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Jean Temeck  
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MEDICAL OFFICER

David Orloff  
7/2/01 08:37:03 PM  
MEDICAL OFFICER

**APPEARS THIS WAY  
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NDA: 21, 137  
 Drug: Levolet (Levothyroxine sodium or T4)  
 Sponsor: Vintage Pharm., Inc.

Date submitted: 4/30/99  
 Date received: 5/3/99  
 Date reviewed: 2/11/2000

Drug: Levolet (Levothyroxine sodium)

**Background:**

The August 14, 1997 Federal Register Notice declared orally administered levothyroxine (T4) drug products new drugs. This was due to significant stability and potency problems which could have potential adverse health effects. Sponsors are required to perform two bioavailability studies.

Vintage Pharm., Inc. has submitted a levothyroxine application in response to this FRN.

In addition to levothyroxine (T4), the Vintage product contains  $\mu$ g potassium iodide (KI) per tablet. The main purpose of this report is to review the published literature to determine the safety of this additional iodide when levothyroxine is used for the following purposes:

as replacement or substitution therapy for diminished or absent thyroid function; or  
 to suppress endogenous TSH in the treatment of goiter, nodules and thyroid cancer.

Vintage Pharm., Inc. has submitted 12 articles from the published literature pertaining to the safety of iodine; \_\_\_\_\_, another sponsor who had interest in manufacturing a similar product, has submitted 15 articles; and I have reviewed here 46 additional articles from my own search of the literature on this topic.

**Evaluation of the Bioavailability Studies As It Pertains To Safety:**

There were no clinically significant changes in any of the safety parameters monitored in these studies (adverse events, vital signs, physical exam, ECG, serum chemistry and hematology and UA).

See Dr. Johnson's biopharmacology review for the pharmacokinetic analysis.

The remainder of this review will be organized as follows:

1. Normal iodine physiology: pages 1-2
2. Normal dietary iodine requirements: page 2
3. General review articles pertaining to iodide toxicity: pages 2-6:
  - A. Mechanisms by which excess iodide suppresses and stimulates the thyroid gland: page 2
  - B. The "No-Effect" level of iodine intake on thyroid gland function: pages 2-3
  - C. Specific clinical situations where excess iodide may be problematic: pp.3-6
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4. Published studies pertaining to iodine toxicity at  $\mu$ g doses: pages 7-14
  - A. Normal individuals: suppressive effects on thyroid function: pages 7-9
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**1. Normal Iodine Physiology as it Pertains to Thyroid Hormone Synthesis (refs. 1 & 2):**

Iodide from the diet is almost completely absorbed in the GI tract, where it enters the inorganic iodide pool in the extracellular fluid (ECF). From this pool, the thyroid gland takes up  $\sim$ 75  $\mu$ g iodide/day for thyroid hormone synthesis, and the remainder is excreted by the kidneys. Immediately after entrance of iodide into the thyroid, it is oxidized to iodine. This is followed by iodination

of thyroglobulin-contained tyrosine molecules to form monoiodotyrosine (MIT) and diiodotyrosine (DIT). These iodinated tyrosine, which are component parts of thyroglobulin, couple with the release of alanine and the formation of T4 and T3.

2. Normal Dietary Iodine Requirements (references 3 and 4):

Per Braverman and Roti (ref. 3), the recommended daily iodine intake is 50 ug/day during the neonatal period, 90-120 ug/day during childhood, 150 ug/day in the those >12 years and adults; and 200 ug/day during pregnancy and lactation.

The following recommended dietary iodine intakes and probably safe upper limits (PSUL) are derived from Fisher and Delange (ref. 4):

AGE	Dietary Iodine Intake (ug/kg/day)	
	Recommended	PSUL
Premature Infants	30	100
Infant 0-6 months	15	150
Infant 6-12 months	7	140
Children 1-10 years	3	50
Adolescents/Adults	2	30

\* PSUL:

The PSUL is based on the following:

- a. levels of iodine intake which did not appear to impair thyroid function in European studies in infants
- b. iodine loading studies in U.S. adults
- c. the highest estimates of dietary intake in the U.S. (in 1978, mean iodine intake was 576 ug/day for infants with an upper limit of 968 ug/day; for toddlers, the mean was 728 ug/day with an upper limit of 1,358 ug/day).

consultant to Vintage Pharm., makes the point that there is a wide margin of safety between the recommended dietary iodine intake and the PSUL in all age groups (1-20 fold) except in premature infants (only ~3 fold margin of safety). He points out that the PSUL of iodine intake would be exceeded in a premature infant receiving iodine from the Vintage tablet as well as iodine in formula. He suggests caution be used in treating premature infants

(However, Kaplan<sup>ref. 5</sup> states that 50-100 ug/kg/day is sufficient to induce hypothyroidism in premature infants).

3. General Review Articles Pertaining to Iodide Toxicity:

A. Mechanisms by Which Excess Iodide Suppresses Thyroid Function<sup>refs. 6, 7, and 8.</sup>

Excess thyroidal iodide paradoxically inhibits its own oxidation, an essential first step prior to iodination of tyrosine and the subsequent synthesis of thyroid hormones. In normal individuals, this acute inhibition of hormone synthesis (the acute Wolff-Chaikoff effect) is transient, lasting ~48 hours, and the thyroid then resumes its normal rate of hormone synthesis and the euthyroid state is preserved. This adaptation to escape from the acute Wolff-Chaikoff effect is most likely due to a decrease in the active transport of the excess plasma iodide into the thyroid, thereby protecting the thyroid from the adverse effects of excessive iodide on thyroid hormone synthesis. Excess iodide also inhibits the release of T4 and T3.

The inhibitory effect of iodide is more marked in patients with underlying thyroid disease than it is in normal individuals. In patients with euthyroid Hashimoto's thyroiditis, the thyroid gland fails to escape from the acute inhibitory effect of iodide on the organification process and, therefore, they manifest a persistent Wolff-Chaikoff effect

Stimulatory Effects of Excess Iodide:

The mechanism(s) by which iodide induces hyperthyroidism is unclear<sup>refs. 6 and 7</sup>

B. What Is The No-Effect Level Of Iodine Intake With Respect To Thyroid Function?

The following "answers" can be found in the published literature:

- a. Becker<sup>ref. 5</sup> states that when a small amount of iodine- 100 to 250 ug/day- is administered along with the usual dietary intake, there is no appreciable change in iodine-131 uptake, and no change in thyroidal organic iodine or in the amount of iodotyrosines and iodothyronines produced. He states that prenatal vitamins usually contain 150ug iodine, which should not constitute a hazard but does pose an additional risk in pregnant women already ingesting iodides from other sources.
- b. Dr. Braverman<sup>ref. 6</sup> states that iodine supplementation of 250-500 ug/day above dietary iodine intake (average dietary iodine intake in the U.S. is ~200 ug) is unlikely to affect thyroid function in areas of adequate dietary iodine (such as the U.S.).
- c. Dunn<sup>ref. 9</sup> states that the upper safe limit of iodine intake is uncertain and varies widely among individuals and populations. He states that intakes up to 1 mg iodine per day are safe for most people, and that much higher amounts are usually tolerated without problem.
- d. This review of the published literature will demonstrate that the safe upper limit of iodine intake is not clear. However, it is clear that the limit is dependent on the age of the individual, if underlying thyroid disease is present and the iodine status of the geographic area where the individual resides. In general, the fetus and newborn and individuals with underlying thyroid disease living in an area of iodine-deficiency are the most susceptible to iodine toxicity. This is because:

-the fetal and neonatal thyroid are particularly sensitive to the Wolff-Chaikoff effect (i.e. blockage of thyroid hormone secretion) given that the immature gland cannot suppress iodide-trapping (i.e. escape from the acute Wolff-Chaikoff effect) and

-with iodine deficiency, there is a decrease in iodine stores in the thyroid which, upon exposure to an increase in iodine intake, will then avidly trap the iodine.

The following data illustrate how iodine status prior to exposure to excess iodine affects the thyroid gland's response to the excess<sup>ref. 4</sup>. In Belgium, an area of moderate iodine deficiency, iodine intake of 37 ug/kg/day, significantly increased the peak TSH response to TRH but did not alter serum T4 concentrations. Thus, these infants had a mild, transient compensated hypothyroid state. Another study conducted in France, also an area of moderate iodine deficiency, suggests that, in Europe, 200 ug daily is the upper limit of iodine intake in premature infants above which a Wolff-Chaikoff effect may occur. Urinary iodine concentrations of 50 ug/dl which can result in a Wolff-Chaikoff effect in Europe are frequently seen in healthy neonates in North America, an area of iodine sufficiency. However, studies to identify the upper safe limit of iodine intake in newborns have not been conducted in the United States.

### C. Specific Clinical Situations Where Excess Iodine May Be Potentially Problematic<sup>ref. 3, 6 and 8</sup>:

#### ***IODINE-INDUCED HYPOTHYROIDISM:***

##### **Euthyroid patients with an underlying thyroid disorder:**

1. Euthyroid patients previously treated for Graves' disease (with <sup>131</sup>I, thyroidectomy or antithyroid drugs): when administered 180-200 mg iodine daily (~1,000 times the dietary iodine allowance), developed hypothyroidism within weeks.

2. Euthyroid patients with Hashimoto's thyroiditis: often these patients have a mild defect in organification of iodine and, therefore, upon exposure to excess iodine, there is a persistent Wolff-Chaikoff effect which may be manifest as hypothyroidism. The inhibition reverses when the excess iodide is withdrawn. Increased dietary iodine intake induced hypothyroidism in Japanese patients with Hashimoto's thyroiditis. In these patients, dietary restriction of iodine resulted in normalization of the serum TSH concentrations<sup>ref. 10</sup>.

3. Euthyroid patients with a history of postpartum thyroiditis.

The hypothyroidism disappears when the iodine is discontinued. Therefore, it is important to monitor thyroid function long after pregnancy in women with a history of postpartum thyroiditis and to try to avoid iodine-containing medications.

4. Euthyroid patients with a history of subacute thyroiditis: a

minority of these patients have persistent subtle abnormalities in thyroid function, and SSKI (38 mg/drop), given years after the subacute episode, may induce hypothyroidism. Therefore, thyroid function should be periodically monitored in patients with a history of subacute thyroiditis and iodine-containing medications avoided, if possible.

5. Euthyroid patients with a history of amiodarone-induced

thyrotoxicosis: SSKI (38 mg/drop) administered years afterwards may induce subclinical hypothyroidism (elevated basal and TRH stimulated hypothyroidism).

6. Euthyroid patients after a hemithyroidectomy for

benign thyroid nodules: may develop hypothyroidism when given pharmacologic quantities of iodine.

7. After Interferon-alpha induced thyroid dysfunction: large doses of

iodine administered to euthyroid patients with a history of interferon-alpha induced thyroid dysfunction may induce subclinical hypothyroidism

**Euthyroid patients with no apparent underlying thyroid disorder and in whom excess iodide may induce hypothyroidism:**

1. Cystic fibrosis: iodide expectorants may induce hypothyroidism.

2. Chronic lung disease: iodide expectorants may induce hypothyroidism

3. Thalassemia major requiring chronic blood transfusions: hypothyroidism may occur secondary to iodine-containing medications (possibly due to hemosiderosis of the thyroid).

4. In dialyzed patients with chronic renal failure, hypothyroidism has been frequently observed. Restriction of iodine results in normalization of serum TSH levels in the majority of these patients.

5. Elderly subjects: hypothyroidism and goiter frequently occurs in this age group particularly in subjects with positive antithyroid antibodies. Iodinated glycerol (mucolytic expectorant containing 15 mg iodine/tab or 25 mg/ml) may induce hypothyroidism with return to the euthyroid state when the medication is withdrawn.

6. Fetus and Newborn<sup>refs. 3, 5, 11-16.</sup>

Unlike T<sub>4</sub>, iodine freely crosses the placenta. The human fetal thyroid begins to accumulate iodine at 10-14 weeks of pregnancy and concentrates a greater amount of iodide per gram of tissue than the adult thyroid gland. Because fetal and neonatal (premature and very low birth weight infant) thyroids are unable to decrease iodide trapping in the presence of excess iodide, their thyroids are susceptible to iodine induced inhibition and TSH mediated thyromegaly. Therefore, maternal ingestion of iodine-containing drugs may result in goiter and hypothyroidism and increased cord blood TSH levels in the newborn. These cases have occurred primarily in areas of iodine deficiency. In addition to the fetus, premature and very low birth weight infants are especially vulnerable to thyroid suppression by iodine. Among the causative agents reported have been topical skin application of iodine containing antiseptics (e.g. povidone iodine or Betadine: 10 mg iodine/ml), the injection of iodinated contrast dye (contain ~330-480 mg iodine/ml) and amiodarone (75 mg iodine/tab). However, the true incidence of hypothyroidism in newborn infants exposed to excess iodine in utero from maternal ingestion of iodine containing medications, has not been accurately assessed<sup>refs. 17 and 18</sup>. It should be noted that, unlike the adult, iodine-induced goiter in the newborn infant may be associated with tracheal obstruction, asphyxiation and death.

