EXPERIENCE WITH RADIOACTIVE IODINE IN THE TREATMENT OF HYPERTHYROIDISM

GEORGE CRILE, JR., M.D., Department of General Surgery,
E. PERRY McCULLAGH, M.D., Department of Endocrinology
and
OTTO GLASSER, Ph.D., Research Division

History

THE use of radioactive iodine in the treatment of hyperthyroidism was initiated seven years ago by Hertz and Roberts[1] in Boston and Hamilton and Soley[2] in San Francisco. The iodine was made in cyclotrons and was not available for general use. Two years ago, however, the Atomic Energy Commission released I^{131}, prepared in the atomic pile at Oak Ridge, to any institution with a committee composed of a qualified radiologist, surgeon, and internist. Since then radioactive iodine has been used extensively throughout the country in the treatment of hyperthyroidism. This paper is a report of the results obtained at the Cleveland Clinic in the treatment of 105 patients with hyperthyroidism.

The Nature of I^{131}

I^{131} differs from many radioactive substances in that its half life, or the length of time it takes to expend one half of its potential radioactivity, is only eight days. At the end of a month most of the radioactivity is gone, and by two or three months practically none remains. Since the radioactivity of I^{131} disappears in a short time there is no danger of later ill effects due to retention of a long-lived radioactive substance in the body.

A second characteristic of I^{131} which increases the safety of its use in the treatment of hyperthyroidism is the fact that its radiation is largely in the form of beta rays. These rays do not penetrate the tissues for more than 1 or 2 mm., about the thickness of a thumbnail. Since the radioactive material is concentrated in the thyroid and the beta rays do not penetrate far enough to damage tissues outside of the thyroid, no demonstrable damage is done to tissues outside of the thyroid gland. Even when doses totaling 100 times as much as the average therapeutic dose are given no changes are demonstrable, either histologically or functionally, in the kidneys, bone marrow, testes, or other organs.[3] Neither tetany nor damage to the recurrent laryngeal nerves has been observed following its use. Thus I^{131}, given in average doses, does not induce any immediate reaction other than destruction of functioning thyroid tissue.

A third property that makes I^{131} well adapted to treating hyperthyroidism is the fact that the chemical and physiologic behavior of the radioactive element is exactly the same as that of ordinary iodine. Therefore the normal thyroid

gland takes up and stores I^{131} the same way it takes up stable iodine and in hyperthyroidism the overactive thyroid takes it up even more rapidly and concentrates it in even greater amounts. Thus it is estimated that in patients with hyperthyroidism I^{131} is concentrated in the thyroid in amounts 10,000 times greater than in the blood or in any other organ.[4] Each gram of thyroid tissue contains 10,000 times as much I^{131} as does a gram of any other tissue in the body and consequently receives a proportional intensity of radiation. The I^{131} is stored in the thyroid until it has lost the major part of its radioactivity after which most of it is excreted by the kidneys as ordinary (nonradioactive) iodine.

Hyperthyroidism is caused by hypersecretion of the iodine-containing hormone thyroxine. The thyroid epithelial cells pick up iodine from the blood and convert it into thyroxine. If the iodine that these cells take up is radioactive, the cells are selectively inactivated or destroyed by the radiation. I^{131} is concentrated in those parts of the thyroid that are functioning most actively. In hyperthyroidism the parts of the gland that are responsible for the hyperthyroidism take up and store I^{131} and are inactivated or destroyed, whereas any inactive parts of the thyroid take up virtually no I^{131} and are spared. In short radioactive iodine selectively inactivates those cells of the thyroid that are overactive and spares those that are not functioning. Theoretically, therefore it should be possible to control hyperthyroidism in all cases if adequate amounts of I^{131} are given.

The amount of irradiation that is received by the thyroid after an average dose of radioactive iodine is much greater than the amount of irradiation that can be given by roentgen therapy without damage to the skin. An average dose of 4 mc.* of I^{131}, given to a patient with Graves' disease and a goiter estimated to weigh 50 Gm. which takes up 50 per cent of the administered dose, delivers the equivalent of 4000 r to the thyroid.

