Hypothyroidism Following Iodine-131 Therapy

In his paper entitled "Changing Annual Incidence of Hypothyroidism After Iodine-131 Therapy for Hyperthyroidism, 1951–1975" (*1*) and its companion work co-authored with Lundell, Israelsson, and Dahlqvist (*2*) (both in this issue), Dr. Lars-Erik Holm, of the Radiumhemmet, Karolinska Hospital, Stockholm, presents a careful and intriguing review of experience with I-131 treatment in a single institution. They analyze five periods of 5 yr each, involving a total of 4,553 hyperthyroid patients. Such a large series allows the author and his colleagues to control variables such as institutional policies related to treatment techniques and variations among therapists. In spite of a (presumably) standardized dose of I-131, their data demonstrate clearly a sequential increase in the incidence of hypothyroidism seen in each five-year period from 1951 to 1975. Figure 1 in Holm's paper dramatically illustrates this phenomenon, and the experience of the individual therapists treating the patients (Table 3) shows that this increasing incidence is seen in the experience of each of the four radiotherapists whose tenure spanned more than one study period (*1*). This paper confirms the recorded experience of others (*3*), together with the subjective impressions of many thyroidologists and nuclear medicine physicians, that late hypothyroidism after I-131 treatment is increasing as a problem. The companion paper makes the related point that, regardless of factors that appear to influence the early incidence of hypothyroidism, the majority of patients will become hypothyroid if one waits long enough. Their tentative conclusion, in accord with the personal opinions of many present-day practitioners, is that eventually hypothyroidism is so likely to develop in patients who have been treated with radioiodine that one might indeed serve the patient better by giving a large dose of radioiodine initially, shortening the hyperthyroid period, accepting from the beginning that the patient will require lifelong replacement therapy. Not all of us are yet willing to accept this conclusion as inevitable.

A review of recent literature suggests that enthusiasm for clinical research on radioiodine therapy of hypothyroidism has begun to wane. Few new technical advances have been proposed in the last five years. This lull probably reflects the natural frustration felt after the relatively disappointing long-term results seen from earlier therapeutic innovations that initially generated enthusiasm.

There are fundamental barriers to progress in the clinical treatment of Graves' disease. The natural history of the condition is poorly defined. Intervention with surgery and stable-iodine treatment were introduced early after the disease was described, and the literature provides us with little information about the natural course of the disease and the effects of environmental and endogenous biologic factors on it. It is clear that Graves' disease is a clinical entity distinct from the hyperfunctioning adenomas, single or multiple. Whether the group with multinodular glands seen rather frequently in the Radiumhemmet series contains a significant number of patients with multiple functioning adenomata rather than Graves' disease is unclear, and probably unknown to the authors. Since hyperfunctioning adenomata are believed to be less radiosensitive than are the diffusely hyperplastic thyroids of Graves' disease, inclusion of some patients with adenomatous disease would certainly influence the outcome in this series.

Research in this area has been inhibited by the lack of a suitable animal model. While early reports suggested spontaneous hyperthyroidism in a certain type of Scandinavian wild rabbit, and no less an authority than Walter Cannon reported experimental induction of Graves' disease in cats (*4*), these observations appear to have been sporadic. Such animals are not available to the modern research investigator, although the recent recognition of a spontaneous Plummer-like disease in cats may be of some help. Without an animal model, we have not even been able to begin unravelling the problems of microdosimetry within the thyroid follicle and within the various components of the follicular cell after treatment under a variety of conditions.

Even the gross dosimetry of a radioiodine dose remains crude. There is biologic variation from day to day in the same subject in such factors as rates of thyroidal trapping and binding of radioiodine and of hormonal and iodide release from the gland. Estimation of the overall size of the thyroid gland is fraught with difficulties, but these problems are overshadowed by the even greater difficulties in knowing the *cellular* mass of a particular thyroid gland, as there are variable amounts of fibrous and interstitial tissue as well as variation in the volume taken up by relatively radioresistant colloid. Since the radiation dose is concentrated in colloid much more heavily than in the follicular cells themselves, the microdosimetry of each follicle is probably the most important factor in determining radiation effects. Even a pretreatment biopsy might not help much, as there may be marked variability in size among the follicles of hyperplastic thyroids just as in normal thyroids.

