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Treatment of Hyperthyroidism: Use of ^{131}I and ^{125}I

The late occurrence of myxedema as a consequence of ^{131}I therapy for hyperthyroidism is the major concern in the present-day management of this condition. It is now over 30 years since the initiation of widespread use of radioiodine in therapy for hyperthyroidism. The rapid onset of myxedema in a significant number of patients following treatment was recognized at an early date.[1] The report of Beling and Einhorn[2] in 1961 drew attention to the cumulative incidence of myxedema each year at a rate of 3 percent per year after the first year. Since then many others have confirmed this finding with incidence rates ranging from 2 to 6.3 percent per year for longer than 15 years.[3-8]

A review of post-thyroidectomy patients has revealed a cumulative incidence of late-onset myxedema in these patients as well, although at somewhat lower rates.[4,7,9-11] Chemotherapy for hyperthyroidism probably results in no increase in myxedema as a late outcome, but there is a high recurrence rate in addition to problems encountered with side reactions.[12]

Radioiodine therapy remains the treatment of choice for most patients suffering from hyperthyroidism. Various strategies are being undertaken by investigators to overcome the problem of late-onset hypothyroidism. This is of particular importance since ^{131}I is now used in the treatment of younger individuals with the former restrictions on use in patients under 40 years of age no longer applied. It is the purpose of this review to discuss the factors which may be important in the etiology of this complication and to indicate the approaches that have been used or proposed to overcome this problem.

FACTORS RELATED TO POST-THERAPY HYPOTHYROIDISM

Investigators who have reviewed their long-term experience have indicated a number of factors which appear to be important in relation to the development of

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hypothyroidism. Consideration of these factors may yield clues to the etiology of post-therapy myxedema and lead to the development of methods to reduce its incidence.

Size of gland. In all series reviewed in which this factor was taken into account, the incidence of post-treatment hypothyroidism was significantly greater in patients who had small glands, either nonpalpable or of normal size.[2-4,6,7] The administered level of ^{131}I has been adjusted downward from the usual calculated amount in some series in consideration of this factor.[7,13]

In the review of their surgical series, Nofal et al.[7] also described this feature, but normal sized glands were rarely operated on.[7] This may be a point of bias in favor of surgery when attempting to compare ^{131}I with surgery in relation to resultant hypothyroidism.[14]

Presence of nodules. The multinodular gland appears to be more resistant to treatment, whether it be radioiodine or surgery. It usually requires multiple doses of ^{131}I more frequently and has a much lower incidence of post-therapeutic hypothyroidism.[2,5-7] Surprisingly, in patients with a single functioning nodule the incidence of subsequent hypothyroidism is greater.[3,7] In these patients it would ordinarily appear appropriate to give large doses since the nonnodular tissue would be relatively spared. However, the same results are found following surgery.[7] Therefore, the incidence of hypothyroidism must be related to something other than just the distribution of radioactivity in the gland following a therapeutic dose of ^{131}I.

Age of patient. There is a suggestion that the thyroid of younger individuals is more sensitive to radiation than that of older individuals and in some institutions the dose is reduced somewhat for the younger patient. The study of Segal et al.[3] showed a slightly higher incidence of myxedema in the younger patients. In some series the ^{131}I-treated younger patients tended to have larger glands,[4] whereas in other series these patients tended to be treated surgically. This factor can certainly bias results. Nofal et al.[7] demonstrated a slightly higher incidence of post-therapy hypothyroidism in the younger age group with ^{131}I treatment, whereas the highest incidence following surgery was in the patients who were between 40 and 49 years when treated.

Size of dose. The size of the initial dose does appear to have an effect on subsequent development of hypothyroidism and has been the basis for several series using lower doses to control the disease.[13,15-19] This may possibly slow the rate of the late cumulative incidence, but it certainly reduces the incidence of hypothyroidism in the first year. It does result in an increased requirement for multiple doses.

Number of doses. There is an inverse relationship between number of doses (and total doses) and the development of late-onset hypothyroidism in most studies.[2,3,7,14] Usually patients requiring multiple doses had multinodular glands. In addition, response to the first dose selected out those patients whose glands were more radiosensitive.