Iodine contamination during perinatal life (e.g. use of povidone iodine at the time of delivery) may cause transient neonatal hypothyroidism (elevations in serum TSH but normal serum T<sub>4</sub> levels) and increase the recall rate of screening for neonatal hypothyroidism<sup>ref. 19</sup>. In Europe, a second sample is recommended to screen for congenital hypothyroidism when there is a history of exposure of the newborn to excess iodine<sup>ref. 20</sup>.

Also, iodides are readily concentrated by the mammary gland and secreted into the milk, and, therefore, may induce goiter and/or hypothyroidism in the breast-fed newborn. Silva<sup>ref. 14</sup> recommends that iodine be avoided during pregnancy or its use be restricted to a minimal duration.

7. Infancy: iodine-induced hypothyroidism has been reported in children chronically treated with amiodarone (75 mg iodine/tablet). However, an acute iodine overload of 50-70 mg KI administered as a single dose to children in Poland to prevent radioiodine uptake into the thyroid from the Chernobyl accident, did not induce significant changes in serum TSH concentrations<sup>ref. 21</sup>.

8. Iodine may act synergistically with other drugs such as lithium, thioureas, sulfonamides, sulfadiazine and sulfisoxazole to induce goiter and/or hypothyroidism<sup>refs. 3, 6, 13 & 16</sup>.

#### **IODINE-INDUCED GOITER:**

This disorder has been described in Japan with ingestion of iodine rich seaweed delivering up to 200 mg iodine daily. This disorder has also been described in China with ingestion of drinking water rich in iodine (462 ug/L). Patients with iodine-induced goiter have an increased tendency to produce thyroid antibodies<sup>ref. 7</sup>. Other studies have shown that the frequency of histologic thyroiditis in thyroidectomy specimens increases after iodine prophylaxis, and that correction of iodine deficiency is followed by the appearance of thyroid autoantibodies and an increase in the incidence of autoimmune thyroid disease (McGregor et al, In Thyroid Disorders Associated With Iodine Deficiency and Excess, pp. 209-216, 1985).

It has been reported<sup>ref. 17</sup> that most patients who develop iodine goiter with or without hypothyroidism have received large quantities of iodide- 8 mg to 1 gm daily and the time to appearance of the goiter usually varies from 4 mos. to 6 yrs. after institution of iodide therapy. However, goiter or hypothyroidism has been observed after only a few weeks of therapy with small quantities of iodine contained in drugs such as Ornade and Combid (1.8 mg iodine/tablet)<sup>ref. 17</sup>. Wolff<sup>ref. 16</sup> states goiter has been induced by as little as 0.5 mg iodine for 3 months.

#### **IODINE-INDUCED HYPERTHYROIDISM<sup>refs. 3, 6, 8, 13, 22-25</sup>**

This disorder is most commonly observed in the following situations:

- a. In an endemic goiter region: when iodine-supplementation (e.g. introduction of iodized salt) is given to iodine-deficient populations (e.g. patients with endemic iodine-deficiency goiter or patients with no underlying thyroid disease but living in an area of iodine deficiency)
- b. In non-endemic regions: when pharmacologic quantities of iodine are administered to patients with nontoxic goiter, most frequently nodular goiter with areas of autonomy, or with an autonomous nodule or with nontoxic diffuse goiter. Although iodine-containing medications and radiocontrast agents are the most common sources of excess iodine in this situation, introduction of iodized salt has also been implicated (a rise in the incidence of thyrotoxicosis occurred in the 1920's when iodized salt was introduced in some areas in the U.S.).
- c. Iodine administration to euthyroid Graves' patients previously treated with antithyroid drugs and patients with borderline hyperthyroidism.
- d. Iodine administration to patients with no recognized underlying thyroid disease, especially in areas of mild to moderate iodine deficiency

Hyperthyroidism is usually transient after iodination and reinduction is rare.

Dunn<sup>ref. 22</sup> points out that, in an area of iodine-sufficiency, older subjects with multinodular goiter are the most vulnerable to this condition, particularly those with underlying heart disease<sup>ref. 20</sup>. Although IIH is usually mild and self-limited, it may be serious and fatal. It appears to be more severe and more difficult to control than in iodine-deficient areas due to the large store of preformed hormone in the thyroid gland<sup>refs. 6 and 13</sup> (e.g. requiring larger doses of antithyroid drugs and requiring a prolonged period to restore euthyroidism). The most important clinical manifestations are cardiovascular, with thyrotoxicosis potentially leading to atrial fibrillation, CHF, angina, thromboembolism and death.

Dunn<sup>ref. 22</sup> recommends that susceptible individuals (namely, the elderly with

multinodular goiter) receive careful follow-up including monitoring of their thyroid function and that they should reduce their iodine intake (decrease or omit intake of iodized salt, iodine-containing mineral preparations or high iodine foods).

It is recommended<sup>refs. 8, 17, 23, 24 and 26</sup> that iodine-containing drugs be administered with caution to patients with goiter, particularly nodular goiter. Others<sup>ref. 27</sup> also recommend that thyroid hormone therapy be avoided in elderly patients or in those with cardiac disease who have nontoxic nodular goiters to avoid precipitation of thyrotoxicosis. In other patients in whom thyroid hormone is used for this condition, the potential for induction of thyrotoxicosis warrants careful follow-up and monitoring of thyroid hormone levels.

#### D. What Are The Clinical Consequences of Increasing Dietary Iodide Intake?

Several authors have addressed this issue:<sup>refs. 7-9, 13, 28-29.</sup>

- a. IHH is likely to become more common, particularly in older individuals with autonomous thyroid nodules.
- b. Graves' disease may become more difficult to control with antithyroid drugs thereby resulting in reduced remission rates and an increased rate of relapse
- c. The results of thyroid surgery for Graves' disease are also influenced by the ambient iodine intake. In an area of high iodine intake, the incidence of hyperthyroidism post surgery for Graves' is 5x higher and hypothyroidism 5x lower than in areas where the iodine intake is low<sup>ref. 30</sup>.
- d. The increase in dietary iodine intake has also resulted in a decrease in the thyroid radioactive iodine uptake and a corresponding increase in the dose of radioactive iodine required to control hyperthyroidism.
- e. Incidence of autoimmune thyroid disease may increase, but this requires confirmation<sup>ref. 31</sup>.
- f. Incidence of papillary cancer may increase and that of follicular and anaplastic thyroid cancer decrease<sup>ref. 31</sup>.

#### E. Iodine nutrition trends in the U.S.<sup>ref. 32.</sup>

Although iodine intake remains adequate for the overall U.S. population, the median urinary iodine (UI) concentration (an accurate measure of the amount of iodine ingested and absorbed) decreased more than 50% between 1971-1974 ( $32.0 \pm 0.6$  ug/dl) and 1988-1994 ( $14.5 \pm 0.3$  ug/dl). (Note: UI concentrations in iodine-sufficient populations should be  $> 10$  ug/dl).

However, the authors state that there is, at present, no data to correlate this decrease in iodine intake over time in the U.S. with changes in thyroid disease patterns. They state it will be important to continue to monitor iodine status in the U.S. and to determine what UI concentrations in a population will predict thyroid dysfunction. Silva<sup>ref. 14</sup> also makes a similar point:

"We do not know whether the generous dietary supply of iodine, such as in Japan and in the United States, has long-term effects upon thyroid function and thyroid disease."

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#### 4. Published Literature Studies Pertaining To Iodine Toxicity:

##### A. Suppressive Effects of Iodine <1 mg/day on Thyroid Function In Normal Individuals:

The following table summarizes the data from the literature (note: M= male, F= female, stat. signif.= statistically significant, inc.= increase, dec.= decrease, plac.= placebo, con.= controlled, ab += thyroid antibody positive, ab - = thyroid antibody negative, y= years, iod. suff.= iodine-sufficient, iod. def.= iodine-deficient, fn.= function, supp.= supplemented, nl.= normal):

Author	Type of Study	# Subjects	Dose/Duration of Iodide Admin.	Thyroid Gland Effect
Paul <sup>1</sup>	Open	9M and 23F	250, 500 or 1500 ug/day x 14 days	Stat. signif. decrease in T4 and FT4I & increase in TSH only at 1,500ug/day <sup>a</sup>
Gardner <sup>2</sup>	Open	30M	500, 1500 and 4500 ug/day x 14 days	All doses: signif. inc. in TSH response to TRH; At 1,500 & 4500ug/day: signif. dec. in T4 and FT4I & inc. in TSH <sup>a</sup>
Chow <sup>3</sup>	Rando mized, plac. con.	20F: ab + age:25-54y 30F: ab - age:25-54y 29 elderly F/ iod. suff. 35 elderly F/iod. def. area	Subjects rec'd 500 ug/day x 28 days or placebo	<ul style="list-style-type: none"> <li>• Changes in thyroid fn. induced by iodide were similar in normals and ab + subjects and in those from iod. suff. and def. areas.</li> <li>• In all iodide-supp. gps., there was a stat. signif dec. in FT4 and inc. in TSH<sup>a</sup>.</li> <li>• On iodide, TSH inc. from nl. to high in 2 subjects and inc. further in 3 other subjects.</li> <li>• No changes in thyroid fn. occurred on placebo.</li> </ul>
Reinhardt <sup>4</sup>	Open, con.	16 (M + F), iod. def. area	½ subjects rec'd 500ug/day x 5 wks, ½: no iodine supp.	Signif. inc. in T4 in iodine supp. group <sup>a,b</sup>

a = the changes in thyroid function refer to mean changes; although mean changes were statistically significant, all means remained within normal limits.

b= with iodine supplementation, T4 would be expected to increase as one is repleting deficient iodine stores.

The following text describes each of the above 4 studies in detail.

1. "The Effect of Small Increases in Dietary Iodine on Thyroid Function in Euthyroid Subjects" by Paul et al, *Metabolism* 37(2):121-124, 1988<sup>ref. 33</sup>.

The purpose of the present study was to determine if at physiological doses of iodine: 250 and 500ug/day and at 1,500ug/day (1.5 mg), given for 14 days to normal subjects, there was an affect on thyroid function.

9 euthyroid men between 26-56 yrs. and 23 euthyroid women between 23 -44 yrs., were studied. All subjects received various doses of iodine in 0.5 ml of water po (NaI and 5 mg ascorbic acid/ml) every 12 hours for 14 days. The men received 1,500 ug/day and the women received 250, 500 or 1,500 ug/day.

Serum T4, T3, TSH, resin T3 uptake and a TRH stimulation test were done at baseline and day 15. Serum FT4 I was calculated as the product of the total T4 and T3 resin uptake.

Results:

At 250 and 500 ug iodine/day, no changes occurred in serum T4, T3, FT4I, TSH or the TSH response to TRH. At 1.5 mg iodine/day, there was a small but statistically significant decrease (using the Student's paired t-test), in mean serum T4, FT4I, T3 and an increase in TSH levels on day 15, but all TFT values remained within the normal range). Also, there was a statistically significant increase in the TSH response to TRH at 1.5 mg iodine/day.

Comment:

Although no significant changes were observed in pituitary-thyroid function in normal subjects receiving 250 or 500 ug iodine/day, the effect was studied for only 14 days.

2. "Effects of Low Dose Oral Iodide Supplementation On Thyroid Function In Normal Men" by Gardner et al Clin Endocr 28:283-288, 1988<sup>ref. 34</sup>

The purpose of this study was to investigate the effects of very low dose iodide supplementation on thyroid function.

30 normal men, ages 22-40 yrs., were randomly assigned to receive 500, 1500 and 4500 ug iodide/day (prepared by dissolving NaI in water and adding ascorbic acid) for 2 weeks. Blood was obtained on days 1 and 15 for serum T4, T3, T3U and TSH. TRH stimulation testing was performed on days 1 and 15. Subjects continued their usual diets.

Results:

Mean serum T4 and FT4I decreased significantly and basal TSH increased only at the 1500 and 4500 ug/day doses, but the mean levels remained within the normal range. No changes occurred in serum T3 or T3U. The TSH response to TRH increased significantly at all 3 doses studied, indicating that even a low dose of iodine- 500 ug- has an anti-thyroid effect. No adverse effects or symptoms of thyroid dysfunction were reported.

The authors make the point that the consequences of prolonged exposure to low levels of iodine and the "no effect" level of iodide supplementation remain to be determined.

3. "Effect of Low Dose Iodide Supplementation on Thyroid Function in Potentially Susceptible Subjects: Are Dietary Iodide Levels in Britain Acceptable?" by Chow et al in Clin Endocr 34:413-416, 1991<sup>ref. 35</sup>

The purpose of the present study was to evaluate the affect on thyroid function of administering 500 ug iodide/day for 28 days to patients with Hashimoto's thyroiditis. The trial was a placebo controlled, randomized trial. The study group enrolled:

- 20 women, aged 25-54 yrs., who were thyroid antibody positive but clinically asymptomatic and with no history of thyroid disease, from an iodine-sufficient area;
- 30 women, aged 25-54 yrs., who were antibody negative, and iodine-sufficient;
- 29 women, aged 60-75 yrs., from an iodine-sufficient area;
- 35 women, aged 60-75 yrs., from an iodine-deficient area.

