

# Orthiodosupplementation: Iodine sufficiency of the whole human body

Guy. E. Abraham M.D.<sup>1</sup>, Jorge D. Flechas M.D.<sup>2</sup> and John C. Hakala R.Ph.<sup>3</sup>

## I. Introduction

The essential trace element iodine (I) is the only one required for and in the synthesis of hormones. These I-containing hormones are involved in embryogenesis, differentiation, cognitive development, growth, metabolism, and maintenance of body temperature. I is highly concentrated in one organ, the thyroid gland, which becomes visibly enlarged when there is a deficiency of that element. It is the most deficient trace element in the world with an acknowledged third of mankind functioning below optimal level due to its deficiency<sup>(1)</sup>. Low intake of I is the world's leading cause of intellectual deficiency<sup>(2)</sup>. Yet, as unbelievable as it may sound, this essential element has suffered from total neglect regarding the amount of it required by the human body for optimal health. In 1930, Thompson et al wrote<sup>(3)</sup>: "The normal daily requirement of the body for iodine has never been determined." This statement is still true today, more than 70 years later.

At the Children's Summit held in 1990, the United Nations and heads of state assembled for that occasion, pledged to eliminate I deficiency by the year 2000. Commenting on this meeting, John T. Dunn stated in 1993<sup>(4)</sup> "The goal is technically feasible, but many obstacles must be overcome before it is realized." In the list of obstacles, no mention was made of the greatest obstacle of them all: Our total ignorance regarding sufficiency of the whole human body for I. It is obvious that I deficiency has been equated with the simple goiter, cretinism, and I-deficiency disorders related to its role in thyroidal physiology. Supplementation was considered adequate if such amount prevented cretinism, simple goiter and symptoms of hypothyroidism<sup>(1,2,4)</sup>. The assumption that the only role of I as an essential element is in its essentiality for the synthesis of T<sub>3</sub> and T<sub>4</sub>, became a dogma. With the advent of sensitive assays, Thyroid Stimulating Hormones (TSH) was promoted to queen of tests for thyroid functions<sup>(5)</sup> and I was forgotten altogether as irrelevant to the point where most endocrinologists and other medical practitioners do not request a single test for urine I concentration, during their whole medical career.

## II. Iodophobia and misinformation about I

It is ubiquitous: the fear of using or recommending I (Iodophobia) and misinformation about I are found in books written by laypersons; in books written by physicians for laypersons; and in articles and books written by physicians for physicians. We will use as examples one book written by a famous endocrinologist for laypersons and a textbook of endocrinology written by physicians for physicians, both books recently published.

First, we will quote excerpts from a book published in 1999 and written by Doctor R. Arem M.D. for consumers, with the title: "The thyroid solution: A revolutionary Mind-Body Program that will help you". As editor of an educational periodical on thyroid disorders, which is read by 25,000 physicians nationwide, Dr. Arem's views influence a large segment of practicing endocrinologists. Anyone awake will realize that eastern mysticism and New Age occultism have penetrated deeply, although insidiously, into the practice of medicine. On pages 309, 310 of his book, Dr. Arem recommends guided imagery, meditation, yoga and tai chi, without a single reference to validate the effectiveness and lack of adverse effects of those practices. "I encourage men and women to perform tai chi, yoga..." In a section with the title "Iodine: A Double Edge Sword", the author stated on page 305: "Research has clearly established that the high dietary iodine content in some areas of the world has resulted in a rise in the prevalence of thyroiditis and thyroid cancer." One reference is given<sup>(7)</sup>, and when that reference is reviewed, there is no high dietary I intake involved. Essentially, that study evaluated the incidence of thyroiditis and thyroid cancer in areas of Argentina with severe I deficiency, before and after iodization of salt was made available. Urine I was  $9.3 \pm 1.7$  ug/gm creatinine before iodization and  $110 \pm 82$

ug/gm creatinine after iodization. Keep in mind that the RDA for I is 150 ug/day. The incidence of the more invasive form of thyroid cancer did not change, but the incidence of papillary carcinoma was: 0.78/100,000/year before and 0.84/100,000/year after iodization of salt. Obviously, the data available in this publication do not agree with Doctor Arem's conclusion about the association between high dietary I intake and thyroid cancer. In fact, the available information on this subject, to be discussed later, points to chronic I deficiency as a predisposing factor for thyroid cancer.

The iodophobic misinformation continues with anecdotal stories from Doctor Arem's archives: A female patient ingested 2-3 gm of kelp daily and developed Grave's disease which necessitated "destruction of the thyroid gland". How strange! The mainland Japanese consumed a daily average of 4.6 gm of seaweed and they are one of the healthiest people on earth <sup>(10,11,12,22,23)</sup>. Another iodophobic story follows: NASA consulted Doctor Arem because their ground personnel became "low grade" hypothyroid, whatever that means. Sherlock Arem discovered the cause. The ground personnel were drinking water with 4 gm iodine per liter. That is interesting because the maximum amount of iodine that can be dissolved in water at room temperature is 3 gm per liter. Doctor Arem saved the day at NASA: "Alarmed by my warnings about the potential consequences...". What is the expert's advice? "I advise not consuming more than 500 to 600 micrograms a day". With such iodophobia and misinformation coming from the top, no wonder there is a trend of decreasing I consumption nationwide in the USA.

As we will now demonstrate, this kind of misinformation may have serious consequences. On page 232, Doctor Arem wrote regarding the evaluation of simple goiter: "To determine the cause of your goiter, your physician may order one or several of the following tests". In that list, no mention was made of urine I levels, when in fact, the most common cause of simple goiter worldwide is I deficiency. However, he may have given the reason for not considering urine I levels in the evaluation of simple goiter, toward the end of the book on page 305: "To function normally, the thyroid requires 150 micrograms a day... In the United States, iodine consumption ranges between 300 and 700 micrograms a day." This statement has no reference and is inaccurate. The last comprehensive nutritional survey <sup>(2)</sup> (NHANES III 1988-1994) revealed that the median urine I concentration was 145 ug/L and 15% of the U.S. adult female population suffered from I deficiency (urine I less than 50 ug/L). That is 1 out of every 7 female patients walking in a doctor's office, interestingly, the same risk ratio for breast cancer in our population, that is 1 in 8 <sup>(63)</sup>. With this high prevalence of I deficiency, including urine I levels in the initial screening of simple goiter is justified. Without the information on urine I levels, the physician will most likely prescribe thyroid hormones to the I-deficient patient.

