Cleveland Clinic Quarterly

Volume 35 April 1968 No. 2

Advantages of radioiodine over thyroidectomy in the treatment of Graves' disease

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ONE of the authors of this paper is a surgeon with long experience in the surgical and medical treatment of hyperthyroidism, and the other is an internist, well versed in the use of antithyroid drugs, but both agree that radioiodine (^{131}I) is the safest and most effective treatment for Graves' disease. Although this opinion is shared by many physicians and surgeons interested in thyroid disease, in two recent papers[1, 2] it was stated that thyroidectomy was preferable to ^{131}I. Because this conclusion appears to be based on misunderstandings or misinterpretations of facts, the purpose of this report is to clarify five of the key points in the controversy.

1. It is sometimes assumed that in a high proportion of cases it is necessary to give repeated doses of ^{131}I and that "... this often requires doses in excess of 100 mc and four or more doses." [1]

Although hyperthyroidism in patients with large nodular goiters is often resistant to control with ^{131}I, the type associated with Graves' disease is usually controlled by a single dose of from 5 to 14 mc. For example, 63 percent of 3,285 patients with Graves' disease treated with ^{131}I at the Cleveland Clinic between 1947 and 1966 were cured by single such treatments. Fewer that 1 percent of the patients required four or more treatments, and only two of the 3,285 required doses in excess of 100 mc.

Since large hyperfunctioning nodular goiters do not shrink much after ^{131}I treatment, and usually require large doses of ^{131}I, most clinicians prefer

to have them treated by thyroidectomy if there is no increased operative risk.

2. Ever since it became apparent that there is a high and progressive incidence of hypothyroidism after treatment with ^{131}I,[3] the seriousness of this complication has been overemphasized. Some surgeons have even gone so far as to speak of the great difficulties involved in correcting the "intractable myxedema" that occurs after treatment with ^{131}I. No such problems have arisen in connection with the treatment of post–^{131}I myxedema at the Cleveland Clinic, nor has it appeared to respond to treatment any less completely than hypothyroidism due to other causes.

Although hypothyroidism is a common occurrence after treatment of Graves' disease with ^{131}I, it occurs also after thyroidectomy. When radical subtotal thyroidectomies have been performed, the incidence of hypothyroidism, in our experience 20 years ago, was as high as 25 percent, with a recurrence rate of less than 5 percent. When conservative operations have been performed, the incidence of hypothyroidism has been as low as 4 percent, but in the latter cases the incidence of recurrent hyperthyroidism was 15 percent.

What is not generally appreciated is that, as Nofal, Beierwaltes, and Patno[4] have emphasized, the incidence of hypothyroidism in from 1 to 16 years after thyroidectomy has been as high as 28 percent, and each year 1.7 percent of the previously euthyroid patients have become hypothyroid. These figures, although lower than the 51 percent reported to occur in a similar series of patients in whom hypothyroidism developed after treatment with ^{131}I, and lower than the 2.8 percent per year of ^{131}I-treated patients in whom hypothyroidism will continue to develop each year, are still significantly high. The point is that hypothyroidism is as much the end point of Graves' disease as it is of ^{131}I treatment. This means that regardless of how the hyperthyroidism of Graves' disease is treated, thyroid deficiency may ensue. For this reason, patients who have had Graves' disease must be examined periodically no matter how their hyperthyroidism had been controlled.

In preference to periodic examinations we have for the last three years alerted all ^{131}I-treated patients in advance to the risk of hypothyroidism, and instructed all of them to take 2 gr of desiccated thyroid or 0.2 mg of l-thyroxine daily for the rest of their lives after the hyperthyroidism has been controlled. The cost is $6.50 and $9.00 a year, respectively. This is less than the cost of a basal metabolism test, a determination of the protein-bound iodine, or an annual clinical examination. In addition, a letter certifying the diagnosis of Graves' disease and the treatment with radioiodine is sent to the patient so that any physician who treats the patient will never inadvertently stop treatment with the thyroid hormone. We believe that the

same procedure should be followed for all surgically treated patients with Graves' disease. Other investigators[5, 6] have tried several ways to reduce the incidence of hypothyroidism after ^{131}I treatment. These are based on the belief that the incidence of hypothyroidism may be directly related to the dosage of ^{131}I. Thus, by decreasing the amount of ^{131}I to one half of previous doses, and using iodide[5] and antithyroid[6] concomitantly, it has been shown that the immediate incidence of hypothyroidism after ^{131}I treatment can be decreased. Further observation will be necessary before the validity and practicality of this approach can be determined, since the incidence of hypothyroidism is likely to increase further in another 10 to 20 years, if the experience with surgically and other ^{131}I-treated patients is any guideline as discussed previously.

3. A recent editorial[1] implied that ^{131}I causes cancer of the thyroid, and stated that "... several recent reports indicate that benign and malignant thyroid tumors may follow radioactive iodine therapy for hyperthyroidism in childhood."

