TEACHING EDITORIAL

# The Role of Radioiodine Treatment in Childhood Hyperthyroidism

When radioactive iodine treatment of hyperthyroidism was introduced in the early 1950's, its use was limited initially to patients over the age of 45 because of the potential hazards of radiation. If radioactive iodine were to be introduced today as a new form of radiation therapy, it would, as a new radiopharmaceutical, require prior approval by our current complex governmental and institutional drug review structure. As treatment for a nonmalignant disease for which alternative effective forms of therapy are available, where therapeutic outcome is unpredictable, and where its use has a high probability of inducing another disease (hypothyroidism), it is likely that approval for clinical use would be granted only with considerable reluctance.

Nevertheless, after 30 yr of use in almost a million hyperthyroid patients, I-131 is today considered to be the most effective and efficient therapy available for the definitive management of hyperthyroidism in *adults*. There is reason for confidence in its safety, since studies of large numbers of patients with long and almost complete follow-up have not shown any increase in leukemia or thyroid cancer, and no obvious birth defects or genetic changes have appeared in the offspring of patients treated with I-131 (*1*,*2*). As a result, the age at which radioiodine is routinely used as the primary form of treatment for hyperthyroidism has gradually been lowered to 30, and in many centers it is used as initial treatment for most patients over the age of 21. It is in this context that the authors of a paper published in this issue of the *Journal* propose the routine use of I-131 in children and adolescents (*3*).

Freitas and his coworkers, with an extensive background in the treatment of hyperthyroid children, point out the problems and risks of surgery and antithyroid drugs in this group of patients. They report the results of treatment with I-131 of 51 hyperthyroid patients under age 18 (only 4 under age 12), re-examined a mean of 14.6 yr later without apparent deleterious findings. They conclude that ". . . . I-131 therapy. . . in children is safe and effective, and that it should be the preferred mode of treatment." This is an important recommendation for a significant change in therapeutic strategy, and their well-presented argument and data deserve and require thoughtful consideration.

Since the safety of radioiodine use in the treatment of hyperthyroid adults is reasonably established, it is appropriate to consider whether that experience can be transferred safely to children. Factors that require specific examination in children include somatic effects of radiation from both external beam and internally deposited radioisotopes, possible genetic and other consequences, efficacy as a therapeutic modality, and available therapeutic alternatives.

Data accumulated over the last 20 yr have demonstrated that external radiation to the head, neck, and mediastinum of children causes a high incidence of benign and malignant thyroid nodules that occur with a latent period of 5 to 35 yr after radiation doses that ranged from 6 to 1200 rads (*4*). Because of factors including differences in the rate at which the radiation is delivered by I-131 and its nonhomogeneous distribution in the thyroid, the neoplastic potential of this radionuclide may be considerably different from external beam radiation (*5*). One estimate suggests that I-131 could reasonably be assumed to be 1/20 as "effective" as external radiation therapy in the induction of thyroid nodules (*6*).

Also relevant is the experience of two groups of Marshall Islanders accidentally contaminated by fallout from a thermonuclear detonation. Although no thyroid nodules appeared until 9 yr after exposure, now 25 yr later, 66% of those under age 10 and 15% of those over age 10 at time of exposure have developed thyroid lesions (*7*). Four thyroid cancers have occurred (two in individuals under age 18 at time of exposure), appearing from 11 to 17 yr after exposure. Although it now appears likely that some of these individuals may have been hypothyroid earlier than recognized, few of them received thyroid hormone

until some years after exposure (*7*). More than half of the internally deposited radiation (estimated at 300 to 1000 rads in children) was due to short-lived isotopes of iodine other than I-131, which produced a risk factor more comparable to x-ray.

Studies of the results of radioiodine treatment of hyperthyroid children are few—the paper in this *Journal* brings to about 400, the reported number so treated and re-examined at a later date. Although the results of these studies are generally reassuring, they vary considerably in important particulars such as duration and completeness of follow-up, administered radioiodine dose, and incidence of hypothyroidism. One study is of particular interest not only because its authors found a relatively high incidence of thyroid nodules, but also because the patients appear to have received less radioiodine than in the other studies.

Sheline et al. (*8*) in their report on the late results of radioiodine treatment of 256 patients with toxic diffuse goiter found that eight had developed thyroid nodules between 5 and 14 yr after treatment. Significantly, six of the eight patients who developed nodules were under age 17, and four of the eight were under age 10 at the time of radioiodine administration. Relatively small amounts of radioiodine were used in the treatment of these patients, and none developed obvious hypothyroidism or was considered to require thyroid hormone treatment. These data, in part, have led to the suggestion that radioiodine-treated hyperthyroid children are ". . . . two to three times as susceptible as adults to radiation induced benign thyroid nodules" (*6*).