Hintze et al <sup>(8)</sup> compared the response of patients with simple goiter to administration of I at 400 ug/day and to the administration of T<sub>4</sub> at 150 ug/day for a period of 8 months and 4 months after cessation of therapy. The results definitely favor I over T<sub>4</sub>. There was a similar suppression of the size of the thyroid gland with I, and with T<sub>4</sub>. This suppression persisted 4 months after discontinuation of I; whereas the mean thyroid volume in the group receiving T<sub>4</sub>, returned to pre-T<sub>4</sub> level 4 months after stopping T<sub>4</sub> administration. The authors concluded: "Our data clearly shows that iodine alone... is at least equally as effective for goiter reduction as levothyroxine alone and offers the further benefit of a sustained effect after cessation of therapy".

Of greater concern, however, is the possibility that I-deficient women are more prone to breast cancer and depriving them of I is not in their best interest. Based on an extensive review of breast cancer epidemiological studies, R.A. Wiseman <sup>(9)</sup> came to the following conclusions: 92-96% of breast cancer cases are sporadic; There is a single cause for the majority of cases; The causative agent is deficiency of a micronutrient that is depleted by a high fat diet; If such an agent is detected, intervention studies with supplementation should lead to a decline in the incidence of breast cancer. It is the opinion of several investigators that this protective micronutrient is the essential element I <sup>(14,16,19,20,54)</sup>. Demographic surveys of Japan and Iceland revealed that both countries have a relatively high intake of I, and low incidences of simple endemic goiter and breast cancer, whereas in Mexico and Thailand, just the reverse is observed: a high incidence of both endemic goiter and breast cancer <sup>(10)</sup>. Thomas et al <sup>(11,12)</sup> has demonstrated a significant and inverse correlation between I intake and

the incidence of breast, endometrial and ovarian cancer in various geographical areas. Thyroid volume measured by ultrasonometry and expressed as ml is significantly larger in Irish women with breast cancer than controls with mean values of  $12.9 \pm 1.2$  in controls and  $20.4 \pm 1.0$  in women with breast cancer<sup>(13)</sup>. Intervention studies in female rats by Eskin<sup>(14-16)</sup> are very suggestive of a facilitating role of I deficiency on the carcinogenic effect of estrogens, and a protective role of I by maintaining normality of breast tissues.

The administration of thyroid hormones to I-deficient women may increase further their risk for breast cancer. In a group of women undergoing mammography for screening purposes<sup>(17)</sup> the incidence of breast cancer was twice as high in women receiving thyroid medications for hypothyroidism (most likely induced by I deficiency) than women not on thyroid supplement. The mean incidences were 6.2% in controls and 12.1% in women on thyroid hormones. The incidence of breast cancer was twice as high in women on thyroid hormones for more than 15 years (19.5%) compared to those on thyroid hormones for 5 years (10%).

Backwinkel and Jackson<sup>(18)</sup> have presented as evidence against the association between I deficiency and breast cancer, the fact that in the state of Michigan, between 1924 and 1951, the prevalence of goiter decreased markedly from 38.6% to 1.4%, but no detectable change was observed in the prevalence of breast cancer, during that same interval of time. These authors are making the assumption that the amount of I required to control goiter is the same as that required for protection against breast cancer. Ghent et al<sup>(19)</sup> and Eskin<sup>(20)</sup> have estimated, based on their studies, that in both women and female rats, the amount of I required for protection against breast cancer and fibrocystic disease of the breast (FDB), is at least 20 to 40 times the amount required for control of goiter.

Medical textbooks written for physicians contain the same iodophobia and misinformation about I. When I is incorporated into a drug, that drug gets all the credit for the good effects and I is blamed for the side effects. Although there are several I-containing drugs used by physicians for various medical condition<sup>(21)</sup>, we will just cover one of these drugs, from information supplied by Roti and Vagenakis in the latest review on I excess<sup>(21)</sup>. Amiodarone is a benzofuranic derivative containing 75 mg I per 200 mg tablet. It is widely used for the long term treatment of cardiac arrhythmia. It is long acting with 100 days half-life and releases 9 mg I daily in patients ingesting the recommended amount. In the United States, Amiodarone induces hypothyroidism in 20% of patients ingesting it. The authors of that review blamed I for the hypothyroidism although no study has been performed with daily administration of 9 mg of inorganic I in a similar group of patients. It would not be surprising if inorganic I alone in equivalent amount resulted in the same beneficial effects without the side effects, amount them, destructive thyroiditis which require large doses of glucocorticoids and in some cases, thyroidectomy. Actually, there is a large population consuming close to 100 times the RDA almost daily, the Japanese living in Japan. According to the Japanese Ministry of Health, the average daily consumption of seaweed by mainland Japanese is 4.6 gm<sup>(22)</sup>. At an average of 0.3% I in seaweed (range 0.08-0.45%)<sup>(22)</sup>, that would compute to an average daily intake of 13.8 mg I. Overall, the Japanese living in Japan are among the healthiest people in the world, based on cancer statistics<sup>(23)</sup>. They have one of the lowest incidence of I-deficiency goiter and hypothyroidism<sup>(10)</sup>.

