, the debilitated and the thyrocardiac.

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