THYROID
Volume 11, Number 5, 2001
Mary Ann Liebert, Inc.

Iodine-Induced Hypothyroidism

K. Markou, N. Georgopoulos, V. Kyriazopoulou, and A.G. Vagenakis

Iodine is an essential element for thyroid hormone synthesis. The thyroid gland has the capacity and holds the machinery to handle the iodine efficiently when the availability of iodine becomes scarce, as well as when iodine is available in excessive quantities. The latter situation is handled by the thyroid by acutely inhibiting the organification of iodine, the so-called acute Wolff-Chaikoff effect, by a mechanism not well understood 52 years after the original description. It is proposed that iodopeptide(s) are formed that temporarily inhibit thyroid peroxidase (TPO) mRNA and protein synthesis and, therefore, thyroglobulin iodinations. The Wolff-Chaikoff effect is an effective means of rejecting the large quantities of iodide and therefore preventing the thyroid from synthesizing large quantities of thyroid hormones. The acute Wolff-Chaikoff effect lasts for few a days and then, through the so-called "escape" phenomenon, the organification of intrathyroidal iodide resumes and the normal synthesis of thyroxine (T_4) and triiodothyronine (T_3) returns. This is achieved by decreasing the intrathyroidal inorganic iodine concentration by down regulation of the sodium iodine symporter (NIS) and therefore permits the TPO-H_2O_2 system to resume normal activity. However, in a few apparently normal individuals, in newborns and fetuses, in some patients with chronic systemic diseases, euthyroid patients with autoimmune thyroiditis, and Graves' disease patients previously treated with radioimmunoassay (RAI), surgery or antithyroid drugs, the escape from the inhibitory effect of large doses of iodides is not achieved and clinical or subclinical hypothyroidism ensues. Iodide-induced hypothyroidism has also been observed in patients with a history of postpartum thyroiditis, in euthyroid patients after a previous episode of subacute thyroiditis, and in patients treated with recombinant interferon-α who developed transient thyroid dysfunction during interferon-α treatment. The hypothyroidism is transient and thyroid function returns to normal in 2 to 3 weeks after iodide withdrawal, but transient T_4 replacement therapy may be required in some patients. The patients who develop transient iodine-induced hypothyroidism must be followed long term thereafter because many will develop permanent primary hypothyroidism.

Introduction

IODINE IS AN ESSENTIAL ELEMENT for the formation of the thyroid hormones, triiodothyronine (T_3) and thyroxine (T_4), which play an important role in the development, growth, and metabolism of almost all organ systems. The thyroid gland has the capacity and holds the machinery to maintain the synthesis and secretions of thyroid hormones even when the availability of iodine becomes scarce, or when it is available in excessive amounts. Thus, in iodine deficiency the decrease in iodine availability results in an increase in TSH secretion, thyroid growth is stimulated resulting in a goiter formation, the iodine trapping mechanism is enhanced and there is a shift of the intrathyroidal formation of T_4, to the more active metabolite T_3. On the other hand, an increased iodide load to the normal thyroid can be easily handled by an autoregulatory mechanism independent of thyrotropin (TSH). The purpose of this manuscript is to review the effects of excessive iodine intake on thyroid hormone economy in patients with an apparently normal thyroid gland function and in those prone to develop clinical or subclinical hypothyroidism when exposed to pharmacological doses of iodides.

Physiological Effects of Iodide on Thyroid Function

In 1944 Morton et al. (1) made the seemingly paradoxical observation that the addition of large quantities of iodide to the culture of sheep thyroid slices, inhibited the organic form of iodide. Wolff and Chaikoff (2) later demonstrated that a similar effect could be elicited *in vivo* by administering large doses of iodide to rats sufficient to maintain high levels of plasma inorganic iodide concentration. This finding was seemingly similar to that induced by the antithyroid drugs such as methimazole and propylthiouracil (PTU). With the passage of time, the intrathyroid iodide concentration pre-

Department of Medicine, Division of Endocrinology, University of Patras Medical School, Patras, Greece.

sumably decreased, the organification of the remaining iodine resumed and returned to pretreatment quantities. The acute inhibition of the formation of organic iodine was then called the acute Wolff-Chaikoff effect and the resumption of the organification of iodine was named the "escape" or "adaptation" phenomenon. The small proportion of organic iodine formed during the acute Wolff-Chaikoff effect was found to be incorporated mainly into monoiodotyrosine (MIT) relative to diiodotyrosine (DIT) leading to an increased MIT/DIT ratio (3). A decreased quantity of iodothyronines were formed, a characteristic effect of antithyroid drugs (4).

It is, therefore, apparent that the acute Wolff-Chaikoff effect operating in a normal thyroid gland is a successful means of preventing the thyroid from forming massive quantities of thyroid hormones, thus preventing a hyperthyroid state to ensue. The adaptive response of the thyroid to small or moderate increments in the available iodine, however, is not perfect. In 1964, Nagataki and Ingbar (5) studied the acute response to a greater range of iodide doses in the rat. With small or moderate doses administered, total organic iodine was increased and the apportionment of organic iodine to MIT, DIT, T_4, and T_3 was not altered. However, after a critical point (i.e., 250 μg/250 g rat) a sharp decline in the total organified iodine was accompanied by an increase in the MIT/DIT ratio and a decrease in T_4 and T_3 formation. These findings demonstrated that the proposed autoregulation of intrathyroidal iodine fails to protect the thyroid from smaller quantities of iodine and that hormonal formation indeed increases (5).

The mechanism responsible for the acute Wolff-Chaikoff effect remains elusive despite the 52 years since the original observation. The pioneer work of Raven (6) clearly showed

Table 1. Commonly Used Iodine-Containing Drugs

Drugs	*Iodine content*
Oral or local	
Amiodarone	75 mg/tablet
Benziodarone[a]	49 mg/100-mg tablet
Calcium iodide (e.g., Calcidrine Syrup)	26 mg/ML
Diiodohydroxyquin (e.g., Yodoxin)	134 mg/tablet
R-Gen	6 mg/mL
Echothiophate iodide ophthalmic solution (e.g., Phospholine)	5–41 μg/drop
Hydriodic acid syrup	13–15 mg/mL
Iodochlorhydroxyquin (e.g., Entero-Vioform)	104 mg/tablet
Iodine-containing vitamins	0.15 mg/tablet
Iodinated glycerol (Iophen)	15 mg/tablet
Idoxuridine ophthalmic solution (e.g., Herplex)	18 μg/drop
Isopropamide iodide (e.g., Darbid.Combid)	1.8 mg/tablet
Kelp	0.15 mg/tablet
Potassium iodine (KI) (e.g., Quadrinal, pima syrup)	24 mg/mL, 255 mg/mL
Mudrane	195 mg/tablet
Lugol's Solution	6.3 mg/drop
Niacinamide hydroiodide + KI (e.g., Iodo-Niacin)	115 mg/tablet
Ponaris nasal emollient	5 mg/0.8 mL
SSKI	38 mg/drop
Parenteral preparations	
Sodium iodide, 10% solution	85 mg/mL
Topical antiseptics	
Diiodohydroxyquin cream (e.g., Vytone)	6 mg/g
Iodine tincture	40 mg/mL
Iodochlorhydroxyquin cream (e.g., Vioform)	12 mg/g
Cellasene	720 μg/serving
Iodoform gauze (e.g., NuGauze)	4.8 mg/100 mg gauze
Povidone iodine (e.g., Betadine)	10 mg/mL
Radiology contrast agents	
Diatrizoate meglumine sodium (e.g., Renografin-76)	370 mg/mL
Iodized oil	380 mg/mL
Iopanoic acid (e.g., Telepaque)	333 mg/tablet
Ipodate (e.g., Oragrafin)	308 mg/capsule
Iothalamate (e.g., Angio-Conray)	480 mg/mL
Metriazamide (e.g., Amipaque)	483 mg/mL before dilution
Lipiodol-™	480 mg/mL