Patients were randomly assigned to receive 500 ug KI/day or placebo for 28 days. Serum FT4 and TSH were measured at baseline and after 14 and 28 days of KI supplementation.

Results:

Changes in thyroid function in elderly subjects living in an iodine-sufficient area were similar to those living in an iodine-deficient area; and for normals and those with underlying thyroid susceptibility.

In all iodine-supplemented groups, there was a small decrease in mean FT4 (-1.22 pmol/l at 14 days and -0.86 pmol/l at 28 days) and a small rise in mean TSH (+0.55 mU/l at 14 days and +0.59 mU/l at 28 days) (note: means remained within the normal range). In contrast, no changes in thyroid function occurred in the placebo groups.

Serum TSH levels rose from normal to high in 2 iodine-supplemented elderly subjects at 28 days. In 3 patients (1 elderly and 2 ab +), an initially high TSH rose further with KI supplementation.

The authors concluded that 500 ug iodine supplementation/day for as short as 28 days, does have a small but measureable effect on thyroid function in both normals living in iodine-deficient or sufficient areas and in those with underlying susceptibility to thyroid disease. 2 patients became biochemically hypothyroid with elevated TSH levels and in 3 additional patients, there was a further rise in TSH. Although the changes were not clinically significant, the study was only 28 days duration. The authors conclude that a dietary iodine intake of 750 ug/day may not be advisable particularly in susceptible individuals (e.g. those with borderline hypothyroidism) as it may adversely affect thyroid function (note:

4. "Effect of Small Doses of Iodine on Thyroid Function During Caloric Restriction in Normal Subjects" by Reinhardt et al in Horm Res 39:132-137, 1993<sup>ref. 36</sup>

The authors evaluated the effect of iodine supplementation on thyroid function before and after a short-term intake of a low carbohydrate diet in normal subjects residing in an iodine-deficient area. The study was performed in 16 euthyroid subjects (11M and 5F, aged 23-42 yrs.). All subjects underwent a 4 week run-in period (study days 1-28) consisting of a normal dietary intake. This was combined with iodine supplementation: 500 ug/day in half the subjects. All subjects were then placed on a low carbohydrate (800 kcal) diet for 4 days (study days 28-32) with iodine supplementation continuing in half

the subjects. All subjects were then placed back on a normal diet for 7 days (study days 33-39) with iodine supplementation continuing in half the subjects. Thyroid volume and function were determined at baseline, day 28 (last day of the normal diet run-in period), day 32 (last day of low carbohydrate diet) and at study end.

#### Results:

##### Normal Diet Run-In Period:

Although mean serum total T4 increased significantly from baseline in the iodine supplemented group, the mean remained within the normal range. There were no significant changes in mean TSH.

##### Restricted Dietary Intake:

In both groups, there was a statistically significant decrease in mean T3, FT3 and the TSH response to TRH and a statistically significant increase in mean rT3. In the iodine-supplemented group only, there was also a significant decrease in mean basal serum TSH and in the mean T3 and T4 response to TRH. All means remained within the normal range for both groups. Serum mean T4 and FT4 were not affected in either group.

##### Refeeding Period:

Serum mean T3, FT3 and rT3 returned to baseline or slightly above baseline in both groups at the end of the refeeding period. In the iodine-supplemented group, mean basal TSH returned to baseline but there was a statistically significant decrease in mean FT4 although it remained within the normal range.

The present study confirms the observation that serum T3 decreases and rT3 increases during fasting, with return to baseline levels during refeeding. Fasting the iodine-supplemented group, also resulted in a decrease in basal TSH and a blunting of the T3 and T4 response to TRH. The authors postulate that the blunted response of T3 and T4 after TRH in subjects receiving short-term iodine supplementation after caloric restriction seems to be mediated by a lower TSH rise.

5. In addition to the above 4 studies, Silva<sup>ref. 14</sup> reported that 750ug iodine-131 to normal subjects produces a transient blockade of organification shown by an abnormal discharge of iodine-131 with perchlorate.

6. There is a case report in the literature<sup>ref. 37</sup> of a term infant who developed transient hypothyroidism (elevated serum TSH and low T4 but clinically asymptomatic). The baby's mother took prenatal vitamins containing 150ug iodine throughout the pregnancy. The infant was started on levothyroxine at 8 weeks of age but the medication was discontinued at 12 weeks when all results were normal. Although the authors state that the cause of the transient hypothyroidism in this case is unknown, they cannot exclude an iodine goitrogenic effect.

7. Finally, Saxena et al<sup>ref. 38</sup> reported that administration of 300 ug iodide daily for 2 weeks to 2 year old children suppressed thyroid function manifested by a decrease in iodine-131 uptake. Administration of 600 ug daily resulted in further suppression. Complete suppression of radioactive iodine uptake was achieved with 1,500- 2,000 ug iodide/m<sup>2</sup>/day. Thus, for the adult, the minimal effective dose of iodide becomes 3-4 mg and for children 1-2 mg.

The authors demonstrated a rebound of uptake within a week after iodine administration was discontinued. In some cases, the uptakes were even higher in subsequent weeks. Their data suggested that after very small doses of iodine (100 ug), the uptakes reached were even higher than that before iodine administration.

#### 4.B. Suppressive Effects of Iodine <1 mg/day on Thyroid Function in Patients With Underlying Thyroid Disease:

The following table summarizes the data from the literature (note: Rand.= randomized; Hash.= Hashimoto's thyroiditis; PPT= post-partum thyroiditis; wnl= within normal limits; for other abbreviations, refer to the previous table on page 7):

Author	Type of study	# Subjects	Dose/Duration of Iodide Administration	Thyroid Gland Effect
Chow <sup>1</sup>	Rand., plac. con.	20F: ab + age:25-54y 30F: ab - age:25-54y 29 elderly F/iod. suff. 35 elderly F/iod. def area	500 ug/day x 28 days or placebo	<ul style="list-style-type: none"> <li>Changes in thyroid fn. induced by iodide were similar in normals and ab + subjects and in those from iod. suff. and def. areas.</li> <li>In all iodide-supp. gps., there was a stat. signif dec. in FT4 and inc. in TSH<sup>a</sup>.</li> <li>On iodide, TSH inc. from nl. to high in 2 subjects and inc. further in 3 other subjects.</li> <li>No changes in thyroid fn. occurred on placebo.</li> </ul>
Reinhardt <sup>2</sup>	Open, con.	83 (M + F) with euthyroid Hash. in iod.-def. area	~1/2 subjects rec'd 250ug KI/day for mean of 4 mos. ~1/2: no rx.	<ul style="list-style-type: none"> <li>Iodine rx'd gp.: 7 subjects became hypothyroid (1 overt &amp; 6 subclinical) and 1 became hyperthyroid</li> <li>Control gp.: 1 subject developed subclinical hypothyroidism</li> </ul>
Fragu <sup>3</sup>	Open, con.	14F with Hash.; 5 controls (M + F); relative iod.-def.	Hash. patients rec'd 500 ug/day x 1-9 mos.	<ul style="list-style-type: none"> <li>Results variable in iodide rx'd Hash. patients: worsening hypothyroidism in 8/14 (57%); improvement in 6 (43%)</li> <li>Controls: no significant changes in thyroid parameters</li> </ul>
Glincoer <sup>4</sup>	Rand., dble-blind plac. con.	180 eu-thyroid, pregnant, mildly iod.-def.	~1/3 subjects rec'd L-T4 rx., ~1/3 subjects rec'd 130ug KI/day + T4; ~1/3 placebo Rx. x 9 mos.	<ul style="list-style-type: none"> <li>Placebo gp.: iodine def. worsened (dec. T4 and inc. TSH and thyroid gland volume)</li> <li>T4 rx'd and T4 + KI rx'd: thyroid fn. improved with more rapid and marked improvement in the group receiving T4 + KI.</li> </ul>
Kampe <sup>5</sup>	Rand., con.	58F at risk for PPT living in an iod.-def. area	~1/3 subjects rec'd T4 rx., ~1/3 rec'd 150ug KI/day x 40 weeks; ~1/3 no rx.	The iodide rx'd gp. had signif. lower median FT4I and signif. higher median TSH compared to the groups that did not receive iodide. Therefore, the iodide intensified the hypothyroid phase of PPT.
Kahaly <sup>6</sup>	Plac. con.	62 (M + F) with euthyroid, diffuse, endemic goiter	1/2 subjects rec'd 200ug iodide/day x 12 mos.; 1/2 rec'd placebo	Iodide rx'd gp. only: signif. dec. thyroid gland volume and signif. inc. T4 but remained wnl. Iodide induced hypothyroidism occurred in 2 patients and hyperthyroidism, in 1 patient.

The following text describes each of the above 6 studies in detail:

1. Chow et al<sup>ref. 33</sup>: see page 8 of this review for details.
2. "Effect of Small Doses of Iodine on Thyroid Function in Patients With Hashimoto's Thyroiditis

Residing in an Area of Mild Iodine Deficiency" by Reinhardt et al, *European J of Endocrinol* 1998, 139: 23-28<sup>ref. 39</sup>.

The purpose of this study was to determine the effect on thyroid function of a small dose of iodine in euthyroid patients with Hashimoto's thyroiditis living in an area of mild iodine deficiency.

40 Hashimoto's thyroiditis patients received 250 ug potassium iodide daily for a mean of 4 months (range 2-13 months). An additional 43 patients with Hashimoto's thyroiditis did not receive KI and, therefore, served as the control group.

Results:

Iodine-treated group: 7 patients became hypothyroid- 1 overt and 6 subclinical. 3/6 subclinical hypothyroid patients became euthyroid when iodine treatment was discontinued.

1 patient became overtly hyperthyroid with a concomitant increase in antibody titer but became euthyroid upon iodine withdrawal (note: this patient also had myasthenia gravis and was taking birth control pills. The authors speculate that this patient may have had underlying Graves' disease rather than Hashimoto's disease).

Control group: 1 patient developed subclinical hypothyroidism.

The authors conclude that administration of even small amounts of iodine may lead to inadequate iodine organification and a consequent defect in hormone synthesis in predisposed individuals.

3. "Thyroid Iodine Content and Serum Thyroid Hormone Levels in Autoimmune Thyroiditis: Effect of Iodide Supplementation" by Fragu et al, *J Nuc Med* 26(2): 133-139, 1985<sup>ref. 40</sup>.

5 euthyroid control subjects and 14 patients with autoimmune thyroiditis received iodide supplementation 0.5 mg/day for 1-9 mos. Thyroid iodine content (TIC) measured by x-ray fluorescence and serum thyroid function tests (TFTs) were followed in all patients.

Results with iodide supplementation:

Euthyroid control subjects-

The TIC increased from 1.5 - 4 mg after 4 weeks of iodide treatment. There were no significant changes in TFTs.

Autoimmune thyroiditis patients-

Thyroid function improved in 6 patients or 43% (as manifest by an increase in serum T4 in these 6 patients and, also, a decrease in TSH in 5 patients). TIC increased in all 6 patients (after 3 months in 5 and after 7.5 months in one patient). In 2 of these 6 patients, TFTs normalized and iodide supplementation was continued for 6-9 months. TIC continued to increase linearly in these 2 patients. The author speculates if hyperthyroidism might have occurred in these 2 patients had iodide supplementation continued (thyroid iodine overload perhaps leading to thyrotoxicosis).

Hypothyroidism worsened in 8 patients (57%) as manifest by a marked rise in serum TSH and a decrease in T4 and T3 which, however, was only transient in 3 of these 8 patients. The authors state that this worsening of thyroid function was probably due to block of iodine organification and hormone synthesis. In these 8 patients, the TIC was progressively depleted in 3 patients, unchanged in 3 and increased in two. In 5 of these 8 patients, the iodide supplementation had to be withdrawn between the 4<sup>th</sup> and 10<sup>th</sup> weeks due to worsening hypothyroidism. Substitution therapy was begun in 2 of these 5 patients; the remaining 3 patients spontaneously recovered. Iodide treatment was restarted in 2 patients, and an escape from the Wolff-Chaikoff effect occurred.

Note: response of the Hashimoto's to low doses of iodine could not be predicted on the basis of the thyroid function parameters studied- high TSH and thyroid iodine depletion were observed in both groups.

4. "A Randomized Trial for the Treatment of Mild Iodine Deficiency During Pregnancy: Maternal and Neonatal Effects" by Glinoeer et al, *JCEM* 80(1), 1995 (Note: this study was done in Belgium, an iodine-deficient country)<sup>ref. 41</sup>.