Experience suggests that, even were one able to standardize dosimetry, the thyroid gland in Graves' disease would be more sensitive to radioiodine than is the adenomatous gland or the normal thyroid. It has been suggested that this increased radiosensitivity is autoimmune in nature (*5*) and represents an extension of the immunologic origin of Graves' disease itself (*6*). Additional factors that may play a part include the effect of nonlethal damage to the follicular cell. In the normal or adenomatous cell, recovery of function may be the rule, albeit with the possibility that this recovery of function may involve alterations that predispose to more frequent development of neoplasm. In the Graves' disease cell, there may be less chance of recovery from this partial damage. The implications of the differential damage to various cell parts are an area needing further investigation, but they are virtually impossible to study in the absence of an animal model. Of particular interest are the different effects of nonlethal damage to the cell membrane [probably the site of active transport of iodide into the thyroid gland (7)], to the nucleus, and to those organelles responsible for the production of thyroglobulin and the enzymes that mediate synthesis of thyroid hormone.

The frustration felt by many therapists in their search for the "perfect" treatment for Graves' disease is reflected in the literature. A number of authors emphasize the importance of careful measurement of the treatment dose. In the Radiumhemmet series reported in this issue, such attempts were made. It is quite possible that the methods used do not completely overcome temporal alterations in gland size and in the kinetics of the treatment dose. While the authors dismiss variations in practice vis-a-vis antithyroid drug preparation, their data are not too convincing on this score. Whereas they minimize the impact of the introduction of iodized salt in Sweden on their temporal findings, their data indeed suggest that this did accentuate the trend found in their basic data. One must also take into account the possibility that, in Sweden as well as in the United States, other sources of unexpected iodine had previously crept into the diet. Unless epidemiologic studies are available to rule this factor out, one must consider the possibility that in Sweden there has been a gradual increase in iodine intake from a variety of sources during the 25 yr of study. Partial confirmation of this might be possible after a more intense review of the turnover rate of tracer doses through the years. Holm reports that the incidence of nodular thyroids increased during his observation period, although the overall distribution of thyroid gland weights remained unchanged. The fact that the effective half-life of the radioiodide tracer increased from 5.3 to 5.8 days during the observation period may be of some importance. These figures correspond to biologic half-lives of 15.7 and 21.1 days, respectively, a 34% increase. This very likely relates to a larger T_4-to-T_3 ratio within the thyroid glands, a finding to be expected with increased dietary iodine in the later portions of the observation period.

The role of antithyroid drug pretreatment on the effect of a standardized dose of I-131 radiation remains unsettled. Whereas the authors in the present series believe that antithyroid drug pretreatment had no effect, they admit that the length and intensity of such pretreatment is not accounted for in their studies. My interpretation of the data they present is that it by no means *rules out* a systematic effect of antithyroid drugs on outcome. It does seem likely that pretherapy preparation by antithyroid drugs would affect the biologic response of the thyroid to a given number of microcuries retained per gram.

A number of approaches have been taken in recent years to affect the rate of long-term hypothyroidism after radioiodine treatment of Graves' disease. A straightforward, and certainly logical, approach has been to lower the treatment dose. In some cases there have been meticulous attempts to measure the radiation dose delivered. While lower doses do reduce the incidence of hypothyroid-

ism in the early years after treatment (*8*), they also prolong the average period before euthyroidism (off antithyroid drugs) is achieved. Recent reports have also suggested that even patients treated with low doses may eventually become hypothyroid (*9*).

The effect of stable-iodide intake on this process is complex and needs more study. Increased dietary iodide, by reducing radioiodine uptake and prolonging the retention of the dose in the gland, complicates the estimate of a treatment dose. In addition, the biologic adaptation of the thyroid gland to differing dietary iodide levels may be quite complex and it is possible that such adaptations are different in Graves' disease than from those in the normal thyroid. Similarly, the biological effects of antithyroid drugs probably differ between Graves' disease and the normal human subject or an experimental animal. These factors force us to use empirical methods in evaluating the effect of iodide or antithyroid drugs on outcome. Furthermore, one must wait many years since the outcome to be measured is late hypothyroidism.