[a]Not FDA approved

[b]Iodine was removed from Organidin and Tuss Organidin in 1995

(Adapted from Braverman LE 1986 Iodide-induced thyroid disease. In: Ingbar SH, Braverman LE (eds). Werner's The Thyroid, 5th ed. Philadelphia, JB Lippincott, p 734.)

that the critical parameter for the Wolff-Chaikoff effect was the amount of intrathyroidal iodine and not the plasma concentration. It was also proposed that the iodine-to-newly-formed-thyroglobulin ratio (I:Tg) was critical for iodinations. Iodine-deficient rats treated with small quantities of the protein inhibitor cycloheximide, and given small quantities of iodides (12 μg per rat), permitted induction of the acute Wolff-Chaikoff effect by an intrathyroid concentration of iodine insufficient to produce this effect in control animals (7).

The above experimental data, however, do not fully explain the acute Wolff-Chaikoff effect. One postulate ascribes the effect to an interaction of oxidized iodine with excess iodide to yield the triiodide ion I_3, a moiety known to be incapable to carry out organic iodinations (8). Recently, organic iodocompounds formed within the thyroid were proposed as a possible mechanism. a-Iodohexadecanal, a major iodolipid has been shown to inhibit nicotinamide adenine, dinucleotide phosphate oxidase, thyroid peroxidase, and TSH-induced cyclic adenosine monophosphate (cAMP) formation in the thyroid (9).

Evidence concerning the mechanism of escape was lacking until the ingenious experiments of Braverman and Ingbar in 1963 (10). Studies on iodine metabolism were carried out in rats and concluded that adaptation to long-term iodide exposure was caused by a decrease in iodine transport, thereby reducing the intrathyroid iodine concentration below the critical inhibitory levels, therefore, allowing the iodinations to resume (10). It was pointed out that the adaptation was TSH-independent because it occurred in normal and hypophysectomized rats. The recent cloning of the sodium iodide symporter (NIS) by Dai et al. (11) led Braverman's group to reexamine the role of this protein in the adaptation of long-term exposure to iodides. Both NIS mRNA and protein were decreased at 1 and 6 days after long-term iodide ingestion. Thyroid peroxidase (TPO) mRNA was decreased at 6 days of long-term iodide ingestion and 24 hours after an acute iodide load (12). Similar results were reported in hypothyroid dogs treated for 48 hours with moderate doses of iodides. The expression of NIS and TPO mRNA was inhibited and the half-life of NIS protein was calculated to be 4 days in the dog (13). These data are in agreement with the data published 37 years ago (10) and support the hypothesis that the escape from the acute Wolff-Chaikoff effect is caused by a decrease of NIS protein resulting in a decrease in the thyroidal iodine transport.

Induction of Hypothyroidism and/or Goiter by Excess Iodide

Many patients are exposed to large quantities of iodide present in proprietary medications, in food as a preservative, and in x-ray contrast media (Table 1). Despite the widespread use of excess iodide, few apparently normal subjects with normal thyroid function prior to iodide exposure develop thyroid dysfunction. However, in subjects with underlying thyroid disease not readily apparent, exposure to large doses of iodide usually results in hypothyroidism and/or goiter which abates after iodide withdrawal (Table 2). Less frequent, but much more difficult to treat and occasionally life-threatening, thyrotoxicosis may follow iodide exposure as discussed elsewhere (14) and in this issue.

TABLE 2. IODINE-INDUCED HYPOTHYROIDISM OR GOITER

Normal subjects
Fetus and neonate
Infant
Adults (high iodine intake in Japan)
Elderly
Chronic nonthyroidal illness
Cystic fibrosis
Chronic dialysis treatment
Thalassemia major
Diabetic nephropathy (?)
Anorexia nervosa
With underlying thyroid disease
Hashimoto's thyroiditis
Graves' disease (after euthyroidism by ^{131}I, thyroidectomy or drug therapy)
Subclinical hypothyroidism, especially in the elderly
after post partum thyroiditis
after hemithyroidectomy for benign nodules
after amiodarone destructive thyrotoxicosis
post-interferon-α–induced thyroid dysfunction
Synergism with other drugs
Lithium, sulfisoxazole, sulfadiazine (?)

Adapted from Roti and Vagenakis (14).

Normal subjects

Iodide-induced goiter occurred in about 10% in the coastal regions of Hokkaido, a northern island of Japan (15,16). The inhabitants of this region were consuming large quantities of seaweed, especially kelp (Laminaria) containing large quantities of iodide. It has been estimated that the quantity of iodide ingested daily may exceed 200 mg. Such goiter has now disappeared after the restriction of intake of kelp products in the affected areas (17,18). However, Kono et al. (19) reported that in coastal areas of the Hokkaido Islands, the prevalence of nonautoimmune hypothyroidism was still 9.7% is some areas and it was proportional to iodide intake whereas the incidence of nonautoimmune thyrotoxicosis was not related to iodide consumption. In an earlier study, Kono et al. (20) reported that when the iodine intake was restricted, the increased serum TSH concentrations was normalized in patients with negative antithyroid antibodies but remained elevated in those with positive antibodies. This suggests that iodine-induced hypothyroidism was an additional component to the etiology of hypothyroidism due to autoimmune thyroiditis.

Similar results were reported by Szabolcs et al. (21) in Slovakia where the cumulative prevalence of hypothyroidism increased progressively in relation to urinary iodine exertion of 72, 100, and 513 μg/g creatinine. Endemic iodide goiter has also been observed in 64% of children in an area located in central China consuming water containing approximately 500 μg/L (22). In another study from China, euthyroid goiter was observed in 10% of the subjects of 19 Chinese counties caused by iodine-rich drinking water (23).

Ingestion of smaller quantities of iodine may affect thyroid function in a population at large. In an elderly Islandic population, the prevalence of serum TSH concentrations above 4 mU/L was 18% in subjects with elevated iodine exertion rates (33 to 703 μg/L; median, 150 μg/L) whereas in

subjects residing in Jutland with low urinary iodine secretion (median, 38 μg/L; range, 6–770), low TSH levels (<0.4 mU/L) were the prevalent finding in 9.7% of the cases. There were no differences in the prevalence of antithyroid antibodies in the two populations (24).

Despite the evidence provided by the previous studies it is still controversial whether completely normal subjects may develop perturbed thyroid function when these subjects are exposed to large doses of iodide. We did not observe abnormal thyroid function tests in 20 normal adults treated with 80 mg of Lugol's solution for 2 months (25). Administration of a single dose of 50 to 70 mg of potassium iodide to children for prophylaxis after the Chernobyl reactor accident was not accompanied by an increment in the serum TSH concentration (26). We believe that iodine-induced hypothyroidism does occasionally occur in normal individuals but is exceedingly rare.

Histologic examination of the thyroid of patients with iodine-induced hypothyroidism revealed extensive lymphocytic infiltration in half of the examined thyroids. Various other findings were observed in other specimens including hyperplasia in the follicles with papillary foldings, columnar, or cuboidal changes in cells with clear and vesicular cytoplasm and markedly reduced colloid. Most of these findings reversed after iodine withdrawal (27).