Sheline's patients received an average of 2 to 4 mCi of I-131 in contrast to those of Freitas' who received a mean of 14.1 mCi, which resulted in 92% hypothyroidism at follow-up 14.6 yr later, when no thyroid nodules were found. In a large series of hyperthyroid adults treated with radioiodine in sufficient dose to cause a high incidence of late hypothyroidism (*9*), at follow-up examination, a mean of 8 yr after treatment, considerably fewer thyroid nodules were found than were expected (*2*).

The potential of radioiodine for causing thyroid neoplasia in man might be expected in view of studies that show such tumors are induced in rats by the administration of small, but not large, amounts of I-131 (*5,10,11*). Continued stimulation of the thyroid by elevated levels of TSH facilitates the growth of such neoplasms, and thyroid hormone administration or hypophysectomy will inhibit thyroid cellular hypertrophy (*12*). This, and other experimental data provide the rationale for the clinical strategy of early and continuous thyroid hormone administration in suppressive doses to those individuals at risk of developing thyroid neoplasms following radiation.

It seems likely that the low incidence of thyroid neoplasia found in adults following radioiodine therapy is due to the fact that thyroid follicular cells are seriously damaged, if not destroyed, by radiation, and few cells remain to undergo neoplastic change. It therefore seems advisable to recommend that if radioiodine is to be used in children, it be used in sufficient amounts to ensure complete destruction of the thyroid gland and that replacement hormone be started immediately and continued for life.

Increasing the amount of radioiodine administered in order to ensure the destruction of the thyroid gland has another consequence, however, and that is the delivery of a larger radiation dose to the blood, marrow, and gonads of the patient. Few studies of the effects of I-131 therapy report the radiation dose received by the blood or, for that matter, the thyroid gland. Green measured the blood radiation dose following a *single* radioiodine treatment and found it averaged 8.4 rads, but a large group treated to euthyroidism was found to have received an average of 16.6 rads to the blood (*13*).

Most of the children in Freitas' study had been receiving antithyroid drugs, and most received them until shortly before radioiodine was to be administered. The use of antithyroid drugs depletes the thyroidal iodine pool, a situation that has been shown to increase the level of the $PB^{131}I$, which is a major determinant of the blood radiation dose (*14,15*). Using Green's figure of 1.7 rads/mCi administered, the average radiation dose to the blood for Freitas' patients would be 24 rads. This dose estimate is predicated upon the usual levels of $PB^{131}I$ found in hyperthyroid patients. Depletion of the thyroidal iodine pool might be expected with consequent further elevation of the $PB^{131}I$ levels, however, and under these circumstances radiation doses to the blood could easily reach 50 rads and more (*15*).

The late biological effects of radiation, particularly at low levels, are difficult to define—in part because risk estimates are largely theoretical and are based upon assumptions and extrapolations from limited human data at higher dose levels (*16*). To a considerable degree, the detection of radiation-induced cancer is possible only in a statistical sense, and large exposed populations are necessary to quantify small risks. A great deal of controversy surrounds most risk estimates: witness the dissenting report by a large minority of members of the committees of the National Research Council that participated in the preparation of the latest version of the report of the Committee on the Biological Effects of Ionizing Radiations (BEIR Report) (*17*).

Freitas et al. found no leukemia in their series. Although radiation-induced leukemia is likely to appear within 10 yr of exposure, its detection would require either a high incidence or a considerably larger population than the 51 patients they studied (*18*). On the other hand, solid cancers induced by radiation appear to have a very long latent period and may continue to appear up to 30 or more yr after exposure (*19*).

Estimates of genetic changes and birth defects are most difficult to quantify and probably can never be accurately determined in man. The anecdotal reports of absence of abnormalities in reproductive histories or in the health of offspring of patients treated with radioiodine is reassuring, but they hardly settle the issue. The high incidence of normally occurring human disorders of genetic origin, estimated to range up to 3 to 5% of all live births, makes radiation-induced risks appear proportionately small and probably not detectible.

In addition to the question of safety, Freitas et al. assure us as to the efficacy of radioiodine treatment of hyperthyroidism in children. In adults, radioiodine has been shown by many studies to readily control the hyperthyroidism of Graves' Disease if given in adequate amounts and, as a matter of fact, is so effective that the majority of patients so treated eventually become hypothyroid (*9*). In their series, Freitas et al. report rapid control, with relief of hyperthyroidism in 73% at 6 mo. When studied at follow-up, the authors considered that 92% of their patients were hypothyroid, although strict criteria for institution of replacement therapy may not have been observed since they note that some of their patients ". . .may retain residual thyroid function. . ."