180 euthyroid pregnant women were selected at the end of the first trimester of gestation on the basis of biochemical criteria for excessive thyroid stimulation, defined as supranormal Tg (Tg >20 ug/L) associated with a low normal FT4I (< 1.23) and/or an increased T3/T4 ratio (>25 x 10<sup>-3</sup>). Women were randomized into 3 groups and treated until term with placebo, 130 ug KI/day (corresponding to 100 ug iodide per day), or 130 ug KI + 100 ug L-T4/day. Serum thyroid function, urinary iodide excretion, and thyroid volume were monitored sequentially in the mother and neonate.

In women on placebo, the excessive thyroid stimulation worsened as pregnancy progressed, with low FT4 levels, markedly increased serum Tg and T3/T4 ratio. Serum TSH doubled on average and was supranormal in 20% of cases at term. Mean thyroid volume increased by 30% and 16% of the women developed goiter. The newborns of these mothers had significantly larger thyroid volumes at birth as well as elevated serum Tg levels.

In the other 2 treatment groups, thyroid function was markedly improved. The increase in serum TSH was almost suppressed, serum Tg decreased significantly, and changes in thyroid volume were minimized (group receiving KI) or almost suppressed (group receiving KI + T4). In the newborns of the mothers in these two groups, serum Tg was significantly lower than in the placebo group, and thyroid volume at birth was normal. The effects of therapy were more rapid and more marked in the group receiving a combination of T4 and KI than in the women receiving KI alone.

The authors state that the combination of KI and T4 is not recommended for all pregnancies in areas with marginally low iodine supply, but can certainly be proposed for pregnant women who display features of excessive thyroid stimulation in the early stages of pregnancy as well as in women with a preexisting goiter.

5. "Effects of L-Thyroxine and Iodide on the Development of Autoimmune Postpartum Thyroiditis by Kampe et al, JCEM 70(4): 1014-1018, 1990<sup>ref. 42</sup>

Women at risk for postpartum thyroiditis (identified by high titers of antibodies against thyroid peroxidase) were randomized to one of three treatment groups to examine the influence of L-T4 and iodide on this condition. 20 patients received no treatment, 18 received 0.1 mg L-T4 daily and 20 received 0.15 mg potassium iodide daily for 40 weeks postpartum.

In each group, thyrotoxicosis occurred at 2-3 months postpartum followed by a hypothyroid phase at 5-5 months postpartum. During the hypothyroid phase, the iodide treated group had significantly lower median serum FT4I and significantly higher median serum TSH levels compared to the groups who did not receive iodide. Therefore, this study from Sweden suggested that small doses of iodide- 150 ug- may intensify the hypothyroid phase of postpartum thyroiditis. The authors conclude that extra iodide should not be given in the postpartum period, as even a dose of 150 ug, may aggravate the disease rather than ameliorate it.

6. "Randomized, Double Blind, Placebo-Controlled Trial of Low Dose Iodide in Endemic Goiter" by Kahaly et al, JCEM 82(12): 4049-4053, 1997<sup>ref. 43</sup>

The purpose of this study was to determine the efficacy and safety of low dose iodide (0.2 mg/day) administered for 12 months to patients with euthyroid, diffuse, endemic goiter. 31 subjects (16F and 15M), mean age of 24 yrs., were administered iodide and 31 (16F and 15M), mean age of 24 years, were administered placebo. Subjects were followed for an additional 6 months after termination of this 1 year study. Iodide reduced thyroid volume by 38% and, at 18 months, this effect was sustained. However, no significant change in thyroid volume occurred in the placebo group. Serum T4 levels significantly increased (but remained within normal limits) and serum thyroglobulin levels significantly declined during iodide administration. High microsomal and thyroglobulin antibody titers were present in 10% of subjects receiving iodide. Iodide-induced hypo- and hyperthyroidism developed in 2 and 1 patient(s), respectively, along with nonspecific symptoms (e.g. tachycardia and weight loss in the hyperthyroid patient). Fine needle biopsy revealed marked lymphocytic infiltration in these 3 subjects. After iodide withdrawal, thyroid dysfunction significantly remitted, and antibody titers and lymphocytic infiltration decreased markedly. Normalization of antibody titers occurred in 2/3 subjects after an additional f/u period of 2 years.

7. Silva<sup>ref. 14</sup> stated that in contrast to normal individuals, patients with underlying thyroid disease, including those with subclinical disease, have a heightened sensitivity to the potential adverse effects of iodine. For example, most patients with Hashimoto's disease will have a positive discharge of radioiodine with perchlorate if the tracer is given along with as little as 250 or 500 ug iodine.

4.C. Stimulatory Effects of Iodine < 1 mg/day on Thyroid Function in Normal Individuals:

The following case reports are derived from Pennington ( Amer Diet Assoc 90(11):1571-1581, 1990)<sup>ref. 44</sup>:

- a. 98 cases of thyrotoxicosis in 10 counties of Minnesota, South Dakota and Iowa from ground beef containing thyroid tissue

- b. peak of thyrotoxicosis in England causally related to high levels of iodine in milk from winter feed supplements (average iodine intake of 0.236 mg/day for women and 0.306 mg/day for men).

#### 4.D. Stimulatory Effects of Iodine < 1 mg/day on Thyroid Function in Patients With Underlying Thyroid Disease:

The following 3 articles suggest that there is an inverse relationship between iodine intake and the relapse rate in euthyroid Graves' patients treated with antithyroid drugs- as iodine intake increases, the relapse rate decreases:

1. "Low Remission After Therapy for Graves' Disease Possible Relation With Antithyroid Therapy Results" by L Wartofsky, JAMA 226(9): 1083-1088, 1973<sup>ref. 45</sup>.

44 patients with Graves' disease were treated with antithyroid drugs for an average of 17.6 mos. (range: 7-46 mos.). Remission occurred in only 4/35 patients (11.4%) who were treated for longer than 12 mos. and in 6/44 (13.6%) patients in the total treatment group. The patients were followed up in a locale in which recent increases in daily iodine intake were observed (note: daily urinary iodide excretion was high: 374±88 ug in the 8 patients in whom this was measured). These remission rates were much lower than in the period from 1952 to 1966 when iodine intake was markedly lower.

The author notes that one adaptation to the increased iodine intake has been a decreasing normal range of values for the 24 hour thyroidal radioactive iodine uptake.

The author postulates there may be an inverse relationship between the increasing average daily dietary intake of iodine and the remission rate that may be anticipated after antithyroid drug therapy.

2. "Remission Rates with Antithyroid Drug Therapy: Continuing Influence of Iodine Intake?" by Solomon et al, Annals of Internal Medicine 107: 510-512, 1987<sup>ref. 46</sup>

For the period 1973-1986, the authors retrospectively reported a 51% remission rate of Graves' disease treated with antithyroid drugs compared to a remission rate of only 14% in their 1973 report. They postulate that the increased remission rate parallels a decrease in dietary iodine intake over the period studied.

The authors point out that relative resistance to antithyroid therapy may be seen in patients from an area of iodine sufficiency in contrast to the more successful outcomes seen in comparable patients who are iodine deficient. They postulate several reasons for this observed difference. Provision of iodine substrate permits excessive hormone synthesis in autonomously functioning thyroid glands. Iodine excess may also relate to the altered immunologic surveillance characteristic of Graves' disease. Iodine has been shown to promote IgG synthesis in lymphocytes, confer greater antigenicity to thyroglobulin or induce autoantigen and precipitate organ-specific immunologic abnormalities.

The authors conclude that further studies will be necessary to confirm the validity of this proposed relationship.

3. "Influence of Iodine Intake After Treatment With Antithyroid Drugs" by Alexander et al; Lancet 2: 866-868, 1965<sup>ref. 47</sup>

9/16 Graves' disease patients (56%) experienced a relapse within 6 months when 200 ug KI was given daily after withdrawal of antithyroid medication compared to 11/41 patients (27%) who did not receive iodine. 11 patients not receiving iodide who remained in remission after 6 months were then given iodide, and 6 relapsed (55%).

Therefore, physiologic amounts of iodide administered up to several months after withdrawal of antithyroid drugs, may induce or hasten relapse of Graves' disease.

**The following article demonstrates that Graves' disease is easier to control with antithyroid drugs (lower dose and more rapid remission) in patients residing in an area of iodine deficiency compared to one of iodine sufficiency:**

- "Environmental Iodine Intake Affects the Response to Methimazole in Patients With Diffuse Toxic Goiter" by Azizi JCEM 61(2):374-377, 1985<sup>ref. 48</sup>.

After only 4 weeks, methimazole 10 mg tid, induced a rapid decrease in FT4I, becoming normal in 9/18 patients and subnormal in 8/18 patients with diffuse toxic goiter living in an area of iodine-deficiency. Half of the patients (4/8) with subnormal FT4I, developed clinical signs and symptoms of hypothyroidism. In only 1 patient, was the FT4I still elevated after 4 weeks of treatment. In contrast, in an iodine-sufficient

area, FT4I was still elevated in 12/18 patients after this dose and duration of methimazole treatment. The author concludes that lower doses of antithyroid drug therapy may be appropriate and adequate treatment in areas of iodine-deficiency and more frequent monitoring of thyroid function is warranted.

The following 2 studies demonstrate that even small amounts of iodide supplementation (100-500 ug/day) may induce thyrotoxicosis in patients with autonomous thyroid tissue (note: these studies were done in iodine-deficient areas which increase the sensitivity of the thyroid gland to iodine- the iodine-hungry thyroid will avidly trap the iodide when it becomes available):

1. "The Toxic Effects of Small Iodine Supplements in Patients with Autonomous Thyroid Nodules" Livadas et al (Clin Endocrinol 7:121-127, 1977)<sup>ref. 49</sup>

KI in doses of 100-400 ug/day, each dose for 1 week, to 16 cases of autonomous hot nodule, resulted in progressive increases in serum T4 and FT4I. Serum TSH remained undetectable. Of the 10 patients who were initially clinically euthyroid, 5 showed clinical signs of thyrotoxicosis. Of the 6 patients who were toxic already, 4 showed an exacerbation. (Note: this study was conducted in Belgium, an iodine-deficient country).

2. "Modifications of Thyroid Function Induced by Chronic Administration of Iodide in the Presence of Autonomous Thyroid Tissue" by Ermans et al, Acta Endocrinologica 70: 463-475, 1972<sup>ref. 50</sup>.

In this Belgium study, a daily supplement of 0.5 mg iodide over a period of 3-10 months induced biochemical hyperthyroidism (manifested by a marked rise in PBI into the thyrotoxic range) after only a few weeks in 4 euthyroid patients with a thyroidal hot nodule. 3 of these 4 patients manifested hyperthyroid symptoms 6 to 9 months after initiation of iodide supplementation. In 2 of these 3 patients, it was possible to reverse the situation by discontinuing iodide administration; in the third, antithyroid drug therapy was begun.

In addition, PBI markedly rose into the thyrotoxic range in one patient with euthyroid Graves' disease previously treated with methimazole, but the patient did not experience symptoms of hyperthyroidism.

The authors conclude that in the absence of an adequate feedback control mechanism, the amount of dietary iodine appears to be one of the main regulatory factors involved in the thyroid activity in humans.

The following case reports derived from Pennington<sup>ref. 44</sup> pertain to the stimulatory effects of iodine on the abnormal thyroid gland from a vitamin-mineral supplement or iodized salt:

- a. Increase in the number of deaths from toxic goiter; increase in the number of thyroid operations for toxic diffuse and toxic nodular goiter; increase in hyperthyroidism in nodular goiter and adenomatous goiter; peak in 1926, 2 years after iodination of salt in Michigan
- b. Rapid rise in incidence of exophthalmic goiter and adenomatous goiter with hyperthyroidism in northwest states in 1924 attributed to iodized salt; reached a peak in 1926 to 1927 and dropped to 1923 level in 1931.

Goiter and hyperthyroidism in a 26 yr. old pregnant woman with underlying Hashimoto's disease who took a vitamin-mineral supplement during pregnancy

5. Published Literature Studies Pertaining to the Toxic Effects of Iodine at Doses  $\geq 1$  mg:

These articles do not directly impact on assessing the safety of the Vintage tablet which contains ug quantities of iodide. However, some of them were submitted

and, therefore, they have been reviewed.

A. Suppressive Effects of Iodine  $\geq 1$ mg /day On Thyroid Function In Normal Individuals:

Pediatric Patients:

1. "Congenital Goitre and Hypothyroidism Produced by Maternal Ingestion of Iodides" by Carswell et al, Lancet 1:1241, 1970<sup>ref. 51</sup>

Maternal intakes of 12-1,650 mg elemental iodine/day taken throughout pregnancy in 6/8 mothers, produced congenital iodine goiters. The authors recommend that iodine-containing preparations not be used in pregnancy.

#### Adult Patients:

##### Summary of the following 14 articles (pages 15-19):

The majority of these studies were short-term (i.e.  $\leq 4$  weeks) and all of the studies enrolled  $< 50$  subjects. The suppressive effect of oral iodide on thyroid function, was accompanied by thyroid hypertrophy in patients exposed to 27-32 mg iodide/day for 1-3 months. This hypertrophy was reversible upon discontinuation of the iodide supplement.