Although a few benign nodules appeared in the series of children reported by Sheline and associates,[7] only two such nodules appeared in 256 adults treated by ^{131}I. No suppressive therapy was given routinely and no nodules appeared in children who were given enough ^{131}I to make them hypothyroid. The authors[7] wisely advise giving enough ^{131}I to induce hypothyroidism, which is then corrected by exogenous thyroid hormone. We have observed no benign nodules or carcinomas in our series of 40 children with Graves' disease treated with ^{131}I, and whose progress has been followed for from 1 to 15 years.[8]

In children, only two malignant tumors have been reported[7] to have developed after ^{131}I treatment. One child, many years before such treatment, had received repeated small doses of diagnostic radiation to the neck. The papillary carcinoma was diagnosed only two years after the treatment of Graves' disease with ^{131}I, making it likely that the tumor resulted from the earlier radiation rather than from the ^{131}I. The other child had an "invasive adenoma" of questionable malignancy. Radioiodine has not been reported to have caused cancers in adults.

4. Although cancers of the thyroid have been induced in rats by giving small doses of ^{131}I followed by thiouracil, the benign and malignant tumors that will develop in rat thyroids after prolonged treatment with thiouracil do not develop when large doses of ^{131}I are given.[9] Irradiation in doses so small that the reproductive power of the thyroid cell is not inhibited, predisposes to cancer, as in the case of small doses of radiation given to an infant for an enlarged thymus. Large doses, in contrast, such as those that are used in the treatment of hyperthyroidism, suppress the ability of the thyroid cells to divide. That is why hypothyroidism is so common after

treatment with ^{131}I, and also why the recurrence rate of hyperthyroidism (1 in 200 in our series) is lower than in surgically treated patients. If a cell cannot divide, even when stimulated by thyroid-stimulating hormone (TSH), it cannot give rise to a mutant cancer cell. For this reason, large doses of ^{131}I, followed by lifelong suppression of TSH by feeding of thyroid hormone, are safer than small doses given without suppression.

5. It has been said that "... many centers list many thousands of consecutive operations for hyperthyroidism with no mortality and extremely low morbidity and complication rates." [1]

If the above statement is based on a recent review by Plested and Pollock,[10] the numbers of patients treated for hyperthyroidism in the series cited were 30, 12, 196 (with two deaths before 1933), 236, 138, and 261. Each of these is a separate series that could have started at the time of the last death and ended at the time of the next. Perhaps there are many unreported series in which the mortality after operations is high. Certainly the small series that were cited by Plested and Pollock[10] and which include the experiences of major clinics, the competence of whose surgeons in the treatment of hyperthyroidism is of the highest order, cannot justify the statement that "many thousands of consecutive operations" have been done without mortality.

At the Cleveland Clinic, one of us (G. C., Jr.) has had three deaths in a consecutive series of 3,000 operations for benign goiters. One patient was a 59-year-old woman who died on the operating table of cardiac arrest due to coronary occlusion, proved at autopsy. One was a 50-year-old man, with moderate emphysema, who two days after operation died of a totally unexplained respiratory failure. The recurrent nerves were proved to be intact by laryngeal examination and at autopsy. The third patient, a man of 60 years of age, four hours after operation died as a result of a ligature cutting through a sclerotic inferior thyroid artery. None of these patients was considered preoperatively to present a poor risk, yet in each case the causal relationship of operation to death is undeniable. Operations and anesthesia, especially in 'high-risk' patients, involve hazards that treatment with ^{131}I avoids. It is perhaps for this reason that a significant further decrease in the national death rate due to hyperthyroidism has occurred since ^{131}I has been used widely. In our series of 3,285 patients with hyperthyroidism due to Graves' disease, there have been no deaths during treatment despite the fact that the group included many so-called high-risk patients.

Although the incidence of permanent parathyroid tetany and of vocal cord paralysis is less than 1 percent when thyroidectomies are done for benign goiters by experienced thyroid surgeons, this does not imply that such results have been obtained in the community at large. A survey of the results of thyroid operations in all hospitals of a large community, and

a careful progress study of the patients treated there, to determine blood calcium values and the functioning status of the vocal cords would be the only way to assess accurately the true mortality and morbidity of thyroidectomy. Until this is done, it is not possible to make judgments based on small, selected series, or even on large series of patients from specialized medical centers.

SUMMARY AND CONCLUSION

The statement, "... surgical thyroidectomy appears to offer significant advantages over any other form of treatment," [1] is valid in so far as it applies to patients with hyperfunctioning nodular goiters, but it is difficult to substantiate when applied to the treatment of Graves' disease. The only complication of adequate treatment with radioiodine (^{131}I) is hypothyroidism, and this can be easily, inexpensively, and completely prevented by prophylactic feeding of desiccated thyroid. We concur with the words of Dunn and Chapman,[3] who were among the first to recognize the progressive increase of hypothyroidism after treatment of Graves' disease with ^{131}I, "... we continue to regard radioiodine as the most effective and probably the safest treatment for hyperthyroidism."

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