In the same review on I excess<sup>(21)</sup>, published in a textbook read by most endocrinologists, and therefore influencing the national trend in the management of thyroid disorders, there is a subsection with the title "Iodine as a Pathogen". This is an essential trace element that is given the attribute of a Pathogen. Commenting on the latest nutritional survey (NHANES III), the authors stated that this trend of decreasing I intake has resulted in a lower percentage of the U.S. population consuming excess I, defining excess I intake as urine I levels above 500 ug/L (0.5 mg/L): "This trend in iodine consumption has also resulted in a decline in the percentage of the population with excessive iodine intake (>500 ug/L) from 27.8% in the 1971 to 1974 survey to 5.3% in the 1988 to 1994 survey". With this iodophobic mentality, a cut off point of 0.5 mg I/L of urine has been arbitrarily chosen for excess I intake. What is considered excess I by these authors represents 3% of the average daily I intake by mainland Japanese, a population with a very low incidence of cancer of the female reproduction organs<sup>(11,12)</sup>. This attitude toward I may play an important role in the high incidence of cancer of the female

reproductive organs in our population. It would be of interest to compare the prevalence of breast cancer with urine I levels from data available in the last two National Nutritional Surveys.

Currently, the average daily intake of I by the U.S. population is 100 times less than the amount consumed by the mainland Japanese. In the 1960's, I-containing dough conditioners increase the average daily I intake more than 4 times the RDA<sup>(24)</sup>. One slice of bread contained the full RDA of 150 ug. The risk for breast cancer in our population was then 1 in 20<sup>(63)</sup>. Over the last 2 decades, food processors started using bromine, a goitrogen<sup>(25)</sup> instead of I in the bread making process. The risk for breast cancer now is 1 in 8, and it is increasing at 1% per year<sup>(63)</sup>. The rationale for replacing I with a goitrogen in a population already I deficient, is not clear, but definitely not logical and against common sense. In rats on a diet with the rat RDA for I (3 ug), adding thiocyanate, a goitrogen, at 25 mg/day caused hypothyroidism<sup>(26)</sup>. Increasing I intake to 80 times rat RDA prevented this effect. In humans, that would be the equivalent of 12 mg I/day. It is likely that a large percentage of patients receiving T<sub>4</sub> for hypothyroidism are I deficient. This I deficiency is worsened by the goitrogens they are exposed to. Prescribing T<sub>4</sub> to them increases further their risk for breast cancer<sup>(17)</sup>. What these patients really need is a supply of I large enough for I sufficiency and to neutralize the effect of most of these goitrogens. Based on the studies of Lakshmy et al<sup>(26)</sup> in rats, that amount of I would correspond to the level of I consumed by mainland Japanese.

For those who trust the food processors to meet their nutritional needs, the last significant source of I is table salt, which contains 74 ug I per gm of NaCl. An editorial in the February 2002 issue of the Journal of Clinical Endocrinology and metabolism<sup>(27)</sup> exhorted the USA and Canada to decrease the amount of I in table salt by one half. "Most other countries use 20-40 PPM as iodine, and the United States and Canada should consider lowering the level of fortification to this range." This recommended low level of I fortification between 20-40 PPM had no significant effect on urine I levels and size of goiters in published studies from Germany and Hungary<sup>(28,29)</sup>. Essentially, this amount of I was designed to give a false sense of I sufficiency but to really be ineffective. It is ironic that the title of this editorial is: "Guarding our Nation's Thyroid Health". With guardians like that, who needs enemies?

Considering that low I intake is associated with intellectual deficiency, if we continue to lower the supply of I from our food sources, if we continue to disseminate misinformation about I and if we promote iodophobia in Christian America, we will end up with a nation of zombies worshipping Satan as Queen of Heaven.

### **III. Requirement of the thyroid gland for I**

After reviewing the available information in published studies designed to assess the effect of various amounts of I on thyroid physiology, it was possible to arrive at a tentative range of intake that would result in sufficiency of the thyroid gland for that element.

With the availability of radioactive isotopes of I and improved understanding of I metabolism, it became obvious that the thyroid gland concentrates this trace element more than 2 orders of magnitude, compared to most other organs and tissues. The percent of radioiodide uptake by the thyroid gland correlated inversely with the amount of I ingested<sup>(30)</sup>. In areas of severe endemic goiter, it was above 80%<sup>(31)</sup>. The % uptake decreases progressively with increased intake of I, and at RDA levels (150 ug), the % uptake was maintained between 20 and 30%<sup>(24)</sup>. In the 1960's I added to bread increased the average daily intake 4-5 times RDA levels, with a concomitant decrease in % uptake below 20%<sup>(24,32)</sup>. During the "Cold War" years, the threat of nuclear attack and radioactive fallout became a topic of national interest<sup>(33)</sup>. Attempts were made to estimate the amount of I required to suppress maximally radioiodide uptake by the thyroid<sup>(34,37)</sup>. It is of interest to note that these studies were not performed to assess requirement of the human body for I, but as a crisis management in case of fallout of radioisotopes of I during a nuclear attack or accident. However, we will use these data to assist us in pinpointing the optimal requirement of the human body for I.

**Table I**

Percent uptake of radioiodide by the thyroid gland and amount of iodide retained by the thyroid gland in response to increasing intake of stable iodide (all values below are means)

Intake mg I/day	Thyroidal Radioiodide Uptake (percent)	Amount of iodide retained by the thyroid gland (ug/day)	References
0.02	84.7		Karmarkar et al Am. J. Clin. Nut 27:96-103, 1974
0.03	68.7		"
0.76	42.4		"
0.11	28.6	31.8	Pittman et al N. Engl. J. Med 280:1431-1434, 1969
0.68	15.4	105	"
3.0	5.0	150	Saxena et al Science 138:430-431, 1962
10.0	4.0	400	Sternthal et al N. Engl. J. Med 303:1083-1088, 1980
15	1.9	285	"
30	1.6	480	"
50	1.2	600	"
100	0.6	600	"
14	3.5	490	Hamilton, J.G. and Soley, M.H. Am. J. Physical 131:135-143, 1940

