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INDUCTION OF MYXEDEMA BY IODIDE IN PATIENTS EUTHYROID AFTER RADIOIODINE OR SURGICAL TREATMENT OF DIFFUSE TOXIC GOITER*

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Abstract In all 10 patients with diffuse toxic goiter of Graves disease rendered euthyroid by radioiodine six months to six years earlier, myxedema (as evidenced by typical signs and symptoms, rises in serum TSH and cholesterol concentrations and decrease in serum thyroxine into the hypothyroid range) developed after small, pharmacologic doses of iodide. Of seven similar patients who had been treated surgically, frank hypothyroidism developed in two, one remained entirely unchanged, and the remaining four displayed slight abnormalities in serum thyroxine or TSH concentrations without overt hypothyroidism. The thyroid gland in Graves disease appears to be inherently susceptible to the induction of iodide myxedema, and such susceptibility may be enhanced or its demonstration facilitated by radioiodine treatment.

IN 1948 it was demonstrated that large doses of iodide, when given acutely to the rat, induce an inhibition of thyroid-hormone synthesis.[1] This phenomenon, often termed the Wolff-Chaikoff effect, was later shown to occur in man as well.[2] Subsequent studies also revealed that the acute Wolff-Chaikoff effect results from the increased intrathyroidal, rather than the plasma, iodide concentration that large doses of iodide produce.[3] Prolonged administration of iodide, however, is associated with relief of the inhibition of hormonal synthesis, a phenomenon termed "escape" or "adaptation."[4] This is thought to result from the decreased activity of the thyroidal iodide transport mechanism that occurs during prolonged iodide administration, preventing accumulation in the thyroid gland of iodide concentrations sufficient to inhibit hormone synthesis.[5]

It is the escape or adaptation mechanism that presumably enables the vast majority of patients to ingest large quantities of iodide for long periods without becoming hypothyroid. In a small proportion of peculiarly susceptible patients, however, goiter and so-called "iodide myxedema" develop when large doses of iodide are given for prolonged periods.[6-8] The underlying abnormality that differentiates such patients from the normal is uncertain, but it is generally thought that iodide myxedema only develops in patients whose thyroid glands have some pre-existing functional defect, most probably in the mechanism by which thyroidal iodide is oxidized and utilized for iodotyrosine synthesis (organic-binding). Since earlier studies had suggested that impairment of the thyroidal organic-binding mechanism occurs not uncommonly after radioiodine therapy,[9,10] we undertook to determine whether patients who are euthyroid after treatment of thyrotoxicosis with radioiodine would be inordinately susceptible to the development of iodide myxedema. While these studies were in progress, Hagen and his co-workers[11] reported on the use of small doses of radioiodine followed in a short time by stable iodine therapy in the treatment of thyrotoxicosis. Mention was made of the fact that in approximately 25 per cent of patients thus treated hypothyroidism soon developed and abated when stable iodine was withdrawn. Further details or comment were not provided, however. Our own studies, carried out at a considerably longer interval after radioiodine therapy in patients who had already achieved a euthyroid state, revealed a remarkable susceptibility to the induction of myxedema by pharmacologic doses of iodide. A less marked, though abnormal, susceptibility was found in patients whose thyrotoxicosis had been treated surgically.

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Materials and Methods

Studies were carried out in 17 patients previously treated for the diffuse toxic goiter of Graves disease. Nine women and one man had received radioactive iodine six months to three years earlier (mean dose, 6.9 mCi); six women and one man had been treated surgically one and a half to six years earlier. All patients were euthyroid as judged by clinical findings and by measurements of both the 24-hour thyroidal uptake of ^{131}I and the serum concentrations of thyroxine (T_4), thyroid-stimulating hormone (TSH) and cholesterol. At the time of study no patient was receiving any form of medication, nor had any done so during the recent past. Pertinent clinical and laboratory data are shown in Table 1.*

unequivocal signs of myxedema appeared or when a total treatment period of 10 weeks had elapsed. After withdrawal of SSKI, patients were again seen at intervals of one to three weeks, if possible, for as long as was deemed necessary.