It requires a major reversal in thinking for those who have spent considerable effort in attempting to reduce the amount of hypothyroidism following radioiodine therapy to embrace a strategy designed to routinely produce ablation and resultant hypothyroidism. Yet, if radioiodine is to be used in children, one must consider that the destruction of the thyroid is a desirable goal because this undoubtedly decreases the potential for thyroid neoplasia.

The advantages and disadvantages of any therapeutic modality must be weighed against those of plausible alternatives. The general dissatisfaction with other methods of therapy has led, in part, to Freitas's proposal for radioiodine as the preferred method of therapy for childhood hyperthyroidism. On careful examination, however, the alternatives might not seem quite as disadvantageous as suggested.

Antithyroid drugs have been widely used and control symptoms in most patients if given *and taken* in adequate dosage. They produce permanent remissions in about 50% of children, with reports ranging from 25 to 75% (*20*). Such drugs are least effective in inducing permanent remissions in boys, in children over 11, and in those with larger goiters (*21*). Problems with compliance may require a less frequent drug schedule than might be optimal, but such schedules have apparently been effective and practical (*20*). A wide variety and occasionally high frequency of toxic reactions to all antithyroids have been reported in children, and although they may require discontinuance of the drug, they do not cause permanent effects and are not life threatening (*22*).

Surgery for hyperthyroidism in children has been widely recommended and in the hands of very experienced thyroid surgeons is highly effective. Recurrences may be frequent unless all but a small remnant is removed, and, as a result, permanent hypothyroidism is frequent, ranging up to 50% and more following what is considered adequate resection. Although experienced thyroid surgeons report no mortality and low morbidity, some significant operative complications may be expected even under optimal circumstances in a small number of patients (*23*).

Freitas et al. suggest that the theoretical risks of radioiodine must be contrasted with the real risks of thyroidectomy and therefore propose radioiodine as initial and preferred mode of therapy. Sufficient doubts remain about the advisability of this suggestion to counsel prudence and discretion. As in adults, therapy must be individualized. Since antithyroid drugs induce permanent remission in a significant proportion of hyperthyroid children, it would appear appropriate to use them initially, particularly in children with small goiters and in situations where good compliance may be expected. Close scrutiny for toxicity is important but hardly unmanageable. Even in the absence of permanent remissions, antithyroid drugs will provide good symptomatic control for prolonged periods in the majority of patients. Ablative therapy should only be considered upon their failure.

The use of surgery must depend to a large degree upon the availability of an experienced thyroid surgeon. Unfortunately, the increasing use of radioiodine has decreased the opportunity for surgeons-in-training to obtain optimum experience (*24*). One solution, possibly unworkable and certainly awkward in our present medical milieu, may be the designation of referral centers for procedures such as this, which are performed infrequently and for which considerable experience is important in minimizing morbidity. If skilled surgeons are not available locally or on convenient referral, and definitive therapy is considered necessary, one should then have little hesitation in recommending therapy with radioactive iodine I-131, and, of course, radioiodine is always preferred to reoperation.

Because of the long latent period of so many of the late effects of radiation, its use in a potentially susceptible and young population requires both special care in patient selection and the assumption of some unique responsibilities. Children have a long lifetime ahead of them, and most will live that lifetime as part of a highly mobile population. For these reasons, some method of guaranteeing long-term surveillance is required for both assurance of drug compliance as well as detection of possible late effects. A central national register should be established for such individuals to assure subsequent follow-up examinations. Such a register has been demonstrated to be effective and workable, and should cost relatively little in view of the small number of patients involved (*25,26*). With its use, sufficient data should eventually be collected to provide the information necessary to evaluate the long-term safety of radioiodine treatment of children.