The ranges of % radioiodide uptake by the thyroid gland from some selected publications are displayed in Table I. The goal of this selection was to cover a wide range of I intake, from severe goiter to intake of excess I. From the publications by Karmarker et al<sup>(31)</sup> 3 areas were selected, representing severe, (<25 ug I/day) moderate (25-50 ug/day) and mild (51-100 ug/day) I deficiency. Moving up into the RDA range, the 2 studies of Pittman et al, in 2 groups of normal subjects before and after I was added to bread at a level of 150 ug I/slice of bread<sup>(24)</sup>. The mean I intake in the 2 groups were 2/3 and 4-5 times RDA levels. Going up in the scale of I intake, Saxena et al<sup>(34)</sup> were the first to attempt a systematic study of the effect of increasing I intake on the % uptake of radioiodide by the thyroid gland in order to find the minimum oral dose of I for maximum suppression of radioactive I uptake by the thyroid gland. These researchers used 63 euthyroid children as subjects and they express the amount of I ingested as mg I/m<sup>2</sup>/day. The range of I intake covered was from 0.1 to 2.5 mg/m<sup>2</sup>/day, which would correspond to a range of 0.2 to 5 mg I in the adult. At 0.1 mg, the percent uptake varied from 20 to 30%. On a semilogarithmic graph, there was a linear relationship between the log of I intake and % thyroid uptake of radioiodide. This linearity persisted up to 1.5 mg/m<sup>2</sup>/day where the % uptake seems to reach a plateau at 5% uptake with oral doses of I up to 2.5 mg/m<sup>2</sup>/day. Because of the apparent leveled off at 5% thyroidal uptake at 1.5 mg/m<sup>2</sup>/day (equivalent to 3 mg I in adults), Saxena et al concluded that this percentage represented maximum suppression of radioiodide uptake by the thyroid gland. Six years later, Cuddihy<sup>(35)</sup> observed a 4% radioiodide uptake when 10 mg I was ingested. Hamilton and Soley<sup>(36)</sup> in 1940, were able to achieve a mean % uptake of 3.5% when 14 mg I was mixed with the radioactive tracer. In 1980, Sternthal et al<sup>(37)</sup> used amounts of I from 10 mg to 100 mg/day. At 10 mg, they confirm the 4% uptake observed by Cuddihy, and they were able to achieve near maximum suppression (0.6% radioiodide uptake by the thyroid gland) with a daily I intake of 100 mg.

If these data are plotted on a semilogarithm graph, with % radioiodine uptake on the y-axis and the logarithm of

the amount of I ingested on the x-axis, 4 slopes and ranges are observed (Fig. 1). By extending the first 2 slopes A and B to the point where their extensions cross the x-axis at zero % uptake, we can estimate the amount of I required for sufficiency of these 2 “pools” of I. Slope A cross the x-axis at 0.27 mg and slope B, at 6 mg I. The range of intake covering slope A could be called the RDA range, or the goiter control range, since no more uptake of radioactive I was required at .27 mg which is the upper limit (0.3 mg) of the RDA for control of goiter under all physiological conditions <sup>(1)</sup>.

Slope A is very steep, and therefore represents a range of I intake where the I-trapping mechanism of the thyroid gland is very inefficient. Within the linear portion of that range, that is, with intake of I less than 100 ug/day, extrathyroidal tissues would be able to compete effectively with the thyroid for available I. To be discussed latter, the mammary glands possess an I-trapping system similar to that of the thyroid and have certain requirements for I to maintain normality. The larger breast of women would retain more I than men, and there would be less I available for the I-trapping of the thyroid gland. This would result in a greater incidence and prevalence of thyroid dysfunction's in women than in men, mainly in areas of marginal I intake. Indeed, the prevalence of goiter in endemic areas is 6 times higher in pubertal girls than pubertal boys <sup>(38)</sup>. Subclinical and overt hypo- and hyperthyroidism are more common in women than in men <sup>(39,40)</sup>. The physiological approach in these cases would be to treat them with I supplementation in optimal amounts, not thyroid hormones and anti thyroid drugs.

In the July 2002 issue of Bottom Line Health magazine, there is an article by Dr. R.L. Shames, M.D. entitled “Thyroid Disease Could Be the Cause Of Your Symptoms”. This article is saturated with misinformation: “The thyroid needs iodine to function, but deficiencies of this mineral are largely a thing of the past because of our high consumption of iodized salt. Especially if you live near a coast, you may be getting too much iodine, which is harmful to the thyroid”. Misinformation #1: I deficiency is a thing of the past. Fact #1: The last National Nutritional Survey (NHANES III 1988-1994) revealed that 15% of the U.S. adult female population suffered from I deficiency, defined as urine I level below 50 ug/L <sup>(2)</sup>, which is a very low level by any standard. Misinformation #2: “High consumption of iodized salt prevents I deficiency”. Fact #2: Iodized salt contains 74 ug I/gm salt. The purpose of iodization of salt was to prevent goiter and cretinism, not for optimal level of I required by the human body. For example, to ingest the amount of I needed to control FDB, that is 5 mg I/day <sup>(19)</sup>, you need to consume 68 gm of salt. To reach levels of I ingested by mainland Japanese, a population with a very low prevalence of cancer of the female reproductive organs, you need 168 gm of salt. Misinformation #3: You may be getting too much I if you live near a coast. Fact #3: Kung et al (Clin. Endo 53:725-731, 2000), after investigating I deficiency in Hong Kong, concluded: “Our experience in Hong Kong has shown that it is not safe to assume that iodine insufficiency does not exist in coastal regions”. Misinformation #4: Too much I from coastal areas is harmful to the thyroid. Fact #4: From the study just mentioned, coastal areas do not even supply enough I to prevent I deficiency. The article by Dr. Shames even has a subsection teaching his readers how to reduce I intake! Considering that 15% of his female readers are already I deficient, even by the low RDA standard, what a shame!

Returning now to Fig. 1, slope B corresponds to I sufficiency of the thyroid gland, and represents a range where the efficiency of the I-trapping mechanism by the thyroid is markedly improved over slope A which is steeper, and therefore less efficient. Slope B starts at 0.1 mg, the upper limit for mild deficiency and extends to 6 mg, theoretically, the optimal I intake for sufficiency of the thyroid gland. Slope C is almost horizontal, representing a range of I between 3 mg and 14 mg. The thyroid gland possesses maximal efficiency of the I-trapping mechanism over the range of I intake in slope C. Slope D from 15 mg to 100 mg of iodide could be called the saturation range. In order to refine further the optimal range of I intake, Fig. 2 displays the range of I intake from 0.1 to 100 mg.