Serum T_4 concentration was measured by the isotopic-binding displacement method of Murphy and Pattee,[13] serum cholesterol by the procedure of Levine and Zak (Auto-Analyzer),[14] and antithyroglobulin antibodies by the tanned red-cell agglutination technic. The distribution of a small tracer concentration of ^{131}I-labeled T_4 among the serum proteins was assessed in filter paper by direct-flow electrophoresis, with the use of barbital buffer, pH 8.6. Serum concentrations of TSH were measured by radioimmunoassay, the double-antibody technic

TABLE 1. *Base-Line Studies in Patients with Graves Disease Treated with Radioactive Iodine or Surgery.*

	Age (Yr)	^{131}I Dose (mCi)	Interval since Treatment (Yr)	24-Hour ^{131}I Uptake (%)	Serum T_4* (μg/100 Ml)	Serum TSH (μU/Ml)	Serum Cholesterol* (Mg/100 Ml)	Serum Antithyroid Antibodies* (Titer)
Radioiodine treatment:								
Range	28-62	3.0-11.2	0.5-3.0	17-36	4.0-8.0	0-19	152-366	0-1:2500
Mean	52.1	6.9	1.5	28.7	6.0	9.2	229	–
SD	11.1	2.8	0.9	5.9	1.2	4.7	63	–
Surgical treatment:								
Range	23-37	–	1.5-6.0	20-45	4.0-8.5	1-18	113-245	0-1:250
Mean	30.7	–	3.0	28.6	6.8	11.3	185	–
SD	5.7	–	1.8	9.3	1.5	6.5	49	–

*Performed at Boston Medical Laboratory, Boston, Mass.

Before the initiation of stable iodide therapy, all patients were carefully examined, particular attention being paid to signs of altered metabolic status and thyroid size. In addition to the laboratory indexes of thyroid status noted above, perchlorate-discharge tests were conducted to detect gross abnormalities in the thyroidal organic-binding mechanism.[12] A tracer dose of ^{131}I was administered orally, and its uptake by the thyroid gland measured at two hours. At this time, 1.0 gm of sodium perchlorate was administered orally, and epithyroid counting was performed every 15 minutes for the next hour. A positive or abnormal perchlorate response was defined as a decrease in thyroidal ^{131}I content of at least 15 per cent of the amount present when perchlorate was administered.

After these control observations, patients were given saturated solution of potassium iodide (SSKI), 5 drops daily, and were examined at intervals of one to three weeks thereafter. Blood was drawn for measurements of the several laboratory tests of thyroid status. Iodide was discontinued either when

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described by Odell et al.[15] being employed. Statistical analyses were conducted according to methods described by Snedecor.[16]

Results

Before iodide administration, none of the patients had detectable goiter. In all, values for the 24-hour thyroidal uptake of ^{131}I, as well as serum T_4 and serum TSH concentrations, were normal (Table 1). An abnormally high value of serum cholesterol was seen in one patient, but this was not accompanied by any clinical or other laboratory evidence of hypothyroidism. Mean values for these functions in the radioiodine-treated and surgically treated groups were remarkably similar. Among patients so tested, the perchlorate-discharge test was normal in seven of the eight treated with radioiodine and in all seven treated surgically. Antithyroglobulin-antibody titers exceeded 1:250 in only one patient.

Effect of Stable Iodide in Patients Treated with Radioactive Iodine

Administration of 5 drops of SSKI daily led to a prompt and sustained decrease in serum T_4 in all 10 patients (Fig. 1A) that was seen as early as one week after iodide administration. By four to six weeks, the mean serum T_4 concentration had fallen