Race. In two series race is taken into account. Apparently blacks are more resistant to therapy, requiring multiple doses more often than whites.[8] In addition, there is less spontaneous, idiopathic, and post-therapeutic (^{131}I and surgery) myxedema in black patients.[14]

Previous surgery. In all series the use of ^{131}I following a partial thyroidectomy resulted in a greatly increased incidence of hypothyroidism.[2-4]

Size of postsurgical remnant. The size of the postsurgical remnant has no correlation with the incidence of subsequent hypothyroidism.[11,20]

Immune status. The incidence of post-therapy hypothyroidism has been considered in relationship to a number of immune factors.

In the surgical series of Green and Wilson,[4] there appeared to be a higher incidence of hypothyroidism in patients whose surgical specimens showed evidence of focal thyroiditis. A slight correlation existed between focal thyroiditis and the titer in the tanned red cell agglutination and complement fixation tests. No consistent effect of operation on the titers was found. Others have also noted the association of thyroiditis in the surgical specimens with postsurgical hypothyroidism.[4,10,21]

On the other hand, in ^{131}I-treated patients, there was no correlation between the results of serologic tests and the clinical state following treatment. In addition, the ^{131}I therapy had no effect on titer levels in patients in whom this was tested prior to and 2 to 3 years after treatment.[4]

The results of other studies are not clear. Burke and Silverstein[22] demonstrated a relationship between increased levels of circulating antithyroid antibodies and ^{131}I-induced hypothroidism in the first year. Others have also found transitory increases in thyroid autoantibodies in the first year following radioiodine therapy for hyperthyroidism, greater in those becoming hypothyroid in the first year, but probably not significant for the occurrence of late hypothyroidism.[23,24]

A lack of significant relationship of humoral antibodies to development of post-therapeutic hypothyroidism following ^{131}I has been found by others.[7,25,26] There does appear to be a higher incidence of postsurgical hypothyroidism in patients who have high titers of antithyroid antibodies.[25,26]

Relationship to prior nondestructive therapy. Segal et al.[3] found the lowest incidence of post-^{131}I hypothyroidism in patients who had received iodine or antithyroid drugs and iodine prior to ^{131}I. The incidence in this group was 4.1 percent compared to 9.4 percent in those having no prior treatment and 23.6 percent in those who had prior drugs and destructive therapy such as x-ray and/or surgery.

ETIOLOGY OF POST-THERAPEUTIC HYPOTHYROIDISM

The reason for the high incidence of post-therapeutic hypothyroidism following ^{131}I is still unknown, but a number of hypotheses have been proposed. Although radiation effects may be a major cause, it does not explain why a similar

situation, albeit somewhat more mild, exists relative to surgical treatment. A means to reduce post-therapeutic hypothyroidism may be found when there exists a better understanding of the etiology of this complication.

A thesis for the effects of ^{131}I has been proposed by Greig.[27] The reproductive capacity of thyroid cells is more radiosensitive than the functional capacity. However, damage to the reproductive capacity is not manifest until the cell attempts to undergo mitosis, which may not occur for some years following ^{131}I. Some cells may die immediately. With time there is an increasing stress on the remaining cells with shortening of life span and inhibition of DNA synthesis under the influence of thyroid stimulating hormone.[28] These cells then attempt to divide but die in the process, eventually resulting in hypothyroidism.

Another possibility is related to the well-known late effects of radiation on blood vessels. The delayed development of endarteritis obliterans can result in the deprivation of an adequate blood supply to the gland. This, in turn, would lead to reduced function and/or cell death.

Early hypothyroidism occurs when all the thyroid cells have received a lethal dose of radiation. Usually, however, the dose distribution is uneven throughout the gland resulting in a frequency distribution of radiation injury. The most marked irregularity in distribution of radioiodine occurs in nodular glands accounting for the relative radioresistance of these glands and the low incidence of postradiation hypothyroidism.

Hypothyroidism developing late after partial thyroidectomy remains unexplained in the light of the above thesis. It is possible that the remnant of gland is put under severe stress to maintain a normal level of function and eventually is "exhausted." Another factor may be increased scarring and consequent reduction in blood flow to the gland. These possibilities are generally unsatisfactory explanations when considered along with the accumulated experience in this field.