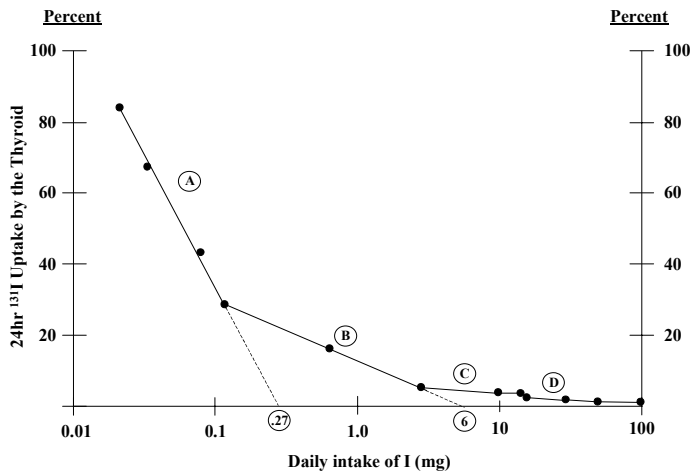


Fig. 1 - Percent 24hr uptake of radioiodide by the thyroid gland with increasing intake of I.

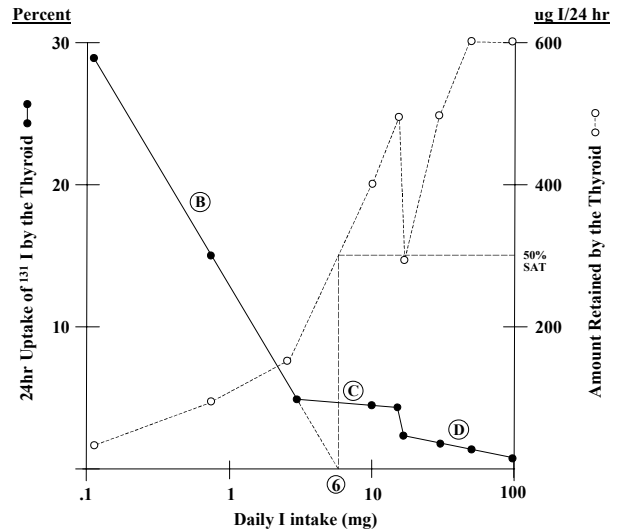


Fig. 2 - Percent 24hr uptake of radioiodide and computed uptake of I/24hr by the thyroid gland, following intake of increasing amount of I.

The amount of I retained by the thyroid gland was also plotted for each intake levels. The amount retained was computed by multiplying the amount of I ingested by the % uptake of radioiodine by the thyroid gland. The 6 mg point is of interest because not only it is the crossing point of slope B at zero radioiodide uptake on the x-axis, but it represents also the 50% saturation point of the I trapping system of the thyroid gland. A system in a state of dynamic equilibrium would be the most stable at midpoint between the 2 extremes, that is at 50% saturation. The RDA for I corresponds to 5% saturation of the I-trapping mechanism of the thyroid gland, a very unstable position, predisposing to both hypo- and hyperthyroidism. The intake of 14 mg was the maximum amount that did not trigger the autoregulatory mechanism of the thyroid gland. This amount may represent the upper limit of I required for sufficiency of the whole human body. At 15 mg intake, the thyroid gland downregulates the efficiency of the I trapping in an attempt to bring down the amount of I retained to 50% saturation (Fig. 2). Above 15 mg intake, the efficiency of the trapping mechanism increases markedly with greater intake of I to reach saturation at 50 mg intake and 0.6 mg/24 hr of trapped I by the thyroid gland (Fig. 2).

Searching the literature, we found evidence supporting the amount observed in our calculation regarding the saturation of the I trapping by the normal thyroid, that is 0.6 mg/day. For example, Wagner et al<sup>(41)</sup> observed in an euthyroid subject who received increasing amount of iodide that the maximum trapping of I by the thyroid was 50 ug/2 hrs. This value multiplied by 12 = 600 ug/24 hr. Fisher et al<sup>(42)</sup> observed in 20 normal subjects receiving different amounts of I, that the computed I accumulation/day by the thyroid gland was highest in 2 subjects with values of 608 and 613 ug/24 hr.

Regarding the optimal I intake of 6 mg/day for sufficiency of the thyroid gland, there are some very interesting observations reported by various investigators, with 6 mg mentioned in connection with various physiological parameters of thyroid function. With optimal intake of I, thyroid functions would be the most stable under adverse conditions, maintaining homeostatis when pathological conditions tend to destabilize homeostatis in both directions, toward hypo- and hyperactivity of the thyroid gland. Therefore, the optimal intake of I for thyroid sufficiency should have the greatest effect in restoring normal functions under both conditions. The amount 6 mg/day happens to be the daily intake of I that gave the maximum reduction in basal metabolism toward the normal range in most cases of Grave's disease (hyperthyroidism)<sup>(3)</sup>.

First, let us describe the form of I used in these studies. The Lugol solution contains 5% iodine and 10% potassium iodide<sup>(43)</sup>. It has been available since 1829 when it was introduced by french physician Jean Lugol, and was used extensively in medical practice during the early part of the 20<sup>th</sup> century. The recommended intake

for I supplementation at that time was 2 drops/day corresponding to 12.5 mg I. This recommendation was still mentioned in the 19<sup>th</sup> Edition of Remington's Science and Practice of Pharmacy, published in 1995<sup>(43)</sup>. As quoted by Ghent et al<sup>(19)</sup>, in 1928 an autopsy series reported a 3% incidence of FDB, whereas in a 1973 autopsy report, the incidence of FDB increased markedly to 89%. Is it possible that the very low 3% incidence of FDB reported in the pre-RDA early 1900's was due to the widespread use of the Lugol solution available then from local apothecaries; and the recently reported 89% incidence of FDB is due to a trend of decreasing I consumption<sup>(2)</sup> with such decreased levels still within RDA limits for I, therefore giving a false sense of I sufficiency?