Although there is little experimental and no clinical evidence to suggest that intensive irradiation of this nature will be carcinogenic, the possibility warrants consideration. We believe it unlikely that the incidence of carcinoma of the thyroid will be significantly altered by treatment with radioactive iodine. In patients treated as long as seven years ago carcinomas have not developed and there is no clinical or experimental evidence that they will develop (Hertz and Roberts[1]). It is therefore safe to prescribe I^{131} for older patients with hyperthyroidism or for patients with short life expectancies.

Although we also believe that it is safe to treat younger patients with I^{131} we are unable to prove its ultimate safety nor will anyone be in a position to do so for fifty years. For this reason the arguments of those who foresee trouble cannot be refuted. One can only point out that the same reasoning applies to any new therapeutic agent, the ultimate effects of which cannot be forecast. In the unlikely event that patients treated with I^{131} should show a tendency to develop carcinoma of the thyroid, prophylactic thyroidectomy still would be a practical method of avoiding this complication.

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Technic of Treatment

I^{131} is flown from Oak Ridge once every two weeks. It is measured and divided into doses of 2, 4, 6, and 8 mc. The I^{131} is in the form of sodium iodide and is dissolved in water. It is colorless and tasteless. The amount of I^{131} contained in the average therapeutic dose is equivalent to the iodine in 1/50,000 of a drop of Lugol's solution.

From the patient's standpoint, treatment consists in merely drinking a third of a glass of what appears to be plain water. From two to four hours later the radiation over the thyroid is measured with a Geiger counter so that an estimate can be made of the amount of I^{131} the thyroid has picked up and of the amount of radiation it will receive. The patient then returns home. There is no reaction except in cases where very large doses are given as in the treatment of cancer of the thyroid. Neither radiation sickness nor irritation of the thyroid area is observed after the ordinary dose.

Further medical observation is not required for two months. At this time the basal metabolism is rechecked and the patient is either released with the hyperthyroidism controlled or is given a second dose. About half of the patients with Graves' disease become symptom free after a single treatment and most of the remainder following a second. Patients with large adenomatous goiters may require three or four treatments before the hyperthyroidism is completely controlled.

From the physician's standpoint the problem of measuring the dose and protecting the person handling the I^{131} is more complicated. These aspects of treatment should be delegated to qualified radiologists.

Dosages*

The initial dose of I^{131} for patients with Graves' disease is one-half to two-thirds of the average dose required to effect a cure. If 4 mc. are given about half of the patients are well after a single treatment and only 10 per cent develop even a transitory hypothyroidism.

The dose employed in the second treatment depends on the response of the hyperthyroidism to the first treatment. If the basal metabolic rate is unchanged two months after the first treatment, the dose for the second treatment may be double the first. If the basal metabolic rate has fallen half way to normal the first dose is repeated. If the basal metabolic rate has dropped two-thirds of the way to normal, half of the original dose is given. But if there is only slight residual hyperthyroidism, or if the basal metabolic rate is at the upper limit of normal, no further treatment is given, because maximum effects of a single dose sometimes are not apparent for three or four months.

In Graves' disease the average initial dose is 4 mc. unless the thyroid is unusually large and the hyperthyroidism severe in which case 6 or even 8 mc. may be given. Our experience has indicated that the dose required to control

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the hyperthyroidism of Graves' disease is dependent more upon the severity of the hyperthyroidism than upon the size of the gland. If the hyperthyroidism is severe it will be necessary to inactivate the thyroid more completely and larger doses of I^{131} are required. If the hyperthyroidism is mild, a smaller dose will suffice to reduce the excessive secretion of thyroid hormone to normal.