There is now important evidence that hyperthyroidism, like Hashimoto's thyroiditis, is a disease related to a defect in the autoimmune surveillance mechanism.[29–31] Although it is thought to be primarily a disease involving cell-mediated immune processes, humoral factors may also play a role.[32,33] Except for some mildly positive evidence in those patients developing postsurgical hypothyoidism, as stated above, the role of autoimmunity in post-therapeutic hypothyroidism is unclear. However, it has been suggested that with both surgery and radiation, partial destruction of the gland releases more thyroidal antigens, in turn leading to eventual complete destruction of the gland.[14]

It is difficult to determine the natural course of hyperthyroidism in the untreated individual in the modern era. Spontaneous remissions occur but the disease can readily have a fatal outcome. It is estimated that only about 1 percent of such cases would end up as hypothyroid.[3] Therefore, the high incidence of late hypothyroidism cannot be attributed to the natural history of the disease or considered a fortuitous occurrence. Most likely it is related to the underlying etiology of the disease as well as to the treatment of it.

THERAPEUTIC STRATEGIES

Attempts to deal with the high incidence of postradioiodine hypothyroidism were energetically pursued by many investigators once this major complication

was recognized. Several strategies have evolved but long-term follow-up over 15 to 20 years is required in order to be sure that any apparent improvement in the first few years is maintained. In addition, it must be ascertained that no selection bias, related to the several factors discussed above, will affect the results.

Reduction of Initial Dose

Estimation of the radiation dose delivered to the thyroid is difficult due to errors in estimating size of the gland by palpation, irregular distribution of radioiodine in the gland, and variations in biological half-life. In early series the activity delivered to the gland tended to be high (150 to 300 μCi/g) resulting in radiation doses in excess of 10,000 rads. The result was a high incidence of hypothyroidism.

Goolden and Fraser[13] devised a treatment schedule which varied the radioiodine concentration per gram of thyroid depending on the overall size of the thyroid. With this method smaller glands received a lower radiation dose (~3500 rads at 60 μCi/g) than larger glands. Their previous schedule called for a uniform dose of 150 μCi ^{131}I per gram except for glands estimated to be greater than 70 grams, which were dosed to a level of 300 μCi/g. Unfortunately, only 1-year results were reported. These showed a hypothyroidism rate of 5 percent compared to their previous experience of 17 percent at 1 year. However, at 1 year 38.5 percent of the group were still toxic and required antithyroid drug therapy.

Two other groups have demonstrated a reduced incidence of hypothyroidism at 5 or more years following initial ^{131}I treatment but at the price of prolonging the hyperthyroid status of some patients. Smith and Wilson[16] reduced the rate of hypothyroidism from 29.0 percent to 7.4 percent at 5 years by reducing the estimated radiation dose delivered to the thyroid from 7000 rads to 3500 rads. Further treatment with antithyroid drugs for persistent hyperthyroidism was necessitated in 43 percent of the high-dose group and 64 percent of the low-dose group. Apparently, additional ^{131}I treatment was not administered for persistent disease.

In the series of Cevallos et al.,[19] patients receiving ^{131}I at 160 μCi/g had a 5.6 year incidence of hypothyroidism of 45.7 percent while 22.9 percent required further ^{131}I. In their lower dose group (80 μCi/g) the hypothyroidism incidence at 5.5 years was 23.5 percent, and 26.5 percent required additional treatment.

In both the series of Smith and Wilson and that of Cevallos et al. there was a continuing rise in the cumulative incidence of hypothyroidism, but the rate of increase was slowed in comparison with the high-dose group in the Smith and Wilson study. In the series of Cevallos et al. the initial incidence at 1 year showed a marked reduction in the low-dose group, but the rate of increase thereafter was higher than in the high-dose group indicating that at some time in the future the two groups would converge.[19]

Another group receiving 50 μCi/g ^{131}I was reported by Rapoport et al.[17] These patients also had a low incidence of hypothyroidism but there was a high retreatment rate. Since that report a dosage scheme was devised similar to that of Goolden and Fraser taking into account the increased radiosensitivity of the smaller glands.[34] Results of this plan are not yet available.