Iodide Goiter and Hypothyroidism in the Newborn

Iodide is readily transferred across the placenta. This may be by active transport in rats but there are no data in humans (28). Iodide may lead to goiter in the newborn in mothers treated for chronic lung disease. The true incidence of hypothyroidism in the newborn infants has not been accurately assessed, although many of them have suggestive evidence of hypothyroidism. Six of 25 and 8 of 22 newborn infants with iodide goiter died of tracheal obstruction and asphyxiation (reviewed by Wolff [28], Benhard et al. [29], and Nagle et al. [30]). Although iodide goiter of the newborn usually disappears in a few months, surgical intervention is often indicated to relieve tracheal obstruction (31,32). Diagnosis and treatment of fetal goiter and hypothyroidism can be obtained by ultrasonography and cordocentesis, as judged by the diagnosis of fetal goiter in a fetus whose asthmatic mother consumed two to three spoonfuls daily of a syrup containing 150 mg per 15 mL of iodide (33).

NIS expression has been found in lactating mammary glands and iodine is actively transported by the breast tissue and is secreted into the milk. Studies in the rat revealed that iodide goiter and hypothyroidism was sustained in nursing pups up to 20 days of nursing dams ingesting large doses of iodides (34).

The thyroid of the fetus and newborn can be exposed to large doses of iodine from various sources. In nonpregnant women, vaginal use of povidone-iodine pessaries do not affect thyroid function. However, application of vaginal solutions or cream of povidone iodine resulted in transient hypothyroidism in the newborn especially when the iodide use was continued during the third trimester of pregnancy and during labor (35,36). Topical application of povidone iodine and administration of an iodinated contrast dye to the newborn resulted in an elevation of serum TSH especially in premature low birthweight infants. This was observed mainly in Europe where iodine intake is relatively low (37–40). Transient hypothyroidism was not a common sequela of routine skin cleansing with iodine in premature newborn infants in North America (41).

After the Chernobyl nuclear reactor accident a single dose of 15 mg of potassium iodide was administered to newborns for radiation prophylaxis of the thyroid. A transient increase of serum TSH concentration was observed in 0.37% of the 3,214 treated newborns. Similarly, exposure of the thyroid to iodine *in utero* due to maternal iodide prophylaxis did not result in an increase in congenital hypothyroidism as judged by screening studies (26). However, it must be pointed out that, at least in Europe, iodide consumption is the major cause of transient congenital hypothyroidism, resulting in 3% of recalls of newborns for verification of hypothyroidism in comparison with 0.1% in newborns from mothers with normal iodine intake (37–40). As mentioned above, this is attributed to relatively low iodine intake in Central Europe in contrast to North America where iodide intake is adequate (41). A number of infants born of mothers suffering from thyrotoxicosis and treated with iodides or Lugol's solution have been reported to have goiter (28). Approximately 6% of newborns from mothers with Graves' disease living in Japan who where treated with 6 to 40 mg iodine daily from 11 to 37 weeks of gestation had elevated cord blood serum TSH concentrations but normal concentration of thyroid hormones (42). It must be noted, however, that the lack of fetal-iodine–induced hypothyroidism in those newborns may be caused by the concomitant presence of autoimmune thyroid hyperfunction and the high ambient iodine intake in Japan.

Iodine-containing drugs consumed during pregnancy by the mother may also result in iodine-induced hypothyroidism in the fetus. A few cases of amiodarone-induced hypothyroidism in the newborn were reported from North America (43) and Europe (44).

Iodine-Induced Hypothyroidism in Nonthyroidal Illness

Patients with chronic nonthyroidal illness are not susceptible to the inhibitory effects of iodide. A few cases, however, have been reported to occur in such patients but an accompanying underlying disease has not been excluded in these cases. Iodides administered to patients with chronic obstructive pulmonary diseases including asthma may lead to hypothyroidism in some cases. However, underlying Hashimoto's thyroiditis which predispose these patients to the inhibitory effects of iodine was not ruled out (14).

Children with cystic fibrosis treated with sulfisoxazole have been reported to be susceptible to iodine-induced hypothyroidism. No apparent underlying thyroid abnormality has been found in these patients (45). Increased amount of lipofuscin has been reported in patients with cystic fibrosis but this has also been found in mice fed large quantities of iodides.

The effect of long-term iodide administration to normal children has not been evaluated. Markou et al administered 80 mg potassium iodide to 30 normal children 8 to 14 years old for 3 months and none developed overt or subclinical hypothyroidism. Transient elevated serum TSH values (5–8 mU/L) were noted in 70% of the children, usually during the first 2 to 3 weeks after the beginning of iodide administration. TSH returned to normal levels despite the continuation of iodide treatment (46).

In children and adults suffering from thalassemia major and who require long-term blood transfusion therapy, iodide administration (60 mg daily) for 30 days resulted in subclinical hypothyroidism in 70% of pubertal and 47% of adult patients. In all patients, TSH levels returned to pretreatment levels after iodide withdrawal. In the follow-up of these patients for 5 years, 64% of those who developed transient hypothyroidism during iodide administration developed permanent clinical hypothyroidism. Only 1 of the 11 patients who remained normal during iodide administration became hypothyroid during the 5 years of observation. It appears that thyroid hemosiderosis renders the thyroids of these patients susceptible to the inhibitory effects of iodide (47).

Patients with chronic renal failure may develop thyroid dysfunction when exposed to large doses of iodide. Iodine is cleared mainly by the kidney, and in renal failure the plasma inorganic iodine has been found to increase substantially. The incidence of iodine-induced hypothyroidism was found in 3.2% of patients on chronic dialysis treatment (48). The thyroid abnormalities in these patients included, thyroid enlargement, normal or elevated thyroid RAI uptakes, positive perchlorate discharge tests, and absence of lymphocyte infiltration. Two patients with diabetic nephropathy developed iodine-induced nonautoimmune hypothyroidism that was reversed after iodide restriction in one patient and hemodialysis treatment in the other (49). However, in another study, no relationship was found to exist between thyroid abnormalities to iodide retention and application of iodide-containing antiseptics (50).

Iodine-induced hypothyroidism was also reported in patients with no apparent thyroid disease. Mild reversible hypothyroidism was observed in elderly patients consuming iodinated glycerol (51). One patient developed hypothyroidism after treatment with eye drops of echothiophate iodide (52). Two Japanese patients with anorexia nervosa developed iodine-induced hypothyroidism. One patient became hypothyroid during the bulimic period of the disease due to consumption of large quantities of Oshaberi-Kombu. In Japan, this food is extensively consumed as low-calorie food and one package of Oshaburi-Kombu contains approximately 13.4 mg of iodine (14,53).

Patients with Underlying Thyroid Disease

Patients with underlying, perhaps mild, autoimmune thyroid disease such as Hashimoto's thyroiditis are particularly susceptible to developing iodine-induced hypothyroidism over the ensuing several weeks after the exposure. Most patients with Hashimoto's thyroiditis exhibit a positive iodine-perchlorate discharge test suggesting a defect in the intrathyroid organic binding of iodine. The first study that conclusively demonstrated the susceptibility of these patients to iodine induced hypothyroidism was done in 1972 when 50% of patients with histologically proven autoimmune thyroiditis developed frank hypothyroidism after administration of 180 mg of iodide daily. The hypothyroidism was observed 2 to 8 weeks after the initiation of iodide administration and was reversed between 2 to 4 weeks after iodide withdrawal. The iodine-perchlorate discharge test was positive in those who developed iodine hypothyroidism and negative in those who did not (54).