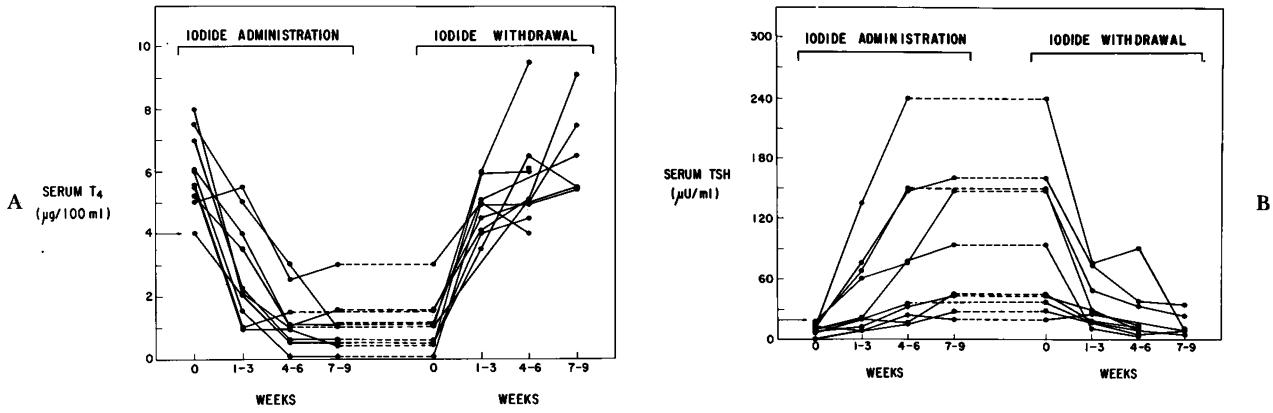

FIGURE 1. *Response of the Serum Thyroxine Concentration* (A) *and TSH Concentration* (B) *to Iodide (SSKI, 5 Drops Daily) in Patients with Diffuse Toxic Goiter Who Had Been Rendered Euthyroid by Treatment with Radioiodine.*

from 6.0 ± 1.2 (mean ± SD) to 1.2 ± 0.9 μg per 100 ml. In all patients, this decrease in serum T_4 concentration was accompanied by a striking rise in serum TSH concentration (Fig. 1*B*). Although the extent of increase in serum TSH concentration was variable, values in the range found in primary myxedema were present in all patients. Four to six weeks after the onset of iodide administration, serum TSH concentrations had increased from a mean of 9.2 ± 4.7 (mean ± SD) to 81.0 ± 75.3 μU per milliliter. When iodide was withdrawn, serum T_4 concentrations rose rapidly, and by the fourth week had returned to normal in all patients. Serum TSH concentrations also returned to normal, but in four patients the return to normal levels was delayed. In two of these patients normal TSH values were not found until 12 and 20 weeks, respectively, after withdrawal of iodide.

The percentage of a tracer quantity of ^{131}I-labeled T_4 bound by thyroxine-binding globulin (TBG) was determined in control serum, in the serum with the lowest T_4 concentration after iodide administration and in serum obtained when the T_4 concentration had returned to normal after withdrawal of iodide (Fig. 2). In eight of 10 subjects, the fraction of T_4 bound by TBG increased during iodide administration and returned to the normal range after withdrawal of iodide (86.5 ± 3.4, 89.1 ± 3.3 and 85.1 ± 3.6 per cent). Finally, in eight of 10 patients, serum cholesterol concentrations increased during iodide administration, the mean rising from 229 ± 63 to 288 ± 125 mg per 100 ml (p less than 0.05) (Fig. 3).

The striking decrease in serum T_4 and the rise in serum TSH concentration induced by iodide were accompanied by severe symptoms of hypothyroidism, including intolerance to cold, weight gain and fatigue. In two patients iodide was discontinued as early as five weeks after it was begun, owing to the severity of these symptoms. Physical examination confirmed the presence of myxedema, with such findings as periorbital edema, dry skin and delay in the relaxation phase of deep tendon reflexes. Despite the emergence of myxedema, no goiter developed during the period of observation. After iodide withdrawal, the clinical signs of hypothyroidism rapidly disappeared, and all patients soon became euthyroid.