Additionally, Philippou showed that pharmacologic doses of iodide do not affect the peripheral metabolism of thyroid hormones.

Although vaginal douching with iodine-containing solutions may have clinically insignificant effects on thyroid function in women, it may cause transient hypothyroidism in a newborn exposed to the excess iodine at delivery.

1. "The Direct Estimation of the Rate of Thyroid Hormone Formation in Man. The Effect of the Iodide Ion on Thyroid Hormone Utilization" by Stanley M, *J Clin Endocrinol* 9:941, 1949<sup>ref. 52</sup>

The author showed that the organic binding of iodine in the thyroid gland was inhibited by single doses of iodide, in the order of 1 mg and upwards. Patients with hyperthyroidism were the most susceptible.

2. "The Effect of Iodide on the Release of Thyroid Hormone in Hyperthyroidism: Further Observations" by Goldsmith et al, *J Clin Endocrinol* 18: 367-378, 1958<sup>ref. 53</sup>

As little as 1 mg of potassium iodide daily may, after 4 days, block the release of thyroid hormone in hyperthyroidism.

3. "Iodide Goiter" by Paris et al, *J Clin Endocrinol* 20:57, 1960<sup>ref. 54</sup>

In patients with hyperthyroidism, as well as iodine goiter, 24 hours after administration of 2 mg KI, an organification defect occurs (manifested by inhibition of iodine-131 uptake).

4. "Effects of Oral Erythrosine (2', 4', 5', 7'-Tetraiodofluorescein) on Thyroid Function in Normal Men" by Gardner et al, *Toxicology and Applied Pharmacology* 91:299-304, 1987<sup>ref. 55</sup>

Significant increase in mean basal TSH and the TSH response to TRH occurred in 30 normal young men receiving 200 mg/day erythrosine for 14 days, which provided a daily iodide load of 1,000 ug/day. Gardner states: "The threshold level of dietary iodine which impairs thyroid hormone release sufficient to affect TSH secretion is not known...additional studies are needed to define an upper limit of iodine intake that will not have detectable effects on pituitary-thyroid function."

5. "A Small Increase in Dietary Iodine Affects Thyroid Function in Euthyroid Subjects" by Myers et al, *Clinical Research* 34: 429A, 1986<sup>ref. 56</sup>

18 young adult euthyroid subjects (9 males and 9 females) received 1500 ug iodine/day for 2 weeks. At the end of the 2 weeks period of iodine supplementation, statistically significant decreases occurred in mean serum T4 and T3 (but mean values remained within the normal range) and significant increases occurred in the TSH response to TRH.

6. "Inverse Relation Between Iodine Intake and Thyroid Blood Flow: Color Doppler Flow Imaging in Euthyroid Humans" by Arntzenius et al *JCEM* 73(5):1051-1055, 1991<sup>ref. 57</sup>

With a color doppler device, thyroid blood flow was measured at baseline iodine intake (1 week), iodine restriction (2 weeks), return to baseline (1 week) and iodine excess (1 week; 12 mg/day sodium iodide) in 10 euthyroid subjects (7F and 3 M, ages 19-30 yrs.). During iodine restriction, thyroid blood flow significantly increased and remained elevated during the second baseline diet. During high iodine intake, thyroid blood flow and serum FT4I and T3 significantly decreased accompanied by a rise in TSH. However, FT4I, T3 and TSH levels remained within normal limits throughout the study.

7. "Evidence of Thyroid Volume Increase in Normal Subjects Receiving Excess Iodide" by Namba et al in *JCEM* 76(3):605-608, 1993<sup>ref. 58</sup>

The objective of this study was to investigate the effects of excess iodide on thyroid volume in 10 normal adult males, aged 25-39 yrs. After 1 week of dietary iodide restriction, all subjects received 27 mg/day of licorice lecithin-bound iodine tablets for 4 weeks. Thyroid function and thyroid volume (by high resolution echoscanner) were monitored.

Results:

During iodide administration, mean serum FT4 levels declined slightly but significantly, but values remained within the normal range. Mean serum TSH increased significantly on days 21 and 28 of iodide administration, with values in 2 subjects becoming abnormally high (9.6 and 6.29 mU/L with normal TSH to 5.5 mU/L). Serum Tg rose in parallel with TSH with Tg becoming abnormally high in all subjects. The mean Tg level was abnormally high after 14 days of iodide administration. The increased TSH and Tg levels returned to baseline 2 weeks after the last day of iodide administration.

Mean thyroid volume significantly increased after 4 weeks of iodide treatment; returning to baseline 4 weeks after iodide withdrawal. However, in 2 subjects, it took 2 months after iodide withdrawal, for thyroid volume to return to baseline.

This study demonstrates that, in normal subjects, inhibition of thyroid function by iodide is accompanied by thyroid hypertrophy which is reversible upon discontinuation of iodide supplementation.

8. "Thyroid Adaptation to Chronic Tetraglycine Hydroperiodide Water Purification Tablet Use" by Le Mar et al *JCEM* 80(1):220-223, 1995<sup>ref. 59</sup>

Tetraglycine hydroperiodide tablets purify water by liberating 8 mg free iodine/tablet. The effects of ingestion 4 tablets daily (32 mg free iodine/day) for 3 months on thyroid function, size (determined by ultrasound) and radioactive iodine uptake was studied in 8 healthy adults (7M and 1F, aged 35-47 yrs.).

Although mean radioactive iodine uptake was 16% at baseline, it was <2% after 7 days and remained below 2% in all subjects at 90 days. There was no statistically significant change from baseline in mean serum T4 or T3. Serum TSH and the TSH response to TRH rose significantly after 7 days and remained elevated at 3 months. The average thyroid volume increased by 31% after 5 weeks of iodine supplementation and by 37% after 3 months. Neither hypo or hyperthyroidism occurred. In 7 subjects, thyroid volume was again determined at 7.1 months after study completion; the mean volume was not different from baseline.

This study confirms the findings of Namba et al that chronic iodide excess induces thyroid enlargement which is reversible upon discontinuation of the iodine excess.

9. "Comparison of the Effects of Iodine and Iodide on Thyroid Function in Humans" by Robinson et al in the *Journal of Toxicology and Environmental Health, Part A*, 55:93-106, 1998<sup>ref. 60</sup>

The first study (data not shown) determined the effect on thyroid function of rising doses of iodine or iodide added to drinking water. 31 male volunteers were randomly assigned to receive 5 single doses of water containing either I<sup>-</sup> or I<sub>2</sub> at increasing levels of 0.01, 0.02, 0.1, 0.3 and 1 mg/kg. A control group received distilled water with concentrations of NaCl matched to NaI and phosphate buffer as in the treatment groups. No statistically significant differences were detected for T3, T4, TSH or T4/T3 among the treatment groups. Thus, it was concluded that single doses of I<sub>2</sub> or I<sup>-</sup> up to 1 mg/kg had no apparent effects on thyroid function in normal males.

The second study randomly assigned 35 male volunteers to one of five treatment groups: either a low (0.3 mg/kg) or high (1.0 mg/kg) dose I<sub>2</sub> or I<sup>-</sup> treatment, or to a control group. All subjects were dosed daily for 14 days. Plasma T4, T3 and TSH were obtained at baseline, day 7, day 14 and day 15 (i.e. 24 hours after the last dose). Results: the only reported side effect was "burned mouth" in the I<sub>2</sub> treated group: 4/6 subjects in the low dose iodine treated group and 5/7 subjects in the high dose group. This irritation was not evident on physical examination. Although decreases in T4 were observed with dose schedules with I<sup>-</sup> and I<sub>2</sub>, none were statistically significant compared to each other or to the control group. Although TSH increased in all treatment groups, only at the high I<sup>-</sup> and I<sub>2</sub> doses, were the TSH levels significantly increased compared to the control group.

10. "The Effect of Iodide on Serum Thyroid Hormone Levels in Normal Persons, in Hyperthyroid Patients, and in Hypothyroid Patients on Thyroxine Replacement" by Philippou et al, *Clin Endocrin* 36:573-578, 1992<sup>ref. 61</sup>.

21 thyrotoxic patients (19 Graves' disease, 1 toxic adenoma and 1 multinodular goiter) and 12 normal controls received KI 150 mg/day for at least 21 days and up to 7 weeks. 12 hypothyroid patients secondary to various etiologies received 150 mg KI/day for 14 days. Serum thyroid function tests were obtained at baseline and during iodide administration.

**Results:**

The KI had a suppressive effect in both the thyrotoxic and normal control subjects.

In the thyrotoxic patients, serum T4 and FT4I decreased on iodide, becoming normal in all patients on days 14 and 21; the serum T3 levels decreased but remained elevated in all patients; TSH remained undetectable. After 21 days, serum T4 and T3 started to increase in some patients while other patients remained euthyroid even after 6 weeks. The authors state the reason for this variability is not clear.

In normal subjects, the KI produced a small but significant decrease in serum T4, FT4 and T3, accompanied by an increase in TSH.

In hypothyroid subjects, there was no consistent change, except for a statistically significant increase in T4 at days 1 and 14 and a transient decrease in TSH on day 1 after KI treatment. Since the hypothyroid patients were essentially made athyroidic by exogenous T4 administration, any effect of iodide observed would be attributable to the effect of iodide on the peripheral metabolism of thyroid hormones. The results of this study suggest that this effect is negligible.

(Note: De Groot, JCEM 26(7):778-779, 1966<sup>ref. 62</sup>, also concluded from his study that 30 mg KI/day for 14 days, does not affect the peripheral metabolism of thyroxine).

11. "Control of Thyroid Hormone Secretion in Normal Subjects Receiving Iodides" by Vagenakis et al, JCI 52:528-532, 1973<sup>ref. 63</sup>

The purpose of this study was to determine the effect of iodine supplementation on thyroid function in euthyroid individuals. The study enrolled 10 euthyroid male volunteers, aged 32-84. Baseline serum TFTs (T4, T3 and TSH) were obtained. All subjects then received 1 drop of SSKI bid (72 mg/day) for 11 days (phase II). In 9 subjects, the dose was then increased to 5 drops bid (360 mg/day) for a period of 12-19 days (phase III). During phases II and III, TFTs were measured qod. In 8 subjects, TFTs were also measured 14 days after SSKI had been discontinued (phase IV). Mean TFT levels during the control phase (phase I) were compared- by a paired t test- to the mean values of the last three samples obtained during phases II and III (i.e. the phases of SSKI administration). The mean serum TFT results during each of these phases were:

	Mean Serum T4 (ug/dl)	Mean Serum T3 (ng/dl)	Mean Serum TSH (uU/ml)
Phase I	6.9 ± 1.8	106 ± 15	3.7 ± 1.3
Phase II	5.8 ± 1.6 <sup>a</sup>	91 ± 19 <sup>a</sup>	6.0 ± 3.5 <sup>a</sup>
Phase III	5.3 ± 1.3 <sup>a</sup>	97 ± 20 <sup>a</sup>	6.6 ± 3.9 <sup>a</sup>
Phase IV	6.8 ± 1.3	104 ± 13	3.7 ± 1.5

a= statistically significant difference (p<0.01 or p<0.05) for phases II or III vs. phase I

All serum mean TFT values remained within the normal range. Serum T4 was low in only 1 subject, both at baseline and during SSKI administration, but was normal during phase IV. In 1 subject, serum TSH rose to above normal during SSKI administration.

The present study demonstrates that administration of 72 and 360 mg of iodide/day for periods as long as 39 days to euthyroid subjects, results in a small, but significant decrease in serum T4 and T3, with a compensatory rise in serum TSH.

12.. "Serum Thyrotropin and Thyroid Hormone Levels in Humans Receiving Chronic Potassium Iodide" by Jubiz et al, JCEM 44:379-382, 1977<sup>ref. 64</sup>.

Jubiz selected, for further study, a group of 13 patients of 37 with COPD, who had a low serum T4 level while taking SSKI 30-60 drops/day (1-2 gm/day) for 1 month to 8yrs. (mean of 2.2 yrs.). All were male except one and ranged in age from 40-79 yrs. None of these 13 patients had a history of thyroid disease. Serum T4, T3, TSH and T3RU were measured on SSKI and, in 7 of these 13 patients, one month after SSKI was discontinued. The effect of SSKI: 30 drops/day (1 gm/day) given for 11 weeks to 4 normal subjects (1 male and 3 females, ages 27-36 yrs.) was also studied. In these normals, TFTs (T4, T3 and TSH) were measured at baseline, weekly during SSKI administration and 6 weeks after SSKI was

discontinued. T4, T3 and TSH were measured by RIA and T3RU by the method of Schoeler. Results were analyzed by paired t-test.

**Serum Thyroid Function Tests On and Off SSKI in the 13 patients With COPD Were:**

	On SSKI	Off SSKI
Serum T4	Low in 13/13	Normal in 7/7
Serum T3	Low in 5/13 Normal in 8/13	Normal in 7/7
Serum TSH	High in 13/13	Normal in 6/7 High in 1/7
Serum T3RU	Normal in 11/13 Low in 2/13	Normal in 7/7

Thyromegaly was present in 7/13 patients with COPD.