Iodine-125 therapy for Graves' disease has been disappointing clinically, though it has theoretical advantages assuming that the most important physiologic effects desired are at the apical cell membrane of the follicular cell and in organelles located near it. It appears that the relative ratio of cure rate to late hypothyroidism did not improve when I-125 therapy was used instead of I-131 (*10*). A theoretical criticism that has been put forward against I-125 treatment as well as against low-dose I-131 treatment is the potential carcinogenic result of nonlethal damage to the thyroid cell. This does not appear to be a problem in Graves' disease. Long-term epidemiological data show no evidence that any of these approaches to treatment is significantly carcinogenic. Perhaps the biology of Graves' disease itself, especially the autoimmune activity in the diseased gland, protects it from possible carcinogenesis, in contrast with the known neoplastic potential from small doses of external radiation to the normal thyroid.

Regardless of its cause, the clear demonstration of an increased rate of hypothyroidism in Holm's series is fascinating. Taken in conjunction with other reports showing that permanent remissions after primary antithyroid drug therapy seem increasingly rare with time (*11*), this finding presents a growing therapeutic challenge. In deciding upon a therapeutic approach, we must not forget that late hypothyroidism is also seen, though less frequently, after thyroid surgery, and also after antithyroid drug treatment alone, without surgery or radioiodine. It may very well be that hypothyroidism is a part of the natural history of Graves' disease even in the absence of *any* specific therapy.

In approaching the patient with Graves' disease, the physician can assume one of at least three therapeutic attitudes. First, expectant anticipation of a spontaneous remission, meantime using antithyroid drug therapy, symptomatic suppression with propranolol, or other less specific measures, perhaps observation alone. This approach must be thought of as long-term in orientation, the ultimate goal being a healthy patient with no need for medication. As spontaneous hypothyroidism may occur even with this type of treatment, such patients must be followed indefinitely. Second, the expectant attitude described above, combined with limited destruction of the thyroid gland. This approach is typified by antithyroid-drug treatment combined with low doses of radioiodine. The patient is maintained euthyroid with antithyroid drugs given as necessary during the (often prolonged) period before a combination of natural history and destruction of thyroid tissue achieves remission. As these patients also may develop late hypothyroidism or recurrence of hyperthyroidism, they also must be followed indefinitely. Third, one could accept the inevitability of late hypothyroidism. Such an approach shortens the morbidity from hyperthyroidism by using a large dose of radioiodine, or by surgically removing sufficient thyroid tissue to produce hypothyroidism. The clinician accepts that these patients will become hypothyroid, and they are put on replacement medication immediately, or when clinical evidence of the expected hypothyroidism appears. Because replacement therapy is generally cheaper, easier on the patient, and easier to monitor than is antithyroid drug therapy, many prefer this approach. However, it minimizes the likelihood that there will be a period of euthyroidism, which can often last many years.

Which of these approaches one takes in an individual therapeutic situation should, I believe, be an individual matter tailored to the needs of the particular patient. In any case, long-term compliance by the patient and a commitment to permanent follow-up by the physician are essential. One must not underestimate the harm from undiagnosed and untreated hypothyroidism. This is equally a danger whether there is late unrecognized hypothyroidism or whether hypothyroidism has been diagnosed but the patient stops replacement therapy. Unfortunately, the same patient who

may not comply with long-term follow-up for detection of late hypothyroidism may also be noncompliant with a lifelong regimen of replacement therapy.

Regardless of the therapeutic approach taken, I believe it is important, both to the individual patient and to long-term understanding of radioiodine therapy, to make every attempt to quantify exactly how much radiation we are actually delivering to the thyroid gland. Except when the goal is total destruction of thyroid function, "shotgun" approaches to sizing of the radioiodine dose will serve only to perpetuate our current confusion. We need more careful epidemiologic studies such as those of Holm and his co-workers and inclusion in these studies of as much information as possible, to provide clues to what is really going on when we treat a patient with radioactive iodine. Most likely, real progress in this field must await methodologic breakthroughs that facilitate research to increase understanding of the biology of Graves' disease and the interaction of that biology with radiation-induced aberrations at the subcellular level.

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