Contradictory results have been obtained when susceptible patients with Hashimoto's thyroiditis are exposed to a moderately increased iodine intake. In one study, ingestion of 1.5 mg of iodide daily for 3 months did not affect thyroid function in such patients (55). In a few Japanese patients with elevated alimentary iodide intake and hypothyroidism, restriction of iodide intake restored normal thyroid function. All had an underlying lymphocytic thyroiditis (56). It must be noted that a large number of these patients developed permanent hypothyroidism with the passage of time even in the presence of normal serum plasma inorganic iodine, suggesting that patients susceptible to transient iodine-induced hypothyroidism are at high risk to develop permanent hypothyroidism, probably due to the underlying destructive autoimmune process in the thyroid.

Small doses of iodide (i.e., 250 μg of iodide per day) were given to 40 patients with positive TPO antibodies and residing in an area of mild iodine deficiency. Eight of them developed subclinical and clinical hypothyroidism and no changes in TPO levels (57). All had TSH higher than 3 mU/L before iodide treatment suggesting incipient thyroid dysfunction. In a recent report from India, patients with juvenile autoimmune thyroiditis develops overt clinical (6.5%) or biochemical hypothyroidism (15%) after salt iodization (58). In another study, a transient increase of serum T_4 and T_3 concentrations followed the administration of small quantities of iodide in patients with TPO-positive antibodies residing in an area with low ambient iodine intake (59).

Studies in rats that were genetically susceptible to chronic lymphocytic thyroiditis (BB/wor rats) and that were fed large quantities of iodide, surprisingly did not develop an increased incidence of hypothyroidism, and no demonstrable abnormality in intrathyroidal iodine organified was found (60). However, in rats demonstrating the most extensive lymphocytic thyroiditis, iodide administration does induce hypothyroidism (61).

Patients with Graves' disease were treated with iodides alone when the antithyroid drugs were not available. Few of them developed reversible hypothyroidism, and in some, the hyperthyroidism worsened during iodide treatment. Euthyroid patients with Graves' disease treated years earlier with ^{131}I, thyroidectomy or antithyroid drugs, are also inordinately sensitive to iodine-induced hypothyroidism (14). Hypothyroidism was rapidly developed in 100% of patients treated with ^{131}I and in 40% of those treated surgically (62). It appears that an underlying organification defect is present in all patients with Graves' disease who developed iodine hypothyroidism because a positive iodine perchlorate discharge test was present. Whether this iodine sensitivity is an inherent component of Graves' disease or to a therapy-induced effect is at present not definite.

The etiology of surgically treated patients with Graves' disease to iodine-induced hypothyroidism is not readily apparent. Similar susceptibility to the inhibitory effect of pharmacologic doses of iodide is observed in patients undergoing hemithyroidectomy for a benign thyroid nodule, and in hemithyrectomized BB/wor rats prone to develop lymphocytic thyroditis (63,64). It appears that the hyperfunctioning thyroid remnant is unable to adapt to iodide excess. It is questionable, however, whether the thyroid gland of a patient with a thyroid nodule should be considered normal.

There are several other thyroid diseases that can predispose susceptible individuals to iodine-induced hypothy-

roidism. Women who are euthyroid after a previous episode of postpartum thyroiditis are prone to iodine-induced hypothyroidism. In 9 of 11 women, ingestion of 300 mg of iodide daily resulted in overt reversable hypothyroidism and in some was accompanied by a goiter (65). Most of these patients had a positive perchlorate discharge test. Small doses of iodide administered to patients predisposed to developing postpartum thyroiditis intensified rather than ameliorated the disease (66). In another study, however, smaller quantities of iodine supplementation (150 μg/d) administered during pregnancy and in the postpartum period, to TPO-Ab–positive women living in an area with mild to moderate iodine deficiency did not induce or worsen postpartum thyroid disease (67).

Patients who have recovered from subacute thyroiditis may develop iodide hypothyroidism when exposed to large doses of iodide, long after the remission of the painful febrile episode. In 10 of 18 subjects, ingestion of 300 mg of iodine resulted in a significant but slight increase in serum TSH concentration. Two of these patients had values higher than 50 mU/L accompanied by goiter (68). Weetman et al. (69) have reported that persistent autoimmunity was found up to 39 months after the episode of subacute thyroiditis but the exact nature of their autoimmunity remains unclear, because they were negative for Tg and antimicrosomal antibodies. The reactive antigen was found in the 2,000-g supernatant of crude thyroid extract.

Treatment of chronic active hepatitis with recombinant inteferon-α (rINF-α) may result in thyroid dysfunction (70). Transient hypothyroidism is a common complication that usually ameliorates after the interferon therapy is discontinued. Euthyroid patients with interferon induced thyroid dysfunction are prone to developing iodine-induced hypothyroidism and some may develop hyperthyroidism independent of the presence or absence of thyroid antibodies (71,72). Minelli et al. (73) recently reported that excess iodine administered for 2 months to patients with chronic hepatitis C virus treated with rINF-α induced small changes in thyroid function similar to those observed in patients treated with iodine alone. This suggests that iodides do not have synergistic effects with interferon-α to induce thyroid dysfunction at least for 2 months.

Synergism with Other Drugs

The sulfonamides, sulfadiazines, and sulfisoxazole are mild inhibitors of thyroid hormone synthesis and when administered alone, they do not exert an apparent effect on thyroid function. In patients with cystic fibrosis who were treated with sulfisoxazole, iodide administration resulted in goiter formation in some and subclinical hypothyroidism in others (45).

Lithium has multiple effects on thyroid function, including inhibition of organification of iodine and the release of thyroid hormones. Hypothyroidism has been reported in a few patients treated with lithium when exposed to high iodide intake. Conversely iodine deficiency may act as a protective factor during lithium therapy, as judged by the lack of reports from countries with low iodine intake such as Germany, Italy, and Spain (74).

Amiodarone-Induced Hypothyroidism

Special emphasis must be given to amiodarone, a benzofuranic derivative used for long-term treatment of cardiac arrythmias. It contains 75 mg of iodine per 200-mg tablet and has a prolonged half-life of at least 100 days. Approximately 9 mg of iodine is released daily during the metabolism of the drug (300 mg dose). Amiodarone-induced hypothyroidism is more common than thyrotoxicosis (75). In the United States it may occur in 20% of patients treated with amiodarone whereas thyrotoxicosis is far less common. The reverse is true in Italy, a country with low ambient iodine intake (75). These differences are attributed to increased ambient iodine intake in the United States.

The mechanism by which amiodarone induces hypothyroidism can be partly explained by the excess of iodine released during the metabolism of the drug. Measurement of intrathyroid iodine content by radiographic fluorescence revealed increased iodine content in patients with hypothyroidism following amiodarone administration (59). Administration of potassium perchlorate, which prevents thyroid iodine uptake and permits the egress of nonorganified intrathyroid iodine, restored euthyroidism in these patients. Hypothyroidism reappeared after potassium perchlorate withdrawal (76,77). Thyroid autoantibodies are common in patients with amiodarone-induced hypothyroidism, suggesting that these patients usually have an underlying autoimmune thyroid disease (75).

