The MOSS NUTRITION REPORT

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## Literature Review & Commentary

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### *A PERSPECTIVE ON HIGH DOSE IODINE SUPPLEMENTATION – PART XII – LABORATORY ANALYSIS TO DETERMINE NEED AND OVERALL SERIES CONCLUSIONS*

### *INTRODUCTION*

As my two year iodine odyssey comes to an end, one important question remains to be examined that I have purposely decided to address last. Why? Of the major questions I intended to answer in this series, it is the only one where, at this time, I have no definitive answers that are supported by reliable published studies and/or consistent clinical reports from multiple sources. What is this question? Stated very simply:

***"What is the best way to determine need for milligram dosing of supplemental iodine?"***

As you will see, many studies by several researchers, including Abraham and colleagues, have examined this question. However, in contrast to the issues of efficacy and risk where I was able to determine a significant consensus using published papers and anecdotal reports from many esteemed researchers and clinicians, as far as I can tell no consensus exists in relation to diagnostic modalities that can be used to determine need in any particular patient. Furthermore, to complicate the issue even more, the recently published paper by Ristic-Medic et al entitled "Methods of assessment of iodine status in humans: a systematic review" (1) suggests that, as you will see, different assays are best for different patient populations. Therefore, what follows is designed to provide a basic overview of the measures that are used to determine need rather than a distillation of available information into a concise diagnostic protocol. As you will see, while the iodine loading test advocated by Abraham and colleagues that has gained a certain amount of popularity recently will be addressed, so too will many other diagnostic modalities be reviewed that, even though they have not received the same attention as the iodine loading test, are still, in my opinion, deserving of our attention.

### *USING ASSAYS OF THE THYROID FUNCTION TO DETERMINE IODINE NEED*

#### Thyroglobulin and thyrotrophin/thyroglobulin ratio

Several researchers have suggested that laboratory tests designed primarily to ascertain thyroid function can also be used to determine iodine need. In the recently published paper by Ristic-Medic et al (1) mentioned above, the authors state the following about serum thyroglobulin measurement:

> **"Thyroglobulin does appear to be a useful marker of iodine status in children and adolescents, but there was little evidence of its usefulness in other groups, and it does not appear to be useful during pregnancy and lactation. Subgrouping did not clarify the sources of heterogeneity in effect size, but the biomarker may be more effective in populations with high baseline thyroglobulin concentrations."**

Why is thyroglobulin measurement useful for ascertaining iodine status? Zimmermann et al (2) state:

> **"In the absence of thyroid damage, the major determinants of serum thyroglobulin are thyroid cell mass and TSH stimulation. Thus, serum thyroglobulin is elevated in iodine-deficient areas due to TSH hyperstimulation and hyperplasia."**

In "Nutrient and toxic elements" by Fitzgerald et al (3) that can be found in the excellent text *Laboratory Evaluations for Integrative and Functional Medicine, 2nd Edition* by Lord and Bralley, the authors state the following about the value of thyroglobulin testing to determine iodine status:

> **"Measuring thyroglobulin in whole blood or dried blood spot specimens (BS Tgb) is a promising new approach. Chronic iodine insufficiency results in increased uptake of Tgb by follicular cells in order to increase the release of thyroid hormone. The process