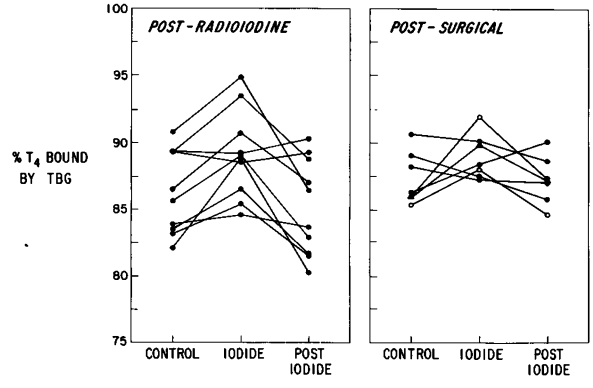

FIGURE 2. *Binding of Thyroxine by TBG (Thyroxine-Binding Globulin) in the Serum of Patients with Treated Diffuse Toxic Goiter before, during and after Iodide Administration.*
In the postsurgical group, open circles represent data in J.H. and M.M., and the triangles data in M.K.

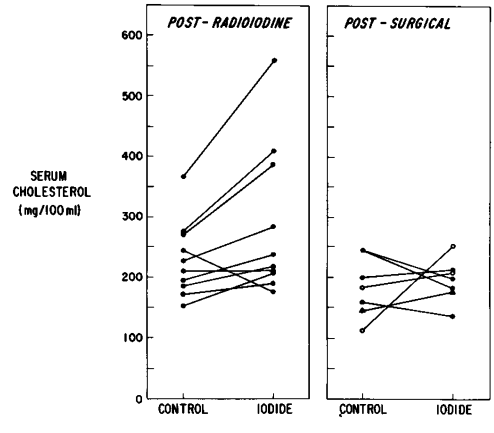

FIGURE 3. *Serum Cholesterol Concentration before and during Iodide Administration in Patients with Treated Diffuse Toxic Goiter.*
In the postsurgical group, open circles represent data in J.H. and M.M., and the triangles data in M.K.

Effect of Stable Iodide in Patients Treated Surgically

Iodide supplements led to a variable response among the seven patients who had undergone subtotal thyroidectomy. For this reason, results in this group are presented in tabular, rather than graphic, form (Table 2).* In two (M.M. and J.H.), the pattern of response resembled that seen in patients treated with ^{131}I. In M.M. the serum T_4 concentration decreased, and serum TSH concentration rose by the third week of iodide administration. In J.H. similar changes occurred, but not until the ninth week of iodide administration. Clinical hypothyroidism occurred in both patients. After iodide was withdrawn, serum concentrations of T_4 and TSH returned to normal in both.

M.K., whose serum T_4 concentration displayed a slight, delayed, decrease during iodide administration. In the other four patients no consistent change in the percentage of ^{131}I-labeled T_4 bound by TBG was seen (Fig. 2). Serum cholesterol concentration increased during iodide administration in the three patients in whom T_4 binding by TBG was increased (J.H., M.M. and M.K.), but remained unchanged in the other four (Fig. 3).

Discussion

In the present studies, all 10 patients who were euthyroid after radioiodine treatment of diffuse toxic goiter became hypothyroid when given relatively small pharmacologic doses of iodide. That hypothyroidism was truly present was evidenced by the appearance of classic signs and symptoms, the increase in serum cholesterol, the rise in serum TSH concentration, the fall in serum T_4 concentration, and the demonstration that the decrease in serum T_4 concentration was not the result of an inhibition of T_4 binding by the serum TBG.

Several features of this response to iodide in the radioiodine-treated patient seem quite remarkable. The first unusual feature is the remarkably high frequency with which myxedema was induced by iodide in this group. To our knowledge, no other group of patients has been shown to display such uniform susceptibility to the development of iodide myxedema. The precise frequency of iodide goiter and myxedema in the population of presumably normal persons receiving iodide chronically is unknown, but the abnormality probably occurs in only a small percentage of the general population.[6-8] Hagen et al.[11] recently noted that in approximately 25 per cent of their patients who were given iodide within two or three weeks after a small therapeutic dose of ^{131}I, hypothyroidism soon developed and was relieved after withdrawal of iodide. No further details were provided; hence, it is not possible to ascertain in what manner, if any, the patients in whom iodide myxedema developed differed from those in whom it did not. The response that these workers observed may be akin to that which we