The American physician H.S. Plummer was the first in 1923 to use Lugol solution pre- and post- operatively in his management of Grave's disease<sup>(44)</sup>. He postulated that the hyperthyroidism of Grave's disease was due to I deficiency and that the high mortality rate associated with the post-operative recovery period could be controlled with I administration pre- and post-operatively. By administering 20-30 drops of Lugol pre-operatively and 10 drops post-operatively, he reported zero mortality rate. His procedure became widely used both in the USA and abroad. In 1930, a systematic study was performed by Thompson et al<sup>(3)</sup> in patients with Grave's disease, using a wide range of I intake from Lugol solution, that is from 1/5 drop to 30 drops/day. In 17 hospitalized patients and in 23 outpatients, one drop of Lugol gave the maximum reduction in basal metabolism toward the normal range in the majority of the patients, following a period of bed rest. One drop of Lugol contains a total of 6.25 mg, with 40% iodine and 60% iodide as the potassium salt.

Koutras et al<sup>(45)</sup> administered increasing amounts of iodide from 0.1 to 0.8 mg to normal subjects over a period of 12 weeks and measured the quantity of I retained by the thyroid gland before an equilibrium with the new plasma inorganic I was reached. With all the doses administered, a total of 6-7 mg I was accumulated by the thyroid gland over a period of weeks before equilibrium was reached. Again, around 6 mg was the amount observed under those physiological manipulations. These authors stated: "From our evidence it appears that, with all the doses we used, the thyroid took up about 6 to 7 mg of iodine before an equilibrium with the new PII (Plasma Inorganic I) was reached. It is of some interest that this is approximately the amount of the intrathyroidal exchangeable iodine". Based on the above observations and the data displayed in Fig. 2, we would like to propose that the optimal daily intake for I sufficiency of the thyroid gland is 6 mg, with a minimum of 3 mg, Saxena's minimal daily amount<sup>(34)</sup>.

#### **IV. Requirement of the extrathyroidal tissues for I**

In 1954, Berson and Yalow<sup>(46)</sup> postulated that following initial clearance of an administered dose of radioiodine, the major portion of the radioiodine in the body is distributed between 2 compartments, the thyroidal and extra thyroidal organic I pools which are in dynamic equilibrium. The results obtained from an elegant experimental design, revealed that the total exchangeable organic I pool ranged from 7 to 13 mg. The total organic pool of I observed in Berson and Yalow's study may correspond to the range of I intake required daily for I sufficiency of the whole human body. The upper limit of 13 mg I is amazingly close to the upper limit of 14 mg observed in slope C (Fig. 2), the maximum intake of I that will not trigger down regulation of the I-trapping mechanism of the thyroid gland.

The amount of I required by the human body for optimal health would not be expected to trigger downregulation of the I trapping system of the thyroid gland. We are proposing that the upper limit of the requirement of the whole human body for I would be 14 mg. If 6 mg I is the optimal amount needed for the thyroid gland, the extra-thyroidal tissues need the difference, that is  $14 \text{ mg} - 6 \text{ mg} = 8 \text{ mg}$ . Although several extrathyroidal organs and tissues have the capability to concentrate and organify I<sup>(47-49)</sup>, the most compelling evidence for an extra thyroidal function of I is its effects on the mammary gland. Eskin et al have published the results of their extensive and excellent studies on the rat model of FDB and breast cancer and the importance of iodine as an essential element for breast normality and for protection against FDB and breast cancer<sup>(14-16,19,20)</sup>. The amount of I required for breast normality in the female rats was equivalent



based on body weight, to the amounts required clinically to improve signs and symptoms of FDB. That amount of I was 0.1 mg I/kg body weight/day. For a 50 kg woman, that daily amount would compute to 5 mg I.

Of interest is the findings of Eskin et al<sup>(20)</sup> that the thyroid gland preferentially concentrate iodide whereas the mammary gland favors iodine. In the I-deficient female rats, histological abnormalities of the mammary gland were corrected more completely and in a larger number of rats treated with iodine than iodide given orally at equivalent doses. This would suggest that iodine is not reduced to iodide during intestinal absorption. Recent textbooks of endocrinology continue the tradition of the past, reaffirming that iodine is reduced to iodide prior to absorption in the intestinal tract, referring to a study by Cohn<sup>(50)</sup>, published in 1932, using segments of the gastrointestinal tract of dogs, washed clean of all food particles prior to the application of I in the lumen. However, Thrall and Bull<sup>(51)</sup> observed that in both fasted and fed rats, the thyroid gland and the skin contained significantly more I when rats were fed with iodide than with iodine; whereas the stomach walls and stomach contents had a significantly greater level of I in iodine-fed rats than iodide-fed animals. Peripheral levels of inorganic I were different with different patterns, when rats were fed with these 2 forms of I. The authors concluded: "These data lead us to question the view that iodide and iodine are essentially interchangeable". Based on the above findings, I supplementation should contain both iodine for the mammary tissue and iodide for the thyroid gland.

The mammary glands can effectively compete with the thyroid gland for peripheral I. Eskin et al<sup>(52)</sup> measured the 24 hr. radioiodide uptake in 57 clinically normal breasts, and in 8 clinically abnormal breasts. The mean  $\pm$  SD % uptake was  $6.9 \pm 0.46\%$  in the normal breasts and  $12.5 \pm 1\%$  in abnormal breasts. These means were statistically significant at  $p < 0.005$ . Considering that these measurements are representative of a single breast and a woman has 2 breasts, the % uptake per patient is twice these amounts. This brings the 24 hr. radioiodide uptake by the mammary glands of a woman in the same range as the 24 hr. radioiodide uptake by the thyroid gland. The higher % uptake in the abnormal breasts suggests that the abnormal breasts were more I deficient than normal breasts. As previously discussed, endemic goiter is 6 times more common in pubertal girls than pubertal boys<sup>(38)</sup>. This suggests that in areas of marginal I supply, the larger breast of pubertal girls with greater I requirement, would leave less I available for thyroid uptake than in pubertal boys, and the expected outcome would be a greater prevalence of goiter in pubertal girls than boys. The presence of simple goiter in a female patient is an indication of I deficiency of both the thyroid and mammary glands. Treating such patients with T<sub>4</sub> instead of I supplementation is non physiological and increases their risk of breast cancer<sup>(17)</sup>.