In the 4 normal subjects, although mean serum T4 and T3 levels remained within the normal range, there was a statistically significant decrease ( $p < 0.05$ ) in the mean T4 level during SSKI administration (8.8 vs. 8.0 ug/dl). This was accompanied by a statistically significant increase ( $p < 0.01$ ) in mean TSH level: 7.3 vs. 10.2 uU/ml. Mean TFT levels returned to baseline during the recovery period. None of the normal subjects developed thyromegaly.

Jubiz et al concluded that subjects with a normal pituitary-thyroid axis can compensate for the iodide effect by a rise in TSH. However, the data is limited to 11 weeks of exposure to iodine supplementation. The point is made that underlying thyroiditis was not excluded in the patients with COPD who were studied (i.e. antithyroid antibodies were not measured). If thyroiditis were present, the thyroid gland would have had a heightened sensitivity to exogenous iodine, specifically, the susceptibility to iodine-induced hypothyroidism would have been increased.

**13. "Effect of Mouth Rinsing with Two Polyvinylpyrrolidone-Iodine Mixtures on Iodine Absorption and Thyroid Function" by Adér et al in JCEM 66(3): 632-635, 1988<sup>ref. 65</sup>**

46 subjects (19M and 27F), mean age: 29 yrs., with plaque and gingivitis, received one of two iodine-containing mouth rinses daily for 6 months. The mouth rinses were: 5% polyvinylpyrrolidone (PVPI)-1.5% hydrogen peroxide (Perimed) and 5% PVPI-water mixture. After a single rinse, ~6 mg iodine was absorbed. Blood and urine samples were collected at baseline, q6 weeks during the study and 3 weeks after cessation of the iodine rinses. Serum T4, T3, TSH, PBI, total and inorganic iodine concentration and urinary iodine excretion were determined at each of these timepoints.

**Results:**

There was significant iodine absorption as demonstrated by a significant increase in serum total and inorganic iodide levels and urinary iodine excretion during the 24 weeks of mouth rinse therapy compared to baseline and 3 weeks after cessation of the rinses.

There were no changes in the mean serum T4, T3 and FT4I values throughout the study. There was a small (0.7 mU/L for Perimed and 1.0 mU/L for PVPI-water) but significant increase in serum TSH levels during mouth rinse therapy compared to baseline and posttreatment values. However, TSH levels remained within normal limits in all subjects. The authors postulate that this small rise in TSH maintains normal T3 and T4 levels.

The authors state that several studies investigating the effect of iodine-containing solutions, PVPI, used as a skin antiseptic, perineal scrub or vaginal douche, demonstrated no evidence of thyroid dysfunction. However, slight increases in TSH with or without concomitant slight decreases in T4 have also been reported, but values have generally remained within the normal range. One study (Ferguson et al, Br Dent J 144:14, 1978) reported small but significant increases in T4 and FT4I after the use of PVPI mouthwash daily for 14 days, but all levels remained within the normal range

**14. "Effect of Chronic Douching with Polyvinylpyrrolidone-Iodine on Iodine Absorption and Thyroid Function" by Safran and Braverman in Obstr and Gyn 60(1):35-40, 1982<sup>ref. 66</sup>**

Daily vaginal douching for 14 days with PVPI (0.3% solution: 300 mg iodine per douche solution) in 12 euthyroid volunteers resulted in a significant increase in serum total iodine and urine iodine excretion. There was a marked decrease in 24 hour <sup>125</sup>I uptake by the thyroid gland, a sensitive indicator of serum iodine concentration (mean uptake was: 22%% at baseline vs. 8.5% on day 14). There was a small but significant increase in serum TSH (but TSH values remained within the normal range) and a slight but statistically insignificant decrease in serum T4. There was also a slight decrease in FT4I which was

statistically significant compared to baseline only on day 7 of douching. There were no changes in serum T3 and no evidence of overt hypothyroidism.

The authors refer to several articles in the literature demonstrating the mild hypothyroidism developing after use of iodinated skin antiseptics in newborns and children (Block in *Cutis* 26:88, 1980-elevated TSH; Chabrolle et al in *Arch Dis Child* 53:495, 1978- goiter and hypothyroidism; and Leger et al in *Ann Endocrinol (Paris)* 39:40A, 1978). Chabrolle and Leger pointed out the particular susceptibility of premature infants to transient iodine-induced hypothyroidism when iodinated skin antiseptics were applied to wide areas of skin. Amniocentography with iodinated dyes may induce neonatal hypothyroidism (Rodesch et al in *Amer J Obstet Gynecol* 126:723, 1976). Etling et al (*Obstr and Gyn* 53:376, 1979) reported no effect on thyroid function in 6 newborns in whom amniotic fluid iodine concentration was markedly elevated secondary to maternal use of pharmacological doses of iodine during pregnancy (2 mothers used iodinated polyvinylpyrrolidone intravaginally- 30 mg iodine/tablet; 1 mother used thyroid extract; 1 mother had intravenous urography with an iodinated medium and was studied on two different occasions; no details were available in the remaining patient). On the other hand, Gruters et al in *Pediatr Res* 16: 1982, reported that ~20% of newborns born to mothers who were exposed to PVP-I intravaginally before delivery, had elevated serum TSH concentrations on day 5. In addition, serum T4 and T3 concentrations were significantly lower than in 5 day old infants born to mothers who did not receive PVP-I.

#### 5.B. Suppressive Effects Of Iodine $\geq$ 1mg/day On Thyroid Function in Patients With Underlying Thyroid Disease:

1. "Small Increases in Iodine Intake Do Not Induce Hypothyroidism in Euthyroid Patients with Hashimoto's Thyroiditis" by Paul et al, *Clinical Research* 35: 400A, 1987<sup>ref. 67</sup>.

9 normal and 7 euthyroid women with Hashimoto's thyroiditis received 1,500 ug iodine/day for 12 weeks. Although no statistically significant changes from baseline were reported in either group for mean T4, T3 and TSH, mean serum TSH did rise from 3.9 uU/ml baseline to 5.9 uU/ml after 12 weeks of iodine supplementation in the Hashimoto's group (note: in the normal subjects, serum TSH rose from 1.9 to 2.6 uU/ml).

2. "Studies of Hypothyroidism in Patients With High Iodine Intake" by Tajiri et al, *JCEM* 1986, 63:412-417<sup>ref. 10</sup>

The authors state there is a high incidence of iodine-induced hypothyroidism in Japan, where foods are rich in iodine. They evaluated the reversibility of iodine-induced hypothyroidism with dietary iodine restriction (avoidance of iodine-rich foods) for 3 weeks in 22 subjects with underlying Hashimoto's thyroiditis. In 12 patients, the hypothyroidism was reversible and in 10 it was not.

In 10/12 subjects with reversible hypothyroidism, the mean iodine was  $2.8 \pm 1.2$  mg with a range of 1-5 mg (equivalent to a normal dietary iodine intake in Japan). In the remaining 2 patients it was 25.4 and 43.1 mg daily. The iodine intake in 8/10 subjects with irreversible hypothyroidism was  $2.3 \pm 0.7$  mg daily. In the remaining 2 subjects, it was 15 and 20 mg.

The patients with reversible hypothyroidism had focal lymphocytic thyroiditis changes on thyroid biopsy while those in whom the hypothyroidism was irreversible, had more severe destruction of the thyroid gland.

Administration of 25 mg iodine (Lugol's solution) for 14-28 days to 7 of the 12 patients with reversible hypothyroidism resulted in exacerbation of hypothyroidism in all 7 patients.

3. "Excess Iodine Intake and Thyroid Function and Growth" by Orlo Clark in *Thyroid*, Volume 1, Number 1, 1990, Mary Ann Liebert, Inc., Publishers<sup>ref. 28</sup>

The author summarizes the results of his investigations regarding the effect of excessive iodine intake on thyroid growth and function:

6 euthyroid patients were studied 2 mos.-10 yrs. after thyroid resection for nodules (hemithyroidectomy in 5/6 patients). Patients received SSKI 5 drops po bid (360 mg iodine/day). Serum TSH increased into the abnormal range within 2-4 weeks in 5/6 patients. There was a direct correlation between the baseline TSH and the increase in TSH while receiving iodide: the patient with a low normal basal TSH did not increase his TSH into the abnormal range on iodine while the 3 patients with high normal basal TSH had the highest TSH levels on iodine. Serum T4 levels decreased to subnormal levels in 4/6 patients and T3 in 3/6 patients. These levels promptly returned to normal when the iodide was discontinued. TRH tests were done in 2 patients. Basal and TRH-stimulated TSH levels were higher in both

patients while receiving iodide. The authors point out that the results of this study suggest that baseline serum TSH may be used to predict who will develop hypothyroidism when exposed to moderate doses of iodide and that one does not require abnormal thyroid tissue to develop iodine-induced hypothyroidism- all that is required is the presence of TSH-stimulated thyroid tissue. It is for the latter reason, that patients with Hashimoto's thyroiditis or treated Graves' disease, are most prone to develop iodine-induced hypothyroidism.

Clark states that it appears that slight increases in the serum TSH level increases the transport of iodide into the thyroid gland. The high levels of intracellular iodide inhibit organification and result in iodine-induced hypothyroidism because of a failure to recover from the Wolff-Chaikoff effect. Iodide also has inhibitory effects on thyroid growth. Iodide inhibits the mitogenic effects of insulin, IGF-1 and phorbol ester TPA. IGF-1 stimulates tyrosine kinase and protein kinase C, so that iodide's effect on growth appears to influence several signal transduction pathways in the thyroid.

4. "The Effect of Iodide on Serum Thyroid Hormone Levels in Normal Persons, in Hyperthyroid Patients, and in Hypothyroid Patients on Thyroxine Replacement" by Philippou et al, Clin Endocrin 36:573-578, 1992- see page 17 for details<sup>ref. 61</sup>.

#### Comment On Above 4 Articles:

The results of Paul<sup>ref. 67</sup> are at variance with those of Chow<sup>ref. 35</sup> who reported a suppressive effect of 500 ug/day iodide on thyroid function. However, this is not unexpected given the small sample size, and failure to control for multiple variables which may effect study outcome- such as patient age (elderly subjects may be more susceptible to the suppressive effects of iodide as manifested in the Chow study where it was in several elderly subjects that TSH became elevated) and iodine status prior to exposure to iodide supplementation.

High dietary iodine intake or ingestion of pharmacologic quantities of iodine may induce hypothyroidism. The hypothyroidism may be reversed with dietary iodine restriction or withdrawal of iodide supplementation. However, in some cases it is not, and this appears to be in patients with more severe destruction of the thyroid gland by autoimmune disease.

Philippou et al showed that pharmacologic doses of iodide do not affect the peripheral metabolism of thyroid hormones.

#### 5.C. Stimulatory Effects of Iodide $\geq 1$ mg/day On Thyroid Function in Normal Individuals:

1. "Iodine-Induced Hyperthyroidism in a Newborn" by Bryant et al, Pediatrics 95(3): 434 -435, 1995<sup>ref. 68</sup>

This is the first report of neonatal IIH. IIH was induced in this term infant by povidone-iodine (Betadine) mediastinal lavage following surgical correction of a patent ductus arteriosus and pulmonary stenosis. The infant received 28.8 g of iodine over 5 days. Serum T4 and FT4 became markedly elevated and TSH suppressed. The infant became clinically thyrotoxic: increased heart rate, mild hypertension and diarrhea. The hyperthyroidism resolved over 1 month after discontinuation of iodine treatment.

2. "Iodine-Induced Thyrotoxicosis: Analysis of 85 Consecutive Cases" by Leger et al, Europ J Clin Invest 14: 449-455, 1984<sup>ref. 69</sup>.

IIH was documented in 85 cases of which 80% (67 cases) occurred in normal thyroid glands. Amiodarone accounted for ~80% of the cases in normal thyroids (the remainder were due to iodide and iodoquinoline). Approximately 70% of the IIH cases (47 cases) occurring in normal thyroids, came from areas without endemic goiter.

The spontaneous cure in non-treated cases was observed within an average of 6 months. A phase of biologic hypothyroidism preceded the return to euthyroidism. Intrathyroid iodine content measured by X-ray fluorescence was high, then fell gradually.

Note: this study was conducted in France where iodine intake is relatively low: 50-100 ug/day.

#### 5.D. Stimulatory Effects of Iodide $\geq 1$ mg/day On Thyroid Function in Patients With Underlying Thyroid Disease:

1. "Effect of Potassium Iodide on Relapse Rate of Thyrotoxicosis Treated with Antithyroid Drugs" by Thalassinos and Fraser, Lancet 2:183-184, 1971<sup>ref. 70</sup>

40 patients with thyrotoxicosis were treated with antithyroid drugs and L-thyroxine (0.3 mg per day) with the addition of potassium iodide 10 mg/day for 2-4 weeks within 3 months of the end of

treatment. The relapse rate and timing of the relapse in this group was compared to another group of 28 patients who were treated in a similar fashion but without the iodide. The 5 year relapse rates were 63% in the iodide-repleted group and 75% in the group not given iodide, nor was the timing of the relapse different.