In nodular goiter with hyperthyroidism the average initial dose is 8 to 15 mg., depending on the size of the gland. Since the take-up of iodine in nodular goiters is irregular many areas do not receive significant amounts of radiation. It is therefore difficult to induce hypothyroidism in patients with nodular goiters and it is difficult to control the hyperthyroidism except by giving large doses and repeating them several times. As the most active areas are inactivated the less active ones begin to function. When treatment is repeated these new areas absorb I^{131} and in turn are inactivated. Thus the thyroid is inactivated area by area, until normal function is restored.

Rationale of Treatment with I^{131}

It requires about 30 mc. of I^{131} to induce myxedema in a patient with a normal thyroid, yet 3 or 4 mc. may induce hypothyroidism in a patient with Graves' disease. This observation parallels our experience in the surgical treatment of hyperthyroidism. A partial thyroidectomy for Graves' disease in which 5 Gm. or more of thyroid is left, often is followed by myxedema, whereas even the most radical subtotal thyroidectomy performed upon patients with normal thyroids or with nodular goiters causes no more than a transitory lowering of the basal metabolic rate. Hence there must be factors other than the amount of thyroid tissue remaining after either thyroidectomy or irradiation that influence the development of hypothyroidism.

Patients with Graves' disease, even without treatment, occasionally will enter a remission and may even develop hypothyroidism. Such cycles of thyroid activity are not so much dependent upon the amount of thyroid tissue present as they are upon the activity of that tissue. In Graves' disease the functional activity of the thyroid is dependent primarily upon the unknown factors that cause the underlying disorder.

We do not therefore believe it is possible to cure Graves' disease either by irradiation or by thyroidectomy without occasionally causing hypothyroidism. Any therapeutic measure which interrupts the vicious circle of thyroid stimulation responsible for the development and maintenance of Graves' disease may effect so complete a suppression of thyroid stimulation that the thyroid remnants will not function. If the hyperthyroidism is controlled no one can predict in any single cases whether the thyroid will function normally, whether hyperthyroidism will later recur, or whether hypothyroidism will develop.

These considerations suggest that the treatment of hyperthyroidism with I^{131} is as empiric as thyroidectomy. Regardless of the care that is exerted in attempting to standardize the amounts of radiation given to each gram of thyroid tissue, in some cases hypothyroidism will occur while other patients will prove refractory to the ordinary doses and will require more than the

average amount of irradiation. Therefore we believe that the best way to estimate the proper total dose is by observation of the physiologic response to a small initial dose. The incidence of hypothyroidism has been lower following this method of treatment than when the estimated full therapeutic dose was given.

Advantages of Treatment with I^{131}

The cost of controlling hyperthyroidism with I^{131} is much less than that incurred by the average patient for professional and hospital services incident to a thyroidectomy and is less than that of a year's treatment with an antithyroid drug.

Hospitalization, loss of work, and the inconvenience involved in repeated visits to the physician are avoided. There is no mortality, no morbidity and no discomfort following its use. We have not yet seen recurrences of hyperthyroidism. The incidence of hypothyroidism so far has been about the same as that following an adequate thyroidectomy—9.5 per cent for patients with Graves' disease and none for those with nodular goiter with hyperthyroidism.

Results of Treatment with I^{131}

In the past year 105 patients with hyperthyroidism have been treated at the Cleveland Clinic with I^{131}. Only 34 patients have been treated long enough to allow three months' observation. Since it takes two to four months for the full effect of treatment to become apparent, the more recent cases are not included in the summary of results. Two elderly patients died within two months after treatment, 1 of a cerebral hemorrhage and 1 of an acute pulmonary disease unrelated to the treatment. One patient decided two weeks after the first treatment to be operated upon elsewhere and did not return for observation. All other patients have been followed from three to ten months.

Results of Treatment of Graves' Disease

In 19 of the 21 patients with Graves' disease the hyperthyroidism has been completely controlled and the goiters have disappeared.

1. The average basal metabolic rate has fallen from +45 per cent before treatment to 0 per cent.
2. Control of the hyperthyroidism was effected by 1 treatment in 12 cases, by 2 treatments in 6, and by 3 treatments in 1.
3. The hyperthyroidism was well controlled in an average of three months after the first treatment.
4. The average total dose was 6.7 mc.
5. The average size of the thyroids has decreased from an estimated weight of 61 Gm. to 27 Gm.