A rather successful long-term result has been obtained by Jackson[18] with the delivering of 3500 rads (~40 μCi/g) to a large series of patients. Approximately 38

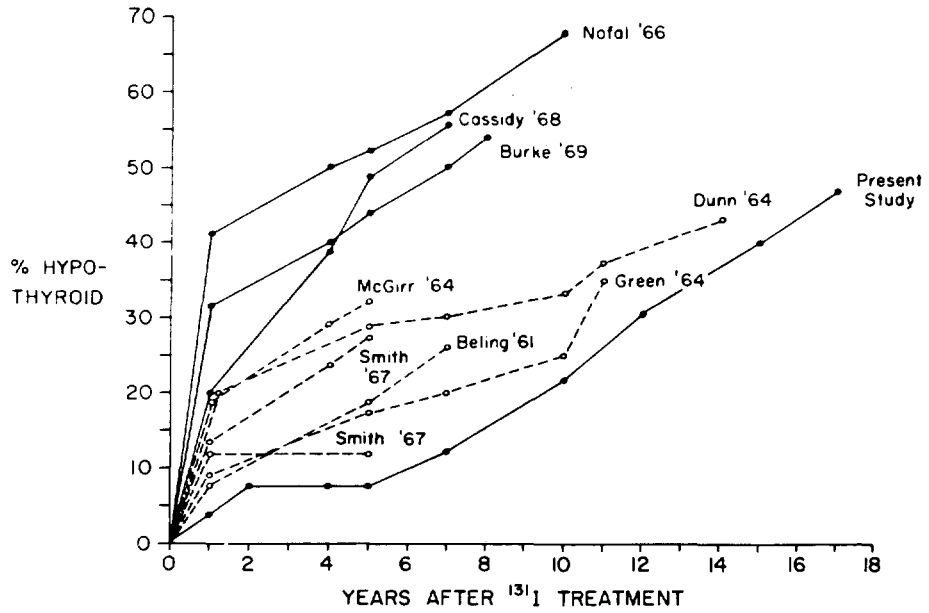

Fig. 6-1. Cumulative incidence of hypothyroidism in study of Glennon et al. (present study) compared with previously reported data. Solid lines indicate data originally reported using the life table method; broken lines indicate data recalculated from the reported data using the life table method. Reproduced with permission from Glennon J.A. et al., Ann. Int. Med. 76:721–723, 1972.

percent required more than one dose. The 10-year incidence of hypothyroidism was an acceptable 18 percent.[35]

Less satisfactory were the results of Glennon et al.[36] who observed the results of a single dose of 3 mCi or less for up to 17 years. Although the incidence of hypothyroidism was low at 1 year (3.7 percent) and at 5 years (7.5 percent), there was an annual increase of 3.4 percent thereafter, equalling the rates for higher dose series (Fig. 6-1). This illustrates the necessity for long-term follow-up and suggests that the eventual cumulated incidence of hypothyroidism cannot be reduced by low dose ^{131}I.

There seems to be no doubt that the incidence of hypothyroidism at 1 and 5 years can be substantially reduced by lowering the administered dose of ^{131}I, but probably at the price of increasing the need for retreatment and prolonging the duration of hyperthyroidism for many patients. The longer term results at 10 to 15 years or more are not yet available in many of these series, and there is the suggestion in the data of Cevallos et al. that the differences due to the different dose regimens may be less marked at that time.[19] The data of Glennon et al. indicate that the long-term follow-up does show a high rate of hypothyroidism even after low doses.[16]

Multiple Small Doses

The advantage of using multiple small doses (less than 50 μCi/g) is that it permits observation of the response prior to retreatment and permits individuali-

zation of the treatment regimen for each patient. Again, it prolongs the time for most patients to become euthyroid, but the results in one such trial appear promising with only 3 percent hypothyroidism at 7 to 16 years following initiation of therapy in 334 patients.[37]

High-Dose Radioiodine Followed by Replacement Therapy

Since it is felt by some that every patient treated with ^{131}I will eventually become hypothyroid, and since the onset may be very gradual and unnoticed by the patient until the process is advanced, an opposite approach has been taken. Using an initial dose which is rather high (160 to 200 μCi/g) causes rapid reversal of the hyperthyroid state with 90 percent of the patients controlled within 3 months.[38] Thyroid replacement therapy was instituted in the controlled patients, to be continued for the remainder of each patient's life. Although this approach appears to be practical in that it brings the hypothyroid state under rapid control and reduces the possibility of an advanced stage of unrecognized hypothyroidism, it is intellectually not satisfactory. This is especially true at this time when patients under the age of 40 years receive ^{131}I. In selected patients with cardiac disease and in the older age group this method is certainly a valid one. A continued search for a way to achieve a euthyroid state in each patient with hyperthyroidism is indicated.