DAVID V. BECKER
New York Hospital–Cornell Medical Center
New York, New York

## REFERENCES

1. SAENGER EL, THOMA GE, TOMPKINS EA: Incidence of leukemia following treatment of hyperthyroidism. Preliminary report of the Cooperative Thyrotoxicosis Follow-Up Study. *JAMA* 205: 855–862, 1968
2. DOBYNS BM, SHELINE GE, WORKMAN JB, et al: Malignant and benign neoplasms of the thyroid in patients treated for hyperthyroidism: a report of the Cooperative Thyrotoxicosis Therapy Follow-up Study. *J Clin Endocrinol Metab* 38: 976–998, 1974
3. FREITAS JE, SWANSON DP, GROSS MD, et al: Iodine-131: Optimal therapy for hyperthyroidism in children and adolescents? *J Nucl Med* 20: 847–850, 1979
4. DEGROOT LJ, FROHMAN LA, KAPLAN E, et al: *Radiation-Associated Thyroid Carcinoma*. New York, Grune & Stratton, 1977
5. MALONE JF: The radiation biology of the thyroid. *Cur Topics in Rad Res Quart* 10: 263–368, 1975
6. MAXON HR, THOMAS SR, SAENGER EL, et al: Ionizing irradiation and the induction of clinically significant disease in the human thyroid gland. *Am J Med* 63: 967–978, 1977
7. LARSEN PR, CONARD RA, KNUDSEN K, et al: Thyroid hypofunction appearing as a delayed manifestation of accidental exposure to radioactive fall-out in a Marshallese population. In *Biological Effects of Ionizing Radiation*, vol 1. Vienna, IAEA, 1978, pp 101–115
8. SHELINE GE, LINDSAY S, MCCORMACK KR, et al: Thyroid nodules occurring late after treatment of thyrotoxicosis with radioiodine. *J Clin Endocrinol Metab* 22: 8–18, 1962
9. BECKER DV, MCCONAHEY WM, DOBYNS BM, et al: The results of radioiodine treatment of hyperthyroidism: a preliminary report of the Thyrotoxicosis Therapy Follow-up Study. *Further Advances in Thyroid Research*, Fellinger K, Hofer R, eds. vol 1, Vienna, Gistel G et Cie, 1971, pp 603–609
10. LINDSEY S: The experimental production of thyroid neoplasms in the rat by irradiation. In *Thyroid Neoplasia*, Young S, Inman DR. London, Academic Press, 1968, pp 279–289
11. DONIACH I: Effects including carcinogenesis of $^{131}I$ and x-rays on the thyroid of experimental animals: a review. *Health Phys* 9: 1357–1362, 1963

12. MALOOF F: Effects of hypophysectomy and of thyroxine on radiation-induced changes in the rat thyroid. *Endocrinology* 56: 209–214, 1955
13. GREEN M, FISHER M, MILLER H, et al: Blood radiation dose after $^{131}I$ therapy of thyrotoxicosis. *Br Med J* 2: 210–215, 1961
14. HARDEN RM, ALEXANDER WD, KOUTRAS DA, et al: Quantitative studies of iodine metabolism after long-term treatment of thyrotoxicosis with antithyroid drugs. *J Clin Endocrinol Metab* 26: 397–401, 1966
15. BARANDES M, HURLEY JR, BECKER DV: Implications of rapid intrathyroidal iodine turnover for $^{131}I$ therapy: the small pool syndrome. *J Nucl Med* 14: 379, 1973
16. United Nations Scientific Committee on the Effects of Atomic Radiation. 1977 Report to the General Assembly. Sources and Effects of Ionizing Radiation. New York, United Nations, 1977
17. MARSHALL E: NAS study on radiation takes the middle road. *Science* 204: 711–714, 1979
18. GOSS SG: Sizes of population needed to detect an increase in disease risk when the levels of risk in the exposed and the controls are specified: examples from cancer induced by ionizing radiation. *Health Phys* 29: 715–721, 1975
19. Report of the Committee on the Biological Effects of Ionizing Radiations, National Research Council. The effects on populations of exposure to low levels of ionizing radiations. Washington, DC. National Academy of Sciences, 1979
20. BARNES HV, BLIZZARD RM: Antithyroid drug therapy for toxic diffuse goiter (Graves' disease): thirty years experience in children and adolescents. *J Pediatr* 91: 313–320, 1977
21. HOTHEM AL, THOMAS CG, VAN WYK JJ: Selection of treatment in the management of thyrotoxicosis in childhood and adolescence. *Ann Surg* 187: 593–598, 1978
22. AMRHEIN JA, KENNY FM, ROSS D: Granulocytopenia, lupus-like syndrome, and other complications of propylthiouracil therapy. *J Pediatr* 76: 54–63, 1970
23. HOWARD CP, HAYLES AB: Hyperthyroidism in childhood. *Clinics in Endocrinol & Metab* 7: 127–143, 1978
24. PARFITT AM: The incidence of hypoparathyroid tetany after thyroid operations: relationship to age, extent of resection and surgical experience. *Med J Aust* 1: 1103–1107, 1971
25. PHILP JR, DUTHIE MB, CROOKS J: A follow-up scheme for detecting hypothyroidism in thyrotoxic patients treated with radioiodine. *Lancet* 2: 1336–1338, 1968
26. HEDLEY AJ: Long-term aftercare for patients treated for thyrotoxicosis. *Br J Surg* 60: 771–774, 1973