The authors speculate that the thyroid supplements might have supplied enough iodine to vitiate the development of the iodine deficiency that is believed to be necessary for remission to occur.

2. "Effects of Chronic Iodide Administration on Thyroid Status in Euthyroid Subjects Previously Treated with Antithyroid Drugs for Graves' Hyperthyroidism" by Roti et al, *JCEM* 76(4):928-32, 1993<sup>ref. 71</sup>.

10 euthyroid women with Graves' disease which had been successfully treated with antithyroid drugs were given 10 drops of SSKI (380 mg) daily for 90 days to determine the effect of chronic iodide administration on thyroid function. During SSKI administration, 2 patients developed subclinical hypothyroidism (elevated serum basal and TRH stimulated TSH but normal serum T3 and T4 levels). After SSKI withdrawal, the 10 women were reevaluated 60 and 120 days later. 2 women developed a blunted TSH response to TRH, but with normal serum T3 and T4; another 2 women developed overt hyperthyroidism requiring methimazole therapy.

The authors conclude with the following statement: "It is advisable, therefore, to avoid iodine-containing substances in euthyroid patients with a history of antithyroid drug therapy for Graves' disease, since it is not possible to predict which patient will develop iodine-induced hyper- or hypothyroidism.."

3. "Five Patients with Iodine-Induced Hyperthyroidism" by Rajatanavin et al, *Amer J Med* 77: 378-384, 1984<sup>ref. 26</sup>.

5 case reports of IIH in adults are presented. Underlying thyroid disease was present in 4 (nontoxic multinodular goiter and Graves' disease; note: the Graves' disease patient was clinically euthyroid but had an elevated T3, suggesting early thyrotoxicosis) and 1 patient had no underlying thyroid disease. The sources of iodine were Betadine, Iodo-Niacin, amiodarone and radiographic contrast dyes. The patient with no underlying thyroid disease was taking Iodo-Niacin twice daily for asthma (each tablet contains 135 mg KI and 25 mg niacinamide hydroiodide).

The hyperthyroidism is usually self-limited, abating after iodine withdrawal (note: abrupt withdrawal of iodine-containing drugs may result in more severe thyrotoxicosis due to the sudden release of excess stored hormone from the thyroid). A brief period of hypothyroidism may occur during recovery from IIH. In view of the risk of IIH in patients with underlying thyroid disease, the authors recommend that iodine-containing medications be prescribed with caution in such patients. If such drugs are given, thyroid function should be carefully monitored.

4. "Iodine-Induced Thyrotoxicosis in a Woman With a Multinodular Goiter taking Levothyroxine" Reith et al, *Arch Int Med* 145:355-356, 1985<sup>ref. 72</sup>

A 63 yr. old woman with multinodular goiter receiving levothyroxine sodium, developed iodine-induced thyrotoxicosis (IIH) after povidone-iodine was applied to the surface of a granulating hip wound. The patient manifested thyrotoxicosis both clinically and biochemically. IIH was controlled by eliminating the exogenous iodine and initiating therapy with PTU. This case illustrates that iodine-containing preparations given to patients with multinodular goiter may result in thyrotoxicosis even if thyrotropin is suppressed with exogenous thyroxine.

#### Comments on above 6 articles:

1. IIH may occur in normal individuals when pharmacologic doses of iodide are administered. This includes 1 case report in a newborn receiving Betadine mediastinal lavage.
2. Iodide supplementation to euthyroid Graves' patients treated with antithyroid drugs, or to patients with multinodular goiter, may induce thyrotoxicosis. Therefore, it is recommended that iodine-containing supplements be avoided.
3. Pharmacologic doses of iodide to patients with multinodular goiter, may induce IIH, even if the patient is on levothyroxine suppressive therapy.

6. Toxicology Study Pertaining to Iodine Toxicity:

"Iodide-Induced Hypothyroidism: A Potential Hazard During Perinatal Life" by Theodoropoulos et al, *Science* 205: 502-503, 1979<sup>ref. 18</sup>

The authors state that the effect of pharmacologic quantities of iodide during perinatal life has not been systematically studied. Because iodide readily crosses the placenta, iodide-induced hypothyroidism may occur in humans "...after long-term exposure to pharmacologic quantities of iodide.

"Since the effects of iodide during perinatal life cannot be studied in humans, iodide was administered to the pregnant and nursing rat, and the effects on fetal and neonatal rat thyroid function was evaluated." The daily iodide intake per rat was 1-2 mg.

#### Results:

The serum TSH levels in the term fetuses whose mothers were administered iodide was markedly increased compared to control fetuses whose mothers did not ingest iodide in their drinking water. Serum and intrathyroidal T3 and T4 levels were significantly decreased in iodide treated offspring of mothers administered iodide compared to controls. The iodide-induced hypothyroidism persisted for 10 days with return to normal thyroid function from age 18-60 days despite continued iodide administration. The data suggest that resistance to the inhibitory effect of iodide on thyroid hormone synthesis is developed at ~18 days of age. The authors conclude that the perinatal rat model can be used to study the mechanisms for iodide-induced hypothyroidism in human newborns whose mothers took iodide-containing medications during pregnancy.

#### 7. Telephone conferences with \_\_\_\_\_, \_\_\_\_\_ and \_\_\_\_\_

I have spoken with \_\_\_\_\_, consultant to Vintage, on several occasions, most recently on Monday, 2/14/2000, with regard to the Levolet package insert. He has consulted with Dr. \_\_\_\_\_ on this. In his safety assessment, he expressed concern regarding the use of the Vintage product in the elderly patient with multinodular goiter in whom an additional amount of iodine might precipitate thyrotoxicosis. He also stated that thyroid function, including antibody titers should be monitored in patients with goiter due to iodine deficiency. I mentioned to him my safety concerns were use of the product in the pregnant or nursing mother, those with autonomous thyroid tissue and when a patient would be receiving radioiodine for diagnostic or therapeutic purposes. He agreed with all my concerns. He will try to send a revised Levolet package insert to FDA in the next two weeks and will obtain input on this from \_\_\_\_\_, one of the subinvestigators for Levolet, and from \_\_\_\_\_

I have spoken to \_\_\_\_\_, consultant to Vintage, on several occasions regarding the safety of Levolet in the pediatric population, especially the fetus and newborn. My last conversation with him was on Monday, 2/7/2000. \_\_\_\_\_ opinion is that the amount of iodide contained in the Vintage tablet is unlikely to adversely effect the fetus, but may in a very small percentage of cases (maybe 1-2%). However, given the potentially serious clinical ramifications of hypothyroidism in the fetus, notably compromise of intellectual outcome, and the fact that ug doses of iodide have been demonstrated to be suppressive to the adult thyroid (we discussed the Chow and Pennington articles), he agreed with my proposed wording regarding use of this product in pregnant and nursing mothers: "There are insufficient data from the published literature to recommend safe use of this product in pregnancy". He also stated that the iodine in the Levolet tablet combined with iodine consumed through formula or breast feeding, will exceed the PSUL of iodine in the premature infant.

I spoke with \_\_\_\_\_ on several occasions (2/4/2000 and 2/7/2000) about the safety of Levolet. He had initially expressed concern that the iodine might induce thyrotoxicosis in patients with autonomous thyroid tissue, such as multinodular goiter (see Levolet \_\_\_\_\_ cover letter dated 2/8/99). Subsequently he stated his chief concern was with a potentially suppressive effect of the iodide on the fetal thyroid. He consulted Dr. \_\_\_\_\_ (a world expert on iodine toxicity in the fetus and newborn), presenting a hypothetical situation of maternal iodide ingestion of 600ug. Dr. \_\_\_\_\_ stated that no one knows how much of this iodide will enter the fetal thyroid gland. He suspects that there will be increased renal clearance of the iodide by the mother. He also stated that generally higher amounts of iodide are needed to pose a risk to the fetus or neonate. \_\_\_\_\_ agreed with my concerns pertaining to the concomitant use of Levolet and radioiodine- namely, that the iodine in Levolet could interfere with radioiodine uptake into the thyroid, and, therefore, it would be advisable not to use both in combination.

#### 8. Evaluation:

##### Overall Assessment:

The published literature pertaining to iodine toxicity, particularly with regard to ug doses, has been extensively reviewed for the purpose of evaluating the safety of the \_\_\_\_\_ug of potassium iodide contained in the Vintage levothyroxine drug product, Levolet. That review has demonstrated that the

upper safe limit of iodine intake is difficult to define as it is dependent on a multitude of factors including the individual's age, presence of underlying thyroid disease, iodine status, use of concomitant medications which may act as co-goitrogens with iodide, etc. In addition, the answer to this question regarding the safe upper limit of iodine intake, is hampered by the following:

- a. Only a few studies have been done to evaluate the safety of ug quantities of iodide
- b. Study sample sizes have been small
- c. Chronic exposure data is sparse, especially for iodine-sufficient areas, such as U.S.
- d. Study results in similar types of patients have been conflicting

The studies which have been done have demonstrated the following suppressive effects of ug doses of iodide:

- a. In normal individuals living in an iodine-sufficient area:
  - as little as 300ug iodide/day for 2 weeks, may decrease thyroidal iodine-131 uptake in 2 year old children (Saxena<sup>ref. 38</sup>). In adults, 500ug iodide supplementation per day for 14-28 days may induce subtle changes in thyroid function manifest as an increased response to TRH (Gardner<sup>ref. 34</sup>), and, also, in a small percentage of patients (2% in the Chow<sup>ref. 35</sup> study), a rise in serum TSH to abnormally high levels.
- b. Patients with underlying thyroid disease are more sensitive than normal individuals to the suppressive effects of iodide on the thyroid gland, especially if they reside in an iodine-deficient area. Therefore,
  - as little as 150ug iodide/day to patients with post-partum thyroiditis living in an iodine-deficient area, prolonged the hypothyroid phase (Kampe<sup>ref. 42</sup>). Administration of 250 ug iodide/day for a mean of 4 months to patients with euthyroid Hashimoto's disease residing in an iodine-deficient area, induced hypothyroidism in 18% compared to only 2% in the control group (Reinhardt<sup>ref. 39</sup>).

In addition, there is a case report of transient hypothyroidism in a newborn whose mother took prenatal vitamins containing 150ug iodide/day throughout pregnancy (La Franchi et al<sup>ref. 37</sup>). The true incidence of transient neonatal hypothyroidism due to exposure to iodine-containing preparations is not known. Furthermore, studies to identify the upper safe limit of iodine intake in newborns have not been conducted in the U.S.

Microgram quantities of iodide may also have a stimulatory effect on the thyroid in specific clinical conditions. 100-500 ug/day have been reported to induce hyperthyroidism in patients with autonomous thyroid tissue living in areas of iodine-deficiency (Livadas<sup>ref. 49</sup> and Ermans<sup>ref. 50</sup>). Furthermore, it has been suggested that there is an inverse relationship between iodine intake and relapse rates in euthyroid Graves' patients treated with antithyroid drugs (Alexander<sup>ref. 47</sup>, Solomon<sup>ref. 46</sup> and Wartofsky<sup>ref. 45</sup>). In addition, Azizi<sup>ref. 48</sup> demonstrated that Graves' disease is easier to control with antithyroid drugs (lower dose and more rapid remission) in patients residing in an area of iodine deficiency compared to one of iodine sufficiency. Furthermore, introduction of iodized salt (280 ug/tsp.) in the 1920's in certain areas in the U.S., was accompanied by a transient increased incidence of thyrotoxicosis<sup>refs. 25 and 44</sup>.

In summary, the review of the literature indicates that microgram quantities of iodine may have stimulatory or suppressive effects on the thyroid gland, even in an iodine-sufficient area such as the U.S. However, more and larger and well-controlled prospective studies assessing the safety of chronic exposure are needed to identify the safe upper limits of iodine intake in this country. Although, the iodine intake has fluctuated over time in the U.S., there is no data to correlate this fluctuation with changes in thyroid disease patterns<sup>refs. 14 and 32</sup>.

However, the Vintage tablet contains T4 in addition to iodine. The majority of patients using this product will be using it for thyroid hormone replacement. They are unlikely to be at risk from the extra iodide in the tablet, because the exogenous T4 will essentially render them athyrotic. In those patients with some residual thyroid function (i.e. patients in whom TSH is not completely suppressed by the exogenous T4), the partially suppressed TSH will reduce iodine uptake by the thyroid gland and,

therefore, help mitigate the adverse effects of iodine on the gland. In addition, both Philippou<sup>ref. 61</sup> and De Groot<sup>ref. 62</sup> demonstrated that iodide does not affect the peripheral metabolism of thyroid hormones.