Use of External Beam Irradiation

The hyperthyroid gland is more sensitive than the normal gland to ionizing radiation. Radiation doses which do not affect normal rat thyroid cell function (1000 rads, x-ray, or 5000 rads, ^{131}I) can have a marked effect on human thyrotoxic thyroid cells.[39]

External beam therapy was used in the treatment of hyperthyroidism prior to the availability of antithyroid drugs and radioiodine.[40-43] The older literature is difficult to evaluate precisely because of problems with specification of dose and in the diagnosis of thyroid status. However, it is apparent that the success rate in curing hyperthyroidism was good (80 to 90 percent) with doses probably under 2000 rads to the thyroid. Post-therapeutic hypothyroidism appears to have been low, both short term and long term, but the adequacy of follow-up and ability to detect developing hypothyroidism are in question.

It is of interest, in view of recent theories of the etiology of hyperthyroidism, that Groover et al.[40] also irradiated the thymus in addition to the thyroid.

On the other hand, much higher doses of radiation delivered to the thyroid in the course of treatment of malignancies in the pharynx and larynx produce only minor suppression of radioiodine uptake without long-term effects. A biphasic suppression is noted at 3 to 4 weeks and again at 3 to 4 months with slightly higher uptakes in the intervening period.[44,45] Einhorn and Wikholm[46] found only 3 cases of hypothyroidism 10 or more years following high-dose irradiation to 43 patients. However, they did demonstrate diminished reserve as evidenced by lack of response to TSH stimulation in the clinically euthyroid patients.

A more recent attempt to treat thyrotoxicosis with external beam therapy has been described by Philp et al.[47] Cobalt 60 irradiation in doses of 115 to 900 rads in

28 patients failed to control the hyperthyroid state in 25. It is interesting that 3 patients did become euthyroid with doses of 400, 600, and 800 rads. The trial was then abandoned.

The advantage of external beam irradiation is the rather precise control of radiation dose. This permits the depletion of a specified fraction of thyroid cells, a situation not possible with an internally deposited radionuclide.

Trotter and Willoughby[48] have demonstrated a biphasic effect of radiation on thyroidal radioiodine uptake following a dose of 400 to 800 rads of ^{60}Co gamma rays on a portion of the thyroid. There is an initial 30 to 50 percent reduction in uptake, demonstrated on scans, which occurs at an interval of 24 hours between irradiation and administration of the dose. A slight compensatory increase in uptake is then noted for 2 weeks followed by a second decrease in uptake at 3 weeks lasting for about 2 weeks.

Fifty patients were treated with radioiodine following irradiation of a portion of the gland with 800 rads in the hope that the portion of the gland temporarily suppressed by ^{60}Co would take up less of a therapeutic dose of ^{131}I and thus be spared destruction. However, no difference in the rate of hypothyroidism was noted in the early results at less than 1 year. Further details have not been published.

With the development of accurate methods for localizing charged particle beams, there is the possibility of using the Bragg peak for precise delineation of a target area within the thyroid while sparing normal tissue. With such a beam of heavy ions it would be possible to selectively irradiate a portion of the thyroid while sparing the remainder, as well as adjacent normal tissues. This approach has not yet been undertaken.

Use of ^{125}I

The highly energetic beta emission combined with the gamma photons of ^{131}I results in a rather uniform distribution of the radiation dose in the individual thyroid cell. Since, as stated above, the reproductive capacity of thyroid cells is more radiosensitive than the functional aspect, it seems very unlikely that reduction of the functional integrity can occur following ^{131}I without subsequent cell death and eventual hypothyroidism.

With ^{125}I the situation is theoretically quite different. Most of the radiation effect is probably due to the very low energy conversion and Auger electrons.[49–51] The lower energy Auger electrons (0.8–2.9 kev) are particularly abundant (Table 6-1). The range of these electrons in tissue is very small (from < 0.4 to 20 μm). Since the radioiodine is primarily in the colloid, the radiation dose distribution is markedly nonhomogeneous, affecting the cellular cytoplasm at the apex of the cell to a much greater extent than the nucleus (Fig. 6-2).