Beside the greater risk for breast cancer in I-deficient women, there is convincing evidence that I deficiency increases also the risk of thyroid cancer. It is common knowledge that simple goiter due to I-deficiency, if left without I supplementation, will progress to nodular goiter with some of these nodules becoming cancerous<sup>(30)</sup>. Since simple goiter is more common in women than in men, because of their greater need for I, it does not take a supranormal intellect but plain common sense to come to the conclusion that I-deficiency will eventually result in a greater prevalence of thyroid nodules in women and subsequently a greater incidence and prevalence of thyroid cancer. Therefore, it is not surprising that with the decreasing trend of I consumption by the U.S. population<sup>(1,2)</sup>, there is a marked increase in thyroid nodules resulting in 19,500 new cases of thyroid cancer in 2001, with 14,900 cases in women. This editorial in the May 2002 issue of the Journal of Clinical Endocrinology and Metabolism<sup>(53)</sup> called this increased incidence of thyroid nodules "an epidemic". It is amazing that the author of the editorial made no mention of I deficiency as a possible cause for this "epidemic", although the connection is very obvious. It is a national tragedy that such preventable diseases continue to rise in our population as I deficiency becomes more prevalent and self-appointed experts continue to spread iodophobic misinformation. The guardians of our Nation's thyroid should be more concerned about supplying the optimal requirement of the human body for I to the U.S. population; and less zealous in their crusade to eliminate I from our food supply.

## **V. Requirement of the human body for I**

So far, the optimal daily requirement for I has been estimated at 6 mg of iodide for the thyroid gland and 5 mg of iodine for the mammary glands. The adrenal glands may also require adequate levels of I for normal function. A recent study of female rats exposed to noise stress revealed a decreased adaptability to stress when these rats were placed on an I-deficient diet. There was an attenuation of the pituitary adrenal axis to stress that persisted after functional recovery of the pituitary thyroid axis. Therefore, this effect of I on the adrenal response to stress is totally independent of thyroid hormones.

Certain roles of I in wellbeing and protection against infections, degenerative diseases and cancer may not involve its action on specific organs and tissues. Instead, such properties of I, affecting every cell in the human body, may depend on its concentration in biological fluids. Derry<sup>(54)</sup> has reviewed some beneficial properties of I: the antimicrobial effect of I in organs capable of concentrating it to reach effective I levels; the apoptotic property of I in the body's surveillance mechanism against abnormal cells; the ability of I to trigger differentiation, moving the cell cycle away from the undifferentiated characteristic of breast cancer, for that matter of all cancer. Besides, as a halogen, and because of its large size, I has the ability to markedly enhance the excited singlet to triplet radiationless transition<sup>(55)</sup>. Reactive oxygen species causing damage to DNA and other macromolecules, are usually excited singlet with a high energy content released rapidly, and characterized by fluorescence, whereas the corresponding triplet state contains lower energy levels which are released slowly, expressed as phosphorescence. Such an effect of I would depend on its concentration in biological fluids. Using a rudimentary phosphoroscope, Szent-Gyorgy was able, 50 years ago, to demonstrate this effect of I on the singlet → triplet radiationless transition, at a concentration of  $10^{-5}$  M<sup>(56)</sup>. It is likely that this effect would persist at  $10^{-6}$  M, which would correspond to a serum I level of 12.7 ug/100 ml. Such a level is easily achieved with I intake in the range consumed by mainland Japanese. This effect of I would markedly decrease the oxydative burden of the body, having a beneficial impact upon degenerative diseases and cancer. Protection of the thyroid from radioiodine fall out in cases of nuclear attack and accident would benefit from the recommended daily intake of I, discussed above. The equivalent of 2 drops of Lugol solution (12.5 mg I) daily would maintain a low radioiodine uptake by the thyroid gland (3-4%). Since the greatest damage to the thyroid occurs during the first few hours of radiation exposure<sup>(57)</sup>, this recommended level of I would serve as a prevention in cases of unexpected exposure.

Collective experience may have played a role in the choice of 2 drops of Lugol daily for I supplementation<sup>(43)</sup>. Amazingly, 0.1 ml (2 drops) of Lugol contains 5 mg iodine and 7.5 mg iodide as the potassium salt, the near perfect total amount of I and ratio of iodine over iodide, for sufficiency of the thyroid and mammary glands. This amount of Lugol solution would then represents an ideal form of orthiodosupplementation. Based on the above criteria for I sufficiency of the whole human body, the mainland Japanese represent the only population in the world consuming adequate amounts of I. Thyroid function is higher in normal Japanese woman, a low risk population for breast cancer than in normal British women who are at high risk for breast cancer<sup>(11)</sup>. When 5 different ethnic groups living in Hawaii were compared with British women and mainland Japanese women, the latter showed the highest serum levels of Free T<sub>4</sub>. There was a significant and inverse correlation ( $p < 0.001$ ) between serum Free T<sub>4</sub> and the incidence of breast cancer in these 7 groups with mainland Japanese women showing the lowest incidence<sup>(11,12)</sup>. Since T<sub>4</sub> therapy in I-deficient women increased their risk for breast cancer<sup>(17)</sup>, the significant correlation between serum Free T<sub>4</sub> and breast cancer is not necessarily indicative of a protective role of T<sub>4</sub>. Instead, this correlation may point to the higher I levels in Japanese women, expressed as increased thyroid function. Prasad et al<sup>(58)</sup> reported significantly lower serum T<sub>4</sub> and higher serum T<sub>3</sub> levels in 40 women with histologically confirmed breast cancer, compared to 10 normal controls. Although these authors did not measure urine I levels in those cases, the pattern they reported in women with breast cancer is typical of I deficiency: increased T<sub>3</sub> levels and lower T<sub>4</sub> levels to compensate for the limited availability of I<sup>(30)</sup>.