One patient is improved three months after a single treatment, and has received a second.

The last patient of the group has received 9 mc. in 2 treatments and is no better. In this case the hyperthyroidism is atypical and the hypermetabolism does not appear to be caused by overactivity of the thyroid gland. Two thyroidectomies performed elsewhere did not control the patient's symptoms, no thyroid is palpable, the thyroid takes up only 25 per cent of the administered I^{131}, and sections of the thyroid removed previously showed no hyperplasia.

Results of Treatment of Nodular Goiter with Hyperthyroidism

In 5 of the 10 patients with nodular goiters the hyperthyroidism has been controlled and the goiters are smaller.

1. The average basal metabolic rate has fallen from +39 to +6 per cent.
2. Control of the hyperthyroidism was effected by 2 treatments in 3 cases and by 3 treatments in 2.
3. The hyperthyroidism was well controlled in an average of five months after the first treatment.
4. The average total dose was 15.4 mc.
5. The average size of the thyroid has decreased from an estimated weight of 123 Gm. to 70 Gm.

Four patients are improved and are still under treatment.

One patient shows no improvement after 1 treatment and is still under treatment.

The patients whose hyperthyroidism has been controlled by treatment with I^{131} appear to be as well as those whose hyperthyroidism has been controlled by thyroidectomy. The diffuse goiters of Graves' disease disappear and are no longer palpable. Nodular goiters usually shrink, but do not disappear. When the hyperthyroidism is controlled auricular fibrillation tends to revert to normal rhythm just as after thyroidectomy.

There has been no radiation sickness and no exacerbation of the hyperthyroidism. No symptoms of local irritation have been observed. There has been no tetany, no change in levels of blood calcium, no change in menstruation, no depression of hematopoiesis, and no alteration in renal function. One patient with a nodular goiter and moderate hyperthyroidism had had one kidney removed and had a hydronephrosis of the other. The level of blood urea was 80 mg. per cent before treatment. Following administration of 11 mc. of I^{131} the hyperthyroidism was controlled and there was no change in renal function or retention of nitrogen.

Two patients with Graves' disease developed hypothyroidism four months after treatment with 8 mc. and 3 mc. of I^{131} respectively. One of these patients already appears to be recovering. In the majority of cases of hypothyroidism that have been reported following treatment with I^{131} the patients have made a spontaneous recovery.[5]

Summary

1. During the past year 105 patients with hyperthyroidism have been treated with I^{131}.

2. Radioactive iodine is a simple, effective, and apparently a safe method of treating patients with hyperthyroidism.

3. Neither hospitalization nor supervision of the patient is required and the cost of treatment is less than that of thyroidectomy or prolonged medical treatment.

4. In 90 per cent of the cases of Graves' disease hyperthyroidism is controlled in two to four months by 1 or 2 treatments. Ten per cent of the patients may require a third treatment.

5. Diffuse goiters disappear after treatment and the symptoms of hyperthyroidism are as completely and effectively controlled as by an adequate thyroidectomy.

6. The only complication which has occurred following treatment with I^{131} is hypothyroidism, usually transitory, which occurs in about the same proportion of cases as after thyroidectomy.

7. Hyperthyroidism associated with nodular goiters is more difficult to control than the hyperthyroidism of Graves' disease, requires larger doses of I^{131} and more treatments.

8. Although nodular goiters become smaller after treatment with I^{131} they do not disappear.

9. I^{131} is the preferred treatment for elderly patients with hyperthyroidism, for those who are poor surgical risks, and for those with recurrent hyperthyroidism.

10. I^{131} appears to be an acceptable method of treatment for younger patients with Graves' disease but final evaluation of its safety in young patients will require many years of observation. At the present time we are employing it in selected cases.

11. I^{131} is not recommended in the treatment of hyperthyroidism occurring in young patients with nodular goiters.

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