Other effects of amiodarone on the susceptible thyroid may be contributing or additive to iodine. Compared with iodine, amiodarone exhibits a potent and persistent inhibitory effect on TSH-stimulated cAMP production in FRTL-5 and JP26 Chinese hamster ovary (CHO) cells. The inhibitory effects of amiodarone occurred at lower concentrations of iodide than seen in sodium iodide-treated cells (78). Amiodarone induces cytochrone c release and apoptosis through an iodine-independent mechanism. When thyroid (TAD-2) and nonthyroid (HeLa) cells were treated with amiodarone both underwent apoptosis. Western blot analysis did not display variations in the expression of p53, Bcl-2, Bcl-XL, and Bax proteins during treatment with amiodarone and its main metabolite, desethylamiodarone (DEA). Generation of reactive oxygen species investigated by flow cytometry with dichloro fluorescein diacetate, did not show the production of free radicals during drug treatment of the cells (79). The latter suggests that the iodine content of amiodarone is not solely responsible for the observed apoptosis because sodium iodide-treated cells develop apoptosis through the generation of free radicals (80).

Mechanism of Maintenance of Hypothyroidism

The exact mechanism of iodine-induced hypothyroidism still remains elusive. From the findings described above, the following inferences concerning the inability of the predisposed thyroid to escape from the inhibitory effects of iodide can be drawn. After acute exposure to large doses of iodide the acute Wolff-Chaikoff effect supervenes. The initial load of iodide is largely rejected through an inhibition of the formation of iodothyronines and organic iodine. The inorganic iodine is therefore excreted by the kidneys. When the administration of iodide continues, the escape mechanism fails

and therefore the inhibition of thyroid hormone synthesis continues. The intrathyroidal inorganic iodine concentration continues to be high, probably due to continued iodine uptake. It is unknown whether the downregulation of NIS as seen in the normal thyroid exposed to iodides operates in the thyroids of patients prone to iodine-induced hypothyroidism. The preformed intrathyroid supply of thyronines is rapidly depleted, serum concentration of T_4 and T_3 decreases, serum TSH secretion increases, and the thyroidal iodine uptake continues uninhibited or actually increases, probably due to stimulation of NIS expression by TSH, further increasing the intrathyroidal iodine concentration. The inhibitory effects of iodine on the TPO regulation persists due to a decrease in TPO mRNA and this decrease may contribute to iodine-induced hypothyroidism. It must also be noted that the increased TSH cannot counteract the inhibitory effects of iodide on the proteolysis of Tg and the release of thyroid hormones, because the available intrathyroidal pool of thyroid hormones is greatly decreased.

There are many unanswered questions concerning the mechanism by which the diseased thyroid fails to adapt to long-term iodide excess. Large quantities of iodides, added to supernatants of human thyroid cells lines lead to excess molecular iodide generated by oxidation of ionic iodine by the endogenous peroxidase and induces apoptosis in these cells through a mechanism involving generation of free radicals (80). It is not known whether the iodine-induced apoptosis contributes to chronic iodine-induced hypothyroidism.

The NIS protein expression pattern in the thyroid cells of patients with autoimmune thyroiditis is similar to normal thyroid tissue with the strongest NIS expression in the cells close to lymphocytic infiltrates (81). This may explain why NIS antibodies have been found in 20% and 80% of Hashimoto's disease and Graves' disease, respectively (82). It is possible that the downregulation of NIS expression by iodides observed in normal thyroid cells is defective in these cells because of the autoimmune process and, therefore, iodine continues to be taken up by the affected thyrocytes. Whether the NIS antibodies as well as the TPO and Tg antibodies contribute to iodine sensitivity in these susceptible individuals in not known.

Megalin (GP 330), a multiligand receptor on the apical surface of thyroid cells plays a role in trancytosis of Tg. It was found that megalin facilitates the transepithelial transport of thyroglobulin across thyrocytes resulting in diversion of Tg from lysosomal pathways and reduction of the extent of thyroid hormone release form internalized Tg molecules (83). Serum antibodies against megalin were found in 50% of patients with autoimmune thyroiditis (84). The role, if any, of these antibodies in the pathogenesis of iodine-induced hypothyroidism is not known.

Clinical and Laboratory Findings

The clinical picture of iodine-induced overt hypothyroidism is similar to that observed in ordinary primary hypothyroidism. Goiter may be present, a bruit may be heard on auscultation, and a metalic taste may occur because of an iodide effect on the gustatory function if the ingested quantities of iodides are high. The serum T_4 and free thyroxine (FT_4), are invariably low and serum T_3 and free triiodothyronine (FT_3) may be low, normal and occasionally increased, and serum TSH is invariably increased. The serum thyroglobulin and TPO antibodies are usually present in patients with underlying thyroid autoimmunity.

The radioactive iodine uptake is usually low, but in some patients normal or elevated values have been reported (28,85). Thyroid ultrasound with color Doppler sonography may reveal normal or increased blood flow.

Treatment

It is readily apparent that a euthyroid patient who develops hypothyroidism when exposed to large quantities of iodides almost invariably returns to their previous thyroid state after iodide withdrawal. The time required for thyroid function to recover varies from 2 to 8 weeks, provided that the iodides are rapidly eliminated from the body. However, in patients treated with amiodarone, the time required may be prolonged due to the long half life of the drug. In most patients, the underlying cardiac disease precludes the discontinuation of amiodarone, and therefore, T_4 replacement therapy must be carefully instituted simultaneously with the amiodarone treatment. Radiocontrast dyes used in the past for myelography, salpingography and lymphography (i.e., Lipiodol-$_{TM}$, Guerbet, Cedex, France) may persist for months or years. Fortunately, these agents are rarely used today. The new radiocontrast dyes, i.e., diatrizoate meglumine sodium, iodothalamate, and metrizamide are quickly cleared from the plasma and the affected thyroid recovers rapidly. However, thyroid hormone replacement therapy for a few months may be required in some patients.

It has to be reemphasized that careful follow-up is required for all patients who developed transient iodine-induced hypothyroidism because many of them will eventually develop permanent hypothyroidism because of the underlying thyroid disease.

References

1. Morton ME, Chaikoff IL, Rosenfeld S 1944 Inhibiting effect of inorganic iodide on the formation in vitro of thyroxine and diiodotyrosine by surviving thyroid tissue. J Biol Chem **154:**381–387
2. Wolff J, Chaikoff IL 1948 Plasma inorganic iodide as a homeostatic regulator of thyroid fynction. J Biol Chem **154:**555–564
3. Galton VA, Pitt-Rivers R 1959 The effect of excessive iodine on the thyroid of the rat. Endocrinology **64:**835–838
4. Slingerland DW, Graham DE, Josephs 1959 The effect of propylthiouracil on the conversion of monoiodotyrosine to diiodotyrosine. Endocrinology **65:**178–198
5. Nagataki S, Ingbar H 1964 Relation between qualitative and quantitative alterations in thyroid hormone synthesis induced by varying doses of iodide. Endocrinology **74:**731–736
6. Raven MS 1949 The paradoxical effects of thiocyanate and of thyrotropin on the organic binding of iodine by the thyroid in the presence of large amounts of iodide. Endocrinology **45:**296–304
7. Vagenakis AG, Ingbar SH, Bravermann LE 1974 The relationship between thyroglobulin synthesis and intrathyroidal iodine metabolism as indicated by the effects of cyclohexamide in the rat. Endocrinology **94:**1669–1680.