Nevertheless, the amount of iodide in the Vintage tablet may pose safety concerns for specific subsets of individuals, namely:

- the fetus or nursing infant via maternal ingestion;
  - patients at risk for iodine-induced hyperthyroidism, particularly when autonomous thyroid tissue is present and, therefore, not subject to normal feedback control; and
  - patients who will receive radioiodine for diagnostic or therapeutic purposes
- Each of these "at risk" groups will be individually addressed.

### 1. The Fetus and Nursing Infant:

It is known that iodine freely crosses the placenta, but that transport of maternal T4 is limited. It is also known that iodides are readily concentrated in the mammary gland and secreted in milk. Once absorbed, the iodide is actively taken up by the fetal thyroid. It is known that the fetal thyroid can concentrate a greater amount of iodide per gram of thyroid tissue than the adult. In addition, the fetal thyroid gland is very sensitive to the inhibitory effects of iodine. This susceptibility is due to failure of the immature gland to suppress iodide trapping (i.e. escape from the acute Wolff-Chaikoff effect).

In animals, Theodoropoulos<sup>ref. 18</sup> demonstrated that 1-2 mg NaI administered daily to pregnant and nursing rats, induced transient hypothyroidism in the term fetus and neonatal rat.

In humans, although there is an extensive body of literature pertaining to the suppressive effects of iodine on the fetal thyroid, the true incidence of hypothyroidism in newborn infants exposed to excess iodine in utero from maternal ingestion, has not been accurately assessed<sup>ref. 17</sup>. The upper limit of iodine intake that will not inhibit thyroid function is not easy to define because it is conditioned by the level of iodine intake before exposure to iodine excess. The "no effect" threshold is attained sooner under conditions of iodine deficiency than sufficiency due to accelerated trapping of iodide within the iodine depleted gland. Studies in European countries with moderate iodine deficiency have revealed that, in Europe, the upper limit of iodine intake which predisposes to blockage of thyroid secretion in premature infants is ~200 ug daily<sup>ref. 4</sup>. Similar studies have not been conducted in the U.S. I found one report in the published literature of transient neonatal hypothyroidism in a term newborn whose mother took prenatal vitamins containing 150ug iodine throughout pregnancy<sup>ref. 37</sup>.

Unlike the adult, neonatal hypothyroidism may have adverse effects on intellectual outcome. In addition, iodine-induced goiter in the newborn may be associated with tracheal obstruction, asphyxiation and death.

I would recommend that the Levolet package insert contain the following statement in the Warnings section:

DRAFT

I would like to briefly discuss here the issue of administering iodide to the premature infant. The probably safe upper limit (PSUL) of iodine intake is 100ug/kg/day in the premature infant. In a 2 kg premature infant, the iodine in the Levolet tablet would be additive to the 50-100ug iodine the infant would be ingesting daily from breast milk or infant formula. Therefore, the PSUL iodine intake would be exceeded in a premature infant taking Levolet. However, this should not pose a safety concern as the product also contains levothyroxine (T4).

### 2. Patients at Risk for Iodide-Induced Hyperthyroidism (IIH):

IIH is more common in iodine-deficient countries where physiological amounts of iodine have been reported to induce this condition. In iodine-sufficient countries, such as the U.S., pharmacological amounts of iodine have generally been implicated<sup>ref. 23</sup>. However, temporary outbreaks of thyrotoxicosis have occurred in the U.S. following the introduction of iodized salt<sup>ref. 44 and 25</sup>. However, IIH appears to be rare in this country given the extensive use of iodine containing medications and

radiocontrast media with the 3.1% incidence of goiter and the few cases of ITH reported in the literature from the U.S.<sup>ref. 23</sup>. ITH is usually self-limited, rarely is it fatal. Elderly subjects with nodular goiter- usually multinodular- are at greatest risk, particularly if there is underlying heart disease. This is because thyrotoxicosis may aggravate pre-existing cardiac disease and lead to atrial fibrillation, CHF, worsening angina, thromboembolism, and, rarely, death. As a preventive measure, Dunn<sup>ref. 23</sup> recommends reducing iodine intake in vulnerable individuals, particularly older subjects with nodular goiters by decreasing or omitting intake of iodized salt, iodine-containing mineral preparations, or high iodine foods such as kelp.

Both Becker<sup>ref. 8</sup> and Rajatanavin<sup>ref. 26</sup> recommend caution when administering iodine-containing drugs to patients with goiter.

I would recommend that the Levolet package insert contain the following statement in the Precautions section:

[

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]

Euthyroid Graves' patients previously treated with antithyroid drugs are also at risk for ITH. Wartofsky<sup>ref. 45</sup> and Solomon<sup>ref. 46</sup> observed that there appears to be a reciprocal relationship between the relapse rate of Graves' disease treated with antithyroid drugs and dietary iodine intake. Azizi<sup>ref. 48</sup> pointed out that Graves' disease is easier to control with antithyroid drug therapy (lower dose needed and more rapid remission) in iodine-deficient areas. Alexander<sup>ref. 47</sup> showed that physiologic amounts of iodide (200ug KI daily) administered up to several months after withdrawal of antithyroid drugs, increases the relapse rate of Graves' disease. In addition, Thjodleifsson<sup>ref. 30</sup> reported that the prevalence of post-op hyperthyroidism for Graves' was 5x higher and hypothyroidism 5x lower in an area of high iodine intake compared to an area where the intakes are lower.

However, when T4 is combined with iodide and antithyroid drugs, the relapse rate and the timing of the relapse are comparable to that with iodide + antithyroid drugs, as demonstrated by Thalassinou<sup>ref. 70</sup>. The data suggest that the extra iodide in the exogenous thyroid hormone may have been sufficient to vitiate the development of iodine deficiency which is a necessary prerequisite to remission. It is also possible that the exogenous thyroxine prevents an increase in TSH and so hinders the development of iodine deficient goiter which, once withdrawn, could be a basis for excessive TSH production.

### 3. Patients scheduled to receive radioiodine diagnostically or therapeutically:

Saxena<sup>ref. 38</sup> demonstrated that 300 ug iodide daily for 2 weeks to 2 year old children decreased thyroidal radioiodine uptake. It is known that for all age groups, that as dietary iodine increases, thyroidal radioiodine uptake decreases<sup>refs. 13, 29, 45 and 73</sup>. Hence, the radioiodine dose administered will need to be increased<sup>ref. 29</sup>, resulting in greater total body exposure to radioactive iodine, to achieve a given diagnostic or therapeutic benefit.

I suggest the following statement be added to the Precautions section of the Levolet package insert:

[

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]

Additional comments pertaining to the Levolet package insert :

1. The Description section should clearly state the potassium iodide content of each tablet strength.
2. Indications and Usage section:
  - a. first paragraph, third line:  
after the word "pregnancy" add "(see WARNINGS)"
  - b. after the word "goiter" and "nodules" in the first paragraph, line 5 and in the second paragraphs, add "(see PRECAUTIONS)"
  - c. third paragraph, delete "
  - d. delete the fifth paragraph pertaining to the use of levothyroxine as a

3. Additional labeling comments will be forthcoming.

**9. Regulatory Action:**

Approvable

The above comments pertaining to the Levolet package insert should be forwarded to the sponsor. Vintage should also be informed that additional labeling comments will be forthcoming.

*ISI*  
Jean Temeck, M.D. *mb*

Reference List Is Appended

cc. NDA Arch 21,137

NDA Div File

~~HFD-102: Dr. Jenkins~~

HFD-510: ~~Dr. Orloff, Dr. Johnson and Mr. McCort~~

*ISI*  
*2-19-00*

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**APPEARS THIS WAY  
ON ORIGINAL**



Safety Update not needed at this time.

APPEARS THIS WAY  
ON ORIGINAL

Statistical review not needed. No clinical studies submitted for this application.

APPEARS THIS WAY  
ON ORIGINAL

08-FEB-2002

NDA: 21,137

Drug: Levolet (Levothyroxine sodium tablets)

Sponsor: Vintage

Date submitted: December 17, 2001

Date reviewed: February 7, 2002

**ADDENDUM TO MEDICAL OFFICER'S REVIEW**

Per the financial disclosure information submitted by the sponsor, they have not entered into any financial arrangements with the clinical investigators of the bioavailability studies.

/s/

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Jean Temeck, M.D.

**APPEARS THIS WAY  
ON ORIGINAL**

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/s/

Jean Temeck  
2/7/02 10:54:35 AM  
MEDICAL OFFICER

Mary Parks  
2/8/02 04:05:58 PM  
MEDICAL OFFICER

**APPEARS THIS WAY  
ON ORIGINAL**

**MEDICAL TEAM LEADER MEMO ON NDA 21-137**

**Product:** Levolet (levothyroxine sodium) tablets

**Sponsor:** Vintage Pharmaceuticals, Inc.

**Date of Submission:** received December 18, 2001 in response to NA letter issued on March 23, 2001

**Background**

The NDA for this levothyroxine-containing drug product was originally submitted on April 30<sup>th</sup>, 1999 in response to the Federal Register notice of August 14, 1997 announcing FDA's position that such products are new drugs and must be marketed under approved NDAs. Review of that submission revealed deficiencies in chemistry, manufacturing, and control, biopharmaceutics, and labeling which resulted in the issuance of an approvable letter on March 10<sup>th</sup>, 2000 by the FDA.

A response to this March 10<sup>th</sup>, 2000 AE letter was submitted on September 25<sup>th</sup>, 2000. Review of this submission, again, revealed deficiencies resulting in a non-approval letter issued on March 23<sup>rd</sup>, 2001. The deficiencies cited in this letter included:

**CMC**

- an unsatisfactory inspection of the manufacturing facilities

**BPH**

- an inappropriate dissolution method that had no discriminatory power to detect differences (or similarities) among different strengths or different lots of the same strength

**Administrative/Regulatory**

- financial disclosure information was required for the *in vivo* bioavailability studies

In addition, this NA letter stated that "Changes in labeling will be addressed after all outstanding issues have been resolved".

**Summary of Data Reviewed for this Submission**

This memo addresses data submitted to NDA 21-137 on December 17<sup>th</sup>, 2001 in response to the aforementioned deficiencies of the March 23<sup>rd</sup>, 2001 NA letter. Drs. David Lewis and Stephen Johnson have reviewed the CMC and BPH sections, respectively, and have found the sponsor's response to these sections adequate for approval. Please see their reviews included in this action package for details and their final recommendations. Financial disclosure information was also provided and found to be satisfactory by Dr. Jean Temeck.

Levolet is unique from other approved levothyroxine sodium products in that it contains potassium iodide (KI). With the original submission, the Agency had raised clinical safety concerns regarding KI exposure in fetus and nursing infants of mothers prescribed Levolet. Such exposures may result in fetal hypothyroidism and severe developmental defects, especially in women who have increased dietary intake of iodides during pregnancy. These safety concerns have been summarized in detail in Drs. Temeck's and Orloff's reviews of the original NDA submission and the original recommendation for pregnancy category labeling was "D". This was conveyed to the sponsor in the March 10<sup>th</sup>, 2000 AE letter.

With this submission, Dr. Karen Davis-Bruno, pharmacology/toxicology team leader, has concluded that the pregnancy category labeling should be "X" based on published literature wherein fetal malformations have been demonstrated in pregnant rats exposed to KI  $\geq 25$  mg/kg/day (150 mg/m<sup>2</sup>) and fetal/neonatal mortality has been observed at doses of 100 mg/kg/day (600 mg/m<sup>2</sup>). These doses correspond to 750x and 3000x the KI exposure associated with Levolet based on body surface area calculations.

This medical reviewer concurs with Dr. Davis-Bruno's recommendation based on 21 CFR 201.57 (d) and (e) which requires that this product be labeled as Pregnancy Category X since there are studies in animals demonstrating fetal abnormalities and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit as other LT4 products are available which do not contain KI that would pose a similar threat to fetuses and neonates. Pregnancy category X is recommended for those products which have positive evidence of human fetal risk based on adverse reaction data derived from investigational or marketing experience; however, the potential benefits from use of the drug during pregnancy may be acceptable despite its potential risk because the condition is life-threatening and there are no safer alternative therapies. This is clearly not the case with Levolet as the FDA has since approved three other LT4 products which do not contain KI.

A template label incorporating special consideration for the presence of KI in Levolet and recommended Pregnancy Category Labeling X was sent to the sponsor on April 18<sup>th</sup>, 2002. The sponsor responded on May 10<sup>th</sup>, 2002 with a labeling amendment that did not include a package insert as they did not agree with the warnings specific to KI presence in their product.

#### Recommendations

This application is approvable as there is no satisfactory package insert submitted to NDA 21-137 which adequately conveys the risk of Levolet use in pregnant and nursing women.

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Mary H. Parks, MD  
Deputy Director  
Medical Team Leader  
HFD-510

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**This is a representation of an electronic record that was signed electronically and  
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/s/

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Mary Parks  
6/12/02 09:04:36 AM  
MEDICAL OFFICER

David Orloff  
6/12/02 06:02:19 PM  
MEDICAL OFFICER

—Concur. Application is approvable pending agreement on final labeling  
related to iodine content.

**APPEARS THIS WAY  
ON ORIGINAL**