TABLE 2. *Response of Serum Thyroxine and TSH Concentrations to the Administration and Withdrawal of Iodide in Patients with Diffuse Toxic Goiter Who Had Been Rendered Euthyroid by Surgery.**

Patient	Control Serum T_4 Concentration (μG/100 Ml)	Serum T_4 Concentration after Iodide Administration (μG/100 Ml)				Serum T_4 Concentration after Iodide Withdrawal (μG/100 Ml)		
		1-3 wk	4-6 wk	7-9 wk	10 wk	1-3 wk	4-6 wk	10 wk
M.T.	7.0 (15)	6.0	6.5 (8)	6.0 (8)			6.5 (0)	
M.G.	7.5 (15)		4.5 (10)	7.0 (25)		7.5 (13)		
K.P.	7.5 (18)	5.5 (38)	6.0 (35)	5.5 (50)		7.0 (15)		
A.B.	4.0 (4)	2.0 (14)	3.0 (14)	4.0 (7)				
M.K.	8.5 (1)	6.0 (4)	8.5 (4)	3.5 (0)	3.5 (0)		9.5 (0)	
J.H.	7.5 (16)	8.0	7.0 (13)	3.0 (203)	2.0 (300)	5.5 (114)	6.5 (68)	7.5 (0)
M.M.	5.5 (10)	2.0 (44)	1.5 (83)				5.5 (1)	

*Values in parentheses represent immunoassayable TSH concentrations (μU/ml) in same sample of serum in which corresponding serum T_4 value was obtained.

In two other patients (M.K. and A.B.) serum T_4 concentration decreased into the hypothyroid range during iodide administration, but without concomitant increase in serum TSH. In M.K. serum T_4 concentration was not abnormal until the ninth week of iodide administration, was accompanied by only minimal evidence of hypothyroidism and returned to normal promptly after iodides were withdrawn. In A.B., serum T_4 concentration decreased to 2.0 μg per 100 ml by the third week and then slowly returned to the control value, despite continued iodide administration.

In three patients (M.T., M.G. and K.P.), serum T_4 concentrations and clinical state were unchanged during 10 weeks of iodide administration. Serum TSH was unchanged in M.T.; however, in M.G. and K.P., serum TSH concentrations increased slightly during, and returned promptly to normal after, iodide treatment.

During iodide administration, the proportion of a tracer quantity of ^{131}I-labeled T_4 bound by TBG in serum increased in the two patients (J.H. and M.M.) in whom definite hypothyroidism developed and in

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have found, but several important differences in the two series of observations are evident. First of all, in the studies of Hagen et al., stable iodine therapy was administered while the patients were still thyrotoxic; the patients in the present series were euthyroid. Secondly, the interval after radioiodine in the former study was far less, stable iodine having been begun two or three weeks after administration of radioiodine, a period after standard ^{131}I therapy in which positive perchlorate-discharge tests are common.[10] Finally, in the former series, small doses of radioiodine had been employed, whereas our patients had received standard doses.

The second unusual feature of the present findings is the rapidity with which iodide myxedema developed. This occurred within one or two weeks in some patients and by six weeks in all. In the general population of susceptible patients, iodide myxedema usually does not appear until iodide has been taken for months – often, for many months. Furthermore, in patients with hyperthyroidism, even large doses of antithyroid agents fail to decrease the PBI within a short time and do not induce hypothyroidism unless they are given for many weeks. This is best explained by the time required for inhibition of new hormone synthesis to result in depletion of the preformed glandular thyroid-hormone pool. In this light, the rapidity with which iodide myxedema developed in radioiodine-treated patients suggests the operation of one of two possible mechanisms. Iodide may have induced an abrupt, severe and sustained inhibition of thyroid-hormone release. This response would be an exaggeration of the mechanism by which iodine is generally considered to ameliorate thyrotoxicosis acutely – that is, inhibiting the hormone-releasing mechanism.[17-20] This seems unlikely to us, for the inhibitory effect of iodine on hormonal release is antagonized by TSH.[19] In view of the very high concentrations of TSH that developed in many of these patients, relief of the inhibition of hormonal release would have been expected. A more likely possibility is that iodine produced an abrupt, severe and sustained inhibition of hormone synthesis. In the first place, in virtually all the patients, perchlorate-discharge tests became distinctly or suggestively abnormal during iodine administration, indicating at least a relative inhibition of the organification mechanism. Secondly, enhanced secretion of TSH would stimulate iodide transport, increase intrathyroidal iodide concentration and intensify thereby any blockade of organic binding that was present. If iodide did indeed act by inhibiting hormonal synthesis, an interpretation we favor, the rapidity with which myxedema developed suggests that the thyroid glands of these patients before iodide treatment must have been almost devoid of hormone and releasing newly synthesized hormone at a very rapid fractional rate.