8. Serif GS, Kirkwood S 1956 The mechanism of the antithyroid action of iodide ion. Endocrinology **58:**23–32
9. Dugrillon A 1996 Iodolactones and iodoaldeydes-mediators of iodine in thyroid autoregulation. Exp Clin Endocrinol Diabetes **104**(Suppl 4)**:**41–45.
10. Braverman LE, Ingbar SH 1963 Changes in thyroidal function during adaptation to large doses of iodide. J Clin Invest **42:**1216–1231
11. Dai G, Levy O, Carrasco N 1996 Cloning and charachterization of thyroid iodide transporter. Nature **42:**458–460.
12. Eng PHK, Cardona GR, Fang S-L, Previti M, Aley S, Carrasco N, Chin W, Braverman LE 1999 Escape from the acute Wolff-Chaicoff effect is assosiated with decrease in thyroid sodium/iodide symporter messenger ribonucleic acid and protein. Endocrinology **140:**3404–3410.
13. Uyttersprot N, Pelgrins N, Carrasco N, Gervy C, Maenhaut C, Dumont JE, Miot F 1997 Moderate doses of iodide in vivo inhibit cell proliferation and the expression of thyroperoxidase and Na^+/I^- symporter mRNAs in dog thyroid. Mol Cell Endocrinol **131:**195–203.
14. Roti E, Vagenakis A 2000 Effects of excess Iodide: clinical aspects. In: Braverman LE, Utiger RT (eds) The Thyroid. Lippincott, New York, pp 316–329
15. Higuchi T 1964 The study of endemic seashore goiter in Hokkaido. Folia Endocrinol Jpn **40:**982–987
16. Suzuki H, Higuchi T, Sawa K, Ohtaki S, Horinchi Y 1965 Endemic coast goitre in Hokkaido, Japan. Acta Endocrinol **50:**161–176.
17. Tajiri J, Higashi K, Morita M, Umeda T, Sato 1986 Studies of hypothyroidism in patients with high iodine intake. J Clin Endocrinol Metab **63:**412–417.
18. Yoshinari M, Okamura K, Tokuyama T, Shiroozu A, Nakashima T, Inoue K, Omae T 1983 Clinical importance of reversibility in primary goitrous hypothyroidism. Br Med J **287:**720–722.
19. Konno N, Makita H, Yuri K, Iizuka N, Kawasaki K 1994 Assosiation between dietary iodine intake and prevalence of subclinical hypothyroidism in the coastal regions of Japan. J Clin Endocrinol Metab **78:**393–397.
20. Konno N, Yuri K, Taguchi H, Miura K, Taguchi S, Hagiwara K, Murakami S. 1993 Screening for thyroid diseases in an iodine sufficient area with sensitive thyrotrophin assays, and serum thyroid autoantibody and urinary iodide determinations. Clin Endocrinol (Oxf) **38:**273–281.
21. Szabolcs I, Podoba J, Reldcamp J 1997 Comparative screening for thyroid disorders in old ages in areas of iodine deficiency, long term iodine prophylaxis and abuntant iodine intake. Clin Endocrinol **47:**87–92.
22. Li M, Liu DR, Qu CY, Zhang PY, Qian QD, Zhang CD, Jia QZ, Wang HX, Eastman CJ, Boyages SC 1987 Endemic goitre in central China caused by excessive iodine intake. Lancet **1:**257–259
23. Zhao J, Chen Z, Maberly G 1998. Iodine rich drinking water of natural origin in China. Lancet **352:**2024.
24. Laurberg P, Pedersen KM, Hreidarsson A, Siqfusson N, Iversen E, Knudsen PR 1998 Iodine intake and the pattern of thyroid disorders: A comparative epidemiological study of thyroid abnormalities in the elderly in Iceland and in Jutland, Denmark. J Clin Endocrinol Metab **83:**765–769.
25. Markou K, Makri M, Heliopoulos A, Alexandridis TK, Vagenakis AG, 1992. Thyroid hormone secretion following discontinuation of large quantities of iodides in normal individuals [Abstract no-05-01-120] Nine International Congress of Endocrinology, Nice, August 30 to September 5, p 305.
26. Nauman J, Wolff J 1993 Iodide prophylaxis in Poland after the Chernobyl reactor accident: Benefits and risks. Am J Med **94:**524–532.
27. Mizukami Y, Michigishi T, Nonomura A, Hashimoto T, Tonami N, Matsubara F, Takazakura E 1993 Iodine-induced hypothyroidism: A clinical and histological study of 28 patients. J Clin Endocrinol Metab **76:**466–471.
28. Wolff J 1969 Iodide goiter and the pharmacologic effects of excess iodide. Am J Med **47:**101–124
29. Benharb WC, Grubin H, Sheller GA, 1955 Congenital goiter. Arch Pathol **60:**635–637
30. Nagle WW, Hope J W, Bongiovanni AM, 1957 Congenital goiter. Radiology **68:**526.
31. Seligman B, Pescovitz H 1950 Suffocative goiter in newborn infant. New York State J Med **50:**1815–1816.
32. Save EB, Watt CH, Foushee JC, Palmer JJ 1952 Congenital thyroid hyperplasia in twins. JAMA **149:**1399–1400.
33. Vicens-Calvet E, Potau N, Carreras E, Bellart J, Albisu MA, Carrascosa A 1998 Diagnosis and treatment in utero of goiter with hypothyroidism caused by iodide overload. J Pediatr **133:**147–148
34. Theodoropoulos T, Braverman LE, Vagenakis AG 1979 Iodide-induced hypothyroidism: a potential hazard during perinatal life. Science **205**:502–503.
35. Darwish NA, Shaaraway M 1993 Effect of treatment with povidone-iodine vaginal pessaries on thyroid function. Postgrad Med J **69**(Suppl 3)**:**S39–42.
36. Sakakura K, Iwata Y, Hayashi S 1993 Study on the usefulness of povidone- iodine obstetric cream with special reference to the effect on the thyroid functions of mothers and the newborn. Postgrad Med J **69**(Suppl 3)**:**S49–57.
37. Chabrolle JP, Rossier A 1978 Goitre and hypothyroidism in the newborn after cutaneous absorption of iodine. Arch Dis Child **53:**495–498.
38. Castaing H, Fournet JP, Leger FA, Kiesgen F, Piette C, Dupard MC, Savoie JC 1979 The thyroid gland of the newborn infant and postnatal iodine overload. Arch Fr Pediatr **36:**356–368.
39. L'Allemand D, Gruters A, Beyer P, Weber B 1987 Iodine in contrast agents and skin disinfectants is the major cause for hypothyroidism in premature infants during intensive care. Horm Res **28:**42–49.
40. Delange F, Heidemann P, Bourdoux P, Larsson A, Vigneri R, Klett M, Beckers C, Stubbe P 1986 Regional variations of iodine nutrition and thyroid function during the neonatal period in Europe. Biol Neonate **49:**322–330
41. Brown RS, Bloomfield S, Bednarek FJ, Mitchell ML, Braverman LE 1997 Routine skin cleansing with povidone-iodine is not a common cause of transient neonatal hypothyroidism in North America: A prospective controlled study. Thyroid **7:**395–400.
42. Momotani N, Hisaoka T, Noh J, Ishikawa N, Ito K 1992 Effects of iodine on thyroid status of fetus versus mother in treatment of Graves' disease complicated by pregnancy. J Clin Endocrinol Metab **75:**738–744.
43. Magee LA, Downar E, Sermer M, Boulton BC, Allen LC, Koren G 1995 Pregnancy outcome after gestational exposure to amiodarone in Canada Am J Obstet Gynecol **172:**1307–1311.
44. De Wolf D, De Schepper J, Verhaaren H, Deneyer M, Smitz J, Sacre-Smits L 1988 Congenital hypothyroid goiter and amiodarone. Acta Paediatr Scand **77:**616–618
45. Azizi F, Bentley D, Vagenakis A , Portnay G, Bush JE, Shwachman H, Ingbar SH, Braverman LE 1974 Abnormal thyroid function and response to iodides in patients with cystic fibrosis. Trans Assoc Am Physicians **87:**111–119.
46. Markou K, Paraskevopoulou P, Karaiskos K, Megrelli C,