Dose estimates for whole-gland distribution can be in serious error relative to the microscopic distribution. Difficulties in calculation are evident because of the marked variation in follicle size and cell size in the normal and hyperthyroid gland. Several authors have made such calculations,[49–54] and these have shown ratios of about 3-4 to 1 for the colloid-cell interface dose to the dose at the nucleus (Table 6-2).

Theoretically this concentration of dose at the colloid-cell interface should

Table 6-1
Decay Characteristics of ^{125}I*

	Radiation	Energy (kev)	N/100 Disintegrations	
Photons	Gamma	35.4	6.66	
	$K_{\alpha 1}$ x-ray	27.4	76.15	
	$K_{\alpha 2}$ x-ray	27.2	39.06	
	$K_{\beta 1}$ x-ray	30.9	20.56	
	$K_{\beta 2}$ x-ray	31.8	4.26	
	L x-rays	3.7	22.26	
Electrons	K int. conv.	3.6	80.0	
	L int. conv.	30.9	11.42	$\Delta_i = 0.0151$
	M int. conv.	34.6	1.9	
	KLL Auger	22.6	14.16	
	KLX Auger	26.4	5.97	$\Delta_i = 0.0107$
	KXY Auger	30.1	0.96	
	LMN Auger	2.9	154.42	$\Delta_i = 0.0159$
	MXY Auger	0.8	364.61	

*Half-life: 60.2 days.

result in more marked effects on the site of hormonogenesis than on the replicative capacity. Studies comparing the effects of ^{131}I and ^{125}I in animal systems have demonstrated recovery of function after initial suppression by ^{125}I. A more marked effect was seen on iodine-concentrating mechanisms than on goitrogenesis,[56–59] and histopathological studies have confirmed the localization of dose.[59]

The cell survival studies of Greig et al.[57] are confirmatory. Only the work of Jongejan and Van Putten[60] indicates an opposite conclusion. They found no difference in the $^{125}I/^{131}I$ ratio for administered levels of activity to produce identical effects on hormonal function and on cell killing.

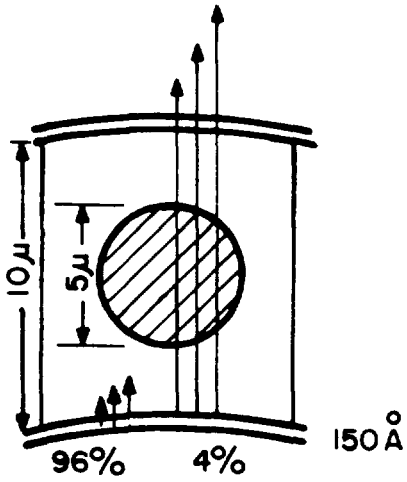

Fig. 6-2. Schematic representation of percentage distribution of electron radiation dose inside thyroid cell. The radiations emanate from ^{125}I in the follicular colloid. (Reproduced with permission from Lewitus Z. et al., Seminars in Nucl. Med. *1*:411–421, 1972.)

Table 6-2
Calculated Radiation Dose to the Thyroid From ^{125}I (1 mCi in a 20-g Gland)

Author	Initial Dose Rate (rads/day)			Total Dose (rads)*		
	Whole Gland	Colloid-Cell Interface	Nucleus	Whole Gland	Colloid-Cell Interface	Nucleus
Harper et al.[52]	36.8			795		
Gillespie et al.[49]	75	170	46	1620	3672	994
Reddy et al.[50]		457	112		9871	2419
Gavron and Feige[51]	78	63.6	32.4	1685	1374	700
Lewitus et al.[53]	88.8	151.2	37.2	1918	3266	804
Ben-Porath et al.[54]		77.8	25.9		1680	559
MIRD†	72			1555		

*Assumes T½ eff. of 115 days.
†Author's calculation using MIRD tables for absorbed dose per unit cumulated activity.[55]

Several clinical trials of ^{125}I for hyperthyroidism were initiated in the hope that late hypothyroidism could be substantially reduced (Table 6-3). These have varied in the dose of ^{125}I used relative to the conventional ^{131}I dose and the results have been mixed. At least two groups have discontinued their study because of lack of improvement in results.