The third unusual feature of the response to iodide in radioiodine-treated patients was the failure of goiter to develop despite the emergence of unequivocal myxedema. As revealed by radioimmunoassay, this cannot be ascribed to lack of a compensatory increase in TSH secretion. Rather, it may reflect radiation damage to the thyroid gland, which prevents thyroid-cell replication. This situation would be analogous to that seen in rats given moderate doses of radioiodine, in which a decreased goitrogenic response to antithyroid agents or to a diet low in iodine has been observed.[21]

Although less common than in radioiodine-treated patients, disturbances in thyroid hormone economy during iodide administration were not infrequent in the group of patients with Graves disease whose thyrotoxicosis had been treated surgically. In two of seven patients clinical hypothyroidism developed in association with both increased serum TSH concentration and decreased serum T_4 concentration during iodide administration. In the other five patients, one displayed no change in thyroid status, and the remaining four had either a slight decrease in serum T_4 concentration or an increase in serum TSH concentration, but not both. These changes were associated with little or no evidence of hypothyroidism. Our data seem generally in accord with those of Thompson and Thompson,[22,23] reported in 1928 and 1929, which indicated that in some patients with Graves disease who are given iodide after subtotal thyroidectomy a subnormal basal metabolic rate (BMR) develops, increasing when iodide is withdrawn. The precise frequency of this response could not be ascertained from the data presented.

The foregoing considerations raise the question of whether the nature of the underlying disorder – that is, diffuse toxic goiter – rather than merely the mode of its treatment conditions the abnormal responses to iodide. Several additional lines of evidence support this view. In early studies of the effects of iodide in Graves disease six cases can be found in which hypometabolism was present during iodine therapy and was reversed after its withdrawal.[22-25] Furthermore, in some patients with iodide myxedema, not known to have had previous thyrotoxicosis or other evidence of Graves disease, the thyroidal uptake of ^{131}I cannot be suppressed by exogenous thyroid hormone.[26] In the absence of autonomously functioning thyroid nodules, lack of suppressibility of thyroid function is generally accepted as a hallmark of Graves disease.

Thus, it seems very likely that something inherent in the thyroid gland of patients with diffuse toxic goiter renders it inordinately susceptible to the induction of myxedema by iodide. We originally postulated that a defect in organic binding induced by radioiodine might result in a further enhancement of susceptibility to iodide myxedema. This may indeed be so, since the frequency of iodide myxedema in the radioiodine-treated group was significantly greater than in the surgically treated group

under the conditions of this study. Although a defect in organic binding demonstrable by an abnormal perchlorate discharge test before iodide administration was present in only one of eight radioiodine-treated patients so tested, a more subtle defect in organic binding may indeed have been present. On the other hand, the greater frequency of iodide myxedema in the group treated with radioiodine than in that treated surgically may not represent a real difference in inherent susceptibility to the effects of iodide in the two groups. It is possible that iodine-induced myxedema would have developed in a greater proportion of the surgically treated patients if administration of iodide had been continued for a longer period. Such longer latency might reflect not a lesser sensitivity to iodide in the surgically treated group, but a larger pool of preformed hormone in the gland.

Since these studies were completed, two of the radioiodine-treated patients who had returned to a normal metabolic state after withdrawal of iodide have slowly become hypothyroid. It may be that the speed and extent of the abnormal response to iodide administration in such patients is a premonitory index for the subsequent development of myxedema.

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