Vagenakis AG 2000 Effects of chronic iodide administration in thyroid function in children and adolescents with a history of transient congenital hypothyroidism [abstract]. 27th Annual Meeting, Greek Endocrine Association, Nicosia Cyprus, p 82.
47. Alexandrides T, Georgopoulos N, Yarmenitis S,Vagenakis AG. 2000 Increased sensitivity to the inhibitory effect of excess iodide on thyroid function in patients with beta-thalassemia major and iron overload and the subsequent development of hypothyroidism. Eur J Endocrinol **143:**319–325.
48. Tacheda S, Mishigish T, Takazakura E 1993 Iodide induced hypothyroidism in patients on regular dialysis treatment. Nephron **65:**51–55.
49. Bando U, Ushiogi Y, Toya D, Tanaka N, Fujisawa M. 1999 Diabetic nephropathy accompanied by iodine-induced nonautoimmune primary hypothyroidism: Two case reports. Endocr J **46:**803–810.
50. Gardner DF, Mars DR, Thomas RG, Bumrungsup C, Misbin RI 1986 Iodine retention and thyroid dysfunction in patients on hemodialysis and continuous ambulatory peritoneal dialysis. Am J Kidney Dis **7:**471–476.
51. Drinka PJ, Nolten WE 1988 Effects of iodinated glycerol on thyroid function studies in elderly nursing home residents. J Am Geriatr Soc **36:**911–913
52. Mezer E, Krivoy N, Scharf J, Miller B 1996 Echothiophate iodide induced transient hyper and hypothyroidism. J Glaucoma **5:**191–192
53. Matsubayashi S, Mukuta T, Watanabe H 1998 Iodine-induced hypothyroidism as a result of excessive intake of confectionery made with tangle weed, Kombu, used as a low calorie food during bulimic period in a patient with anorexia nervosa. Eating Weight Disord **3:**50.
54. Vagenakis AG, Braverman LE 1975 Adverse effects of iodides on thyroid function. Med Clin North Am **59:**1075–1088.
55. Paul T, Reinhardt W, Meyers B 1987 Small increases in dietary iodine intake do not induce hypothyroidism in euthyroid patients with Hashimoto's thyroiditis. Clin Res **35:** 400A
56. Tajiri J, Higashi K, Morita M, Umeda T, Sato T 1986 Studies of hypothyroidism in patients with high iodine intake. J Clin Endocrinol Metab **63:**412–417.
57. Reinhardt W, Luster M, Rudorff KH, Heckmann C, Petrasch S, Lederbogen S, Haase R, Saller B, Reiners C, Reinwein D, Mann K 1998 Effect of small doses of iodine on thyroid function in patients with Hashimoto's thyroiditis residing in an area of mild iodine deficiency. Eur J Endocrinol **139:**23–28.
58. Marwaha RK, Tandon N, Karak AK, Gupta N, Verma K, Kochupillai N 2000 Hashimoto's thyroiditis: Countrywide screening of goitrous healthy young girls in postiodization phase in India. J Clin Endocrinol Metab **85:**3798–3802
59. Fragu P, Schlumberger M, Tubiana M 1985 Thyroid iodine content and serum thyroid hormone levels in autoimmune thyroiditis: effect of iodide supplementation. J Nucl Med **26:**133–139.
60. Allen EM, Appel MC, Braverman LE 1986 The effect of iodide ingestion on the development of spontaneous lymphocytic thyroiditis in the diabetes-prone BB/W rat. Endocrinology **118:**1977–1981.
61. Rajatanavin R, Appel MC, Reinhardt W, Alex S, Yang YN, Braverman LE 1991 Variable prevalence of lymphocytic thyroiditis among diabetes-prone sublines of BB/W or rats. Endocrinology. **128:**153–157.
62. Braverman LE, Woeber KA, Ingbar SH. 1969 Induction of myxedema by iodide in patients euthyroid after radioiodine or surgical treatment of diffuse toxic goiter. N Engl J Med **281:**816–821.
63. Clark OH, Cavalieri RR, Moser C, Ingbar SH 1990 Iodide-induced hypothyroidism in patients after thyroid resection. Eur J Clin Invest Dec **20:**573–580
64. Allen EM, Appel MC, Braverman LE 1987 Iodine-induced thyroiditis and hypothyroidism in the hemithyroidectomized BB/W rat. Endocrinology **121:**481–485.
65. Roti E, Minelli R, Gardini E, Bianconi L, Neri T, Gavaruzzi G, Ugolotti G, Salvo D, Braverman LE 1991 Impaired intrathyroidal iodine organification and iodine-induced hypothyroidism in euthyroid women with a previous episode of postpartum thyroiditis. J Clin Endocrinol Metab **73:**958–963.
66. Kampe O, Jansson R, Karlsson FA 1990 Effects of L-thyroxine and iodide on the development of autoimmune postpartum thyroiditis. J Clin Endocrinol Metab **70:**1014–1018.
67. Nohr BS, Jorgensen A, Pedersen KM, Lauberg P 2000 Post partum thyroid dysfunction in pregnant thyroid peroxidase antibody-positive women living in an area with mild to moderate iodine deficiency. Is iodine supplementation safe? J Clin Endocrinol Metab **85:**3191–3198
68. Roti E, Minelli R, Gardini E, Bianconi L, Neri T, Braverman LE 1990 Iodine-induced hypothyroidism in euthyroid subjects with a previous episode of subacute thyroiditis. J Clin Endocrinol Metab **70:**1581–1585.
69. Weetman AP, Smallridge RC, Nutman TB, Burman KD 1987 Persistent thyroid autoimmunity after subacute thyroiditis. J Clin Lab Immunol **23:**1–6.
70. Marcellin P, Pouteau M, Benhamou JP 1995 Hepatitis C virus infection, alpha interferon therapy and thyroid dysfunction. J Hepatol **22:**364–369.
71. Roti E, Minelli R, Giuberti T, Marchelli S, Schianchi C, Gardini E, Salvi M, Fiaccadori F, Ugolotti G, Neri TM, Braverman LE 1996 Multiple changes in thyroid function in patients with chronic active HCV hepatitis treated with recombinant interferon-alpha. Am J Med **101:**482–487.
72. Minelli R, Braverman LE, Giuberti T, Schianchi C, Gardini E, Salvi M, Fiaccadori F, Ugolotti G, Roti E 1997 Effects of excess iodine administration on thyroid function in euthyroid patients with a previous episode of thyroid dysfunction induced by interferon-alpha treatment. Clin Endocrinol (Oxf) **47:**357–361.
73. Minelli R, Braverman LE, Schianchi C, Pedrazzoni M, Fiaccadori F, Salvi M, Magotti MG, Roti E 1999 Recombinant interferon alpha (rIFN-alpha) does not potentiate the effect of iodine excess on the development of thyroid abnormalities in patients with HCV chronic active hepatitis. Clin Endocrinol (Oxf) **50:**95–100.
74. Leutgeb U 2000 Ambient iodine and lithium-associated clinical hypothyroidism. Br J Psychiatry **176:**495–496.
75. Lombardi A, Martino E, Braverman LE 1990 Amiodarone and the thyroid. Thyroid Today **23:**2–7.
76. Martino E, Mariotti S, Aghini-Lombardi F, Lenziardi M, Morabito S, Bascheri L, Pinchera A, Braverman L, Safran M 1986 Short term administration of potassium perchlorate restores euthyroidism in amiodarone iodine-induced hypothyroidism. J Clin Endocrinol Metab **63:** 1233–1236.
77. Wolff J 1988 Perchlorate and the thyroid gland Pharmacol Rev **50:**89–105.
78. Pitsiavas V, Smerdely P, Boyages SC 1999 Amiodarone compared with iodine exhibits a potent and persistent inhibitory effect on TSH-stimulated c-AMP production in vitro: A pos-