## **VI. Physician-supervised orthiodosupplementation**

Based on the information previously discussed, the optimal daily I intake for I sufficiency of the whole human body would be equivalent to 2 drops of Lugol solution. In the USA, the initial implementation of I

supplementation at this level would require medical supervision. Administration of I in liquid solution is not very accurate, may stain clothing, has an unpleasant taste and causes gastric irritation. We decided to use a precisely quantified tablet form containing 5 mg iodine and 7.5 mg iodide as the potassium salt. To prevent gastric irritation, the iodine/iodide preparation was absorbed onto a colloidal silica excipient; and to eliminate the unpleasant taste of iodine, the tablets were coated with a thin film of pharmaceutical glaze.

Our preliminary experience with I supplementation at 12.5 mg/day, confirmed the findings of Ghent et al <sup>(19)</sup>, regarding subjective and objective improvements of FDB, following I supplementation. Our findings in 3 patients with Polycystic Ovarian Syndrome (PCOS) confirmed the positive response observed following supplementation with 10 to 20 mg of potassium iodide by Russian investigators 40 years ago <sup>(62)</sup>. Prior to I supplementation, those PCOS patients were oligomenorrheic, menstruating one or twice a year. Following I supplementation for 3 months, they resumed normal monthly cycles. In 2 patients with subclinical hypothyroidism and elevated TSH levels, I supplementation suppressed TSH levels markedly in both cases. In one patient, serum TSH level was 7.8 mIU/L pre-supplementation and 1.7 mIU/L 3 months post I supplementation. In the other patient, TSH level was 21.5 mIU/L before and 11.9 mIU/L after 3 months of I supplementation.

Surprisingly, this program improved the symptoms of tremor and restless legs, two symptoms usually present in neurologic cretinism <sup>(59)</sup>. There was some evidence of improved T<sub>3</sub> receptor responsiveness, reflected by a decreased need for T<sub>3</sub> in some patients previously receiving this hormone. One female patient with normal size and echopattern of the thyroid gland required 45 ug T<sub>3</sub> to maintain clinical euthyroidism. Following I supplementation at 12.5 mg/day, she was able to titrate her daily dose of T<sub>3</sub> down to 7.5 ug during the first month of I supplementation. Previously, missing one or 2 days of T<sub>3</sub> elicited symptoms. Currently, she noticed that she can remain asymptomatic without T<sub>3</sub> for one week. TSH levels in this patient were below detection limits prior to I supplementation. Over the last 12 months on I supplementation, TSH levels are maintained between 1 and 2.5 mIU/L. The calculated T<sub>3</sub> secretion rate by the normal thyroid gland varies between 4.6 and 8.3 ug/day. (Chopra, I.J., and Sabatino, L., In Werner and Ingbar's The Thyroid – Braverman LE and Utiger R-D. Editors Lippincott, p123, 2000). Therefore, with adequate supply of endogenous or exogenous T<sub>4</sub>, the daily need for exogenous T<sub>3</sub> should not exceed 8.3 ug to maintain clinical euthyroidism. Is it possible that the large number of patients currently on supraphysiologic levels of T<sub>3</sub> to maintain clinical euthyroidism are in reality I deficient by our definition of I sufficiency of the whole human body? Could it be that all they need is orthiodosupplementation?

Eskin and Ghent have observed a modulating role of I at levels of 0.1 mg/kg body weight/day in the response of mammary tissue to estrogens <sup>(14-16,19)</sup>. We have some evidence of improved T<sub>3</sub> receptor function in female patients receiving 12.5 mg I/day. T<sub>3</sub> and steroid hormones share the same superfamily of receptors for hydrophobic small molecules <sup>(60)</sup>. Clur <sup>(61)</sup> has postulated that iodination of tyrosine residues in the hydrophobic portion of these receptors normalized their response to the corresponding hormones. Optimal intake of I in amounts 2 orders of magnitude greater than I levels needed for goiter control, may be required for iodination of these receptors. Our observation has important clinical implications. If optimal intake of I reduces the need for exogenous T<sub>3</sub>, one would expect the same effect of I supplementation on endogenous T<sub>3</sub>. I intake below optimal levels would result in clinical hypothyroidism in the presence of normal levels of thyroid hormones because of decreased T<sub>3</sub> receptor function. If this common condition is due to Iodine deficiency, the proper treatment would then be orthiodosupplementation.

## **VII. Epilogue**

Such high requirements for I in an environment depleted of this element, do not have a logical explanation. Unless sometimes in the distant past, the top soil of planet earth contains significant levels of I and meeting these high requirements for I sufficiency could then be achieved with any diet. The theory of evolution does not offer an intellectually satisfying answer to this paradox. However, the Biblical account of the origin of the

world through creation 6000 years ago followed by the fall of man and the flood fits very well the current situation. According to the biblical narrative, the Creator declared planet earth and everything in it perfect. Therefore, the original planet earth contained a top soil rich in I, and all elements required for perfect health of Adam, Eve and their descendants. A rebelled archangel was expelled from God's Habitation for attempting a hostile takeover (Isaiah 14:12-15). His name was Lucifer before the attempt (Isaiah 14:12) and Satan after his expulsion (Luke 10:18). Satan deceived Eve into believing that she could become a goddess by disobeying her Creator (Genesis 3:4,5). A sequence of events followed, culminating in the worldwide flood 4500 years ago. Following this episode, the receding waters washed away the top soil with all its elements into oceans and seas. The new top soil became deficient in I and most likely other essential elements, whose essentialities are still unknown. Mountainous areas became the most I-deficient because the receding waters were the most rapid over the steep slopes, eroding deeper into the soil. The post-deluvian worldwide I deficiency may be a reminder to mankind of the flood, their fallen state and their need for a Redeemer.

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