In Glasgow the initial trial used a dose in millicuries of ^{125}I four times the usual dose of ^{131}I. This resulted in a rapid reversal of the hyperthyroid state but with a substantial percentage of ensuing hypothyroidism. With reduction in the amount of ^{125}I administered the incidence of hypothyroidism decreased, but with an increase in persistent hyperthyroidism.[62–64]

On the other hand, Israeli investigators have used fewer millicuries of ^{125}I than of ^{131}I, assuming a quality factor of 3 for the rad dose in the apical region of the cell from the low-energy Auger electrons.[65] The relapse rate was high leading to the use of increased doses and finally to a combination of ^{125}I and ^{131}I in equal millicurie amounts.[66] With this combined therapy it was felt that a rapid response by affecting hormonogenesis was initiated by ^{125}I and that long-term effects were maintained by the cell killing action of ^{131}I. This combination led to the lowest incidence of recurrence but without much effect on the incidence of hypothyroidism.

A series of patients treated by Siemsen et al.[67] initially showed a low rate of hypothyroidism but with a high rate of persistent hyperthyroidism. No further patients are being added to this study because of the conclusion that the results were no better than with ^{131}I. The series of Werner et al.[68] and that of Weidinger et al.[69] continue, and a recent study by Glanzmann and Horst[70] shows promising results.

In this last study there was no hypothyroidism at 18 to 24 months and 18 percent persistent hyperthyroidism. Of those patients with persistent or relapse of thyrotoxicosis, more than 30 percent had T_3 thyrotoxicosis.

Another small series of patients was treated with ^{125}I by Gimlette and Hoschl.[71] The dose of ^{125}I was identical to the dose of ^{131}I used in a control group.

Table 6-3
Results of ^{125}I Therapy for Thyrotoxicosis

Author	Radioactivity Level (*N*)		Euthyroid (%)	Hyperthyroid (%)	Hypothyroid (%)	Follow-up (years)
Bremner et al.[63]	1000 μCi/g	(18)	64	0	36	3.3 (ave.)
	600 μCi/g	(86)	42	24	34	3 (ave.)
	300 μCi/g	(193)	64	18	18	2.3 (ave.)
Lewitus et al.[66]	12–72 μCi/g	(45)	44.4	48.9	6.7	0.5–2
	87–94 μCi/g	(11)	54.5	36.4	9.1	
	24–107 μCi/g ^{125}I + 35–100 μCi/g ^{131}I	(43)	90.7	2.3	7.0	
Weidinger et al.[69]	4–9.5 mCi	(30)	73.3	20	6.7	
	10–19.5 mCi	(21)	42.9	38.1	19	0.3–4
	20–36 mCi	(12)	50	41.7	8.3	
	Total	(63)	58.7	30.2	11.1	
Siemsen et al.[67]	200 μCi/g	(60)	71	24	5	1–2
	100 μCi/g	(40)	43	53	4	0.75–2
Glanzmann and Horst[70]	~50 μCi/g	(99)	82	18	0	1.5–2
Gimlette and Hoschl[71]	3–6 mCi	(31)	32.3	58	9.7	1.9–3

The study was discontinued after 36 months follow-up because of the high rate of persistent hyperthyroidism (58 percent) along with an incidence of 9.7 percent hypothyroidism. This compares with 32 percent hyperthyroidism and 10.7 percent hypothyroidism following ^{131}I.

For full evaluation of ^{125}I more time must pass and the late results at 15 to 20 years be apparent. Hypothyroidism following ^{125}I may be more transient than after ^{131}I. Assessment of ^{125}I at this time does not appear to be particularly encouraging with regard to its ability to restore the euthyroid state without excessive hypothyroidism.

CONCLUSIONS

Hypothyroidism occurring within the first year of radioiodine therapy can be reduced by lowering the amount of administered ^{131}I. The incidence appears to be directly related to the dose in μCi/g.[72] This probably reflects direct killing of thyroid cells or a mechanism related to interphase death.

Late-onset hypothyroidism does not appear to be directly related to the administered dose of radioiodine. It is probably a result of cell death during mitosis and may be related to biological factors affecting the rate of cell replication.

This late-onset hypothyroidism remains a problem. The various methods that have been applied to reduce the incidence have had unimpressive results. The wide variation in results from one locality to another suggests that environmental and dietary factors may also be important.

The differences between surgical and radioiodine therapy results may be due largely to a bias in selection of patients. If so, improved results with less post-therapeutic hypothyroidism must await a better understanding of the etiology of thyrotoxicosis, and treatment must be directed toward that etiology.

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