sible mechanism to explain amiodarone-induced hypothyroidism. Eur J Endocrinol **140:**241–249.
79. Di Matola T, D' Ascoli F, Fenzi G, Rossi G, Martino E, Bogazi F, Vitale M 2000 Amiodarone induces cytochrome c release and apoptosis through an iodine-independent mechanism. J Clin Endocrinol Metab **85:**4323–4330.
80. Vitale M, Di Matola T, D'Ascoli F, Salzano S, Bogazzi F, Fenzi G, Martino E, Rossi G 2000 Iodide excess induces apoptosis in thyroid cells through a p53-independent mechanism involving oxidative stress. Endocrinology **141:**598–605.
81. Caillou B, Troalen F, Baudin E, Talbot M, Filetti S, Schlumberger M, Bidart JM 1998 Na^+/I^- symporter distribution in human thyroid tissues: An immunohistochemical study. J Clin Endocrinol Metab **83:**4102–4106.
82. Endo T, Kogai T, Nakazato M, Saito T, Kaneshige M, Onaya T 1996 Autoantibody against Na+/I− symporter in sera of patients with autoimmune thyroid disease. Biochem Biophys Res Commun **224:**92–85.
83. Marino M, McCluskey RT 2000 Megalin-mediated transcytosis of thyroglobulin by thyroid cells is a calmodulin-dependent process. Thyroid **10:**461–469.
84. Marino M, Chiovato L, Friedlader JA, Latrofa F, Pinchera A, McCluskey RT 1999 Serum antibodies against megalin (GP330) in patients with autoimmune thyroiditis. J Clin Endocrinol Metab **84:**2468–2474.
85. Wiersinga WM, Touber JL, Trip MD, Van Royen EA 1986 Uninhibited thyroidal uptake of radioiodine despite iodine excess in amiodarone-induced hypothyroidism. J Clin Endocrinol Metab **63:**485–491.

Address reprint requests to:
A. Vagenakis
Department of Medicine
Division of Endocrinology
University of Patras Medical School
Patras 26500
Greece

E-mail: vag.inmd@med.upatras.gr

This article has been cited by:

1. Felix Flohr, Jan Harder, Jochen Seufert, Hubert E. Blum, Hans C. Spangenberg. 2008. Hypothyroidism in patients with hepatocellular carcinoma treated by transarterial chemoembolization. *Hepatology* **47**:6, 2144-2144. [CrossRef]
2. L. I. Nadolnik, Z. V. Niatsetskaya, S. V. Lupachyk. 2008. Effect of oxidative stress on rat thyrocyte iodide metabolism. *Cell Biochemistry and Function* **26**:3, 366-373. [CrossRef]
3. Nobuyuki Takasu, Jaeduk Yoshimura Noh. 2008. Hashimoto's thyroiditis: TGAb, TPOAb, TRAb and recovery from hypothyroidism. *Expert Review of Clinical Immunology* **4**:2, 221-237. [CrossRef]
4. Venetsana Kyriazopoulou, Marina Michalaki, Neoklis Georgopoulos, Apostolos G Vagenakis. 2008. Recommendations for thyroxin therapy during pregnancy. *Expert Opinion on Pharmacotherapy* **9**:3, 421-427. [CrossRef]
5. Katrin Franke, Friedrich Schöne, Andreas Berk, Matthias Leiterer, Gerhard Flachowsky. 2008. Influence of dietary iodine on the iodine content of pork and the distribution of the trace element in the body. *European Journal of Nutrition* **47**:1, 40-46. [CrossRef]
6. Brenda Anguiano , Pablo García-Solís , Guadalupe Delgado , Carmen Aceves Velasco . 2007. Uptake and Gene Expression with Antitumoral Doses of Iodine in Thyroid and Mammary Gland: Evidence That Chronic Administration Has No Harmful Effects. *Thyroid* **17**:9, 851-859. [Abstract] [PDF] [PDF Plus]
7. Harri Niinikoski, Anu-Maaria Hämäläinen, Henrik Ekblad, Hanna Soukka. 2007. Neonatal hypothyroidism after amiodarone therapy. *Acta Paediatrica* **96**:5, 773-774. [CrossRef]
8. Yozen Fuse , Nanako Saito , Toshiko Tsuchiya , Yoshimasa Shishiba , Minoru Irie . 2007. Smaller Thyroid Gland Volume with High Urinary Iodine Excretion in Japanese Schoolchildren: Normative Reference Values in an Iodine-Sufficient Area and Comparison with the WHO/ICCIDD Reference. *Thyroid* **17**:2, 145-155. [Abstract] [PDF] [PDF Plus]
9. Haibin Shi, Tian Xia, Andre E Nel, Joanne I Yeh. 2007. Part II: coordinated biosensors – development of enhanced nanobiosensors for biological and medical applications. *Nanomedicine* **2**:5, 599. [CrossRef]
10. Marie Hansson, Mats Isaksson. 2007. A Monte Carlo (MC) based individual calibration method for in vivo x-ray fluorescence analysis (XRF). *Physics in Medicine and Biology* **52**:7, 2009. [CrossRef]
11. Andrew J Seal, Paul I Creeke, Daniella Gnat, Fathia Abdalla, Zahra Mirghani. 2006. Excess dietary iodine intake in long-term African refugees. *Public Health Nutrition* **9**:01. . [CrossRef]
12. Richard Brough, Caroline Jones. 2006. Iatrogenic iodine as a cause of hypothyroidism in infants with end-stage renal failure. *Pediatric Nephrology* **21**:3, 400. [CrossRef]
13. N. Haydn, E. Lunedei, L. Rossi, G. Turchetti, S. Vaienti. 2005. Multiple returns for some regular and mixing maps. *Chaos An Interdisciplinary Journal of Nonlinear Science* **15**:3, 033109. [CrossRef]
14. Vani Sethi, Umesh Kapil. 2004. Iodine deficiency and development of brain. *The Indian Journal of Pediatrics* **71**:4, 325. [CrossRef]
15. Daniel Kurnik, Ronen Loebstein, Zvi Farfel, David Ezra, Hillel Halkin, David Olchovsky. 2004. Complex Drug-Drug-Disease Interactions Between Amiodarone, Warfarin, and the Thyroid Gland. *Medicine* **83**:2, 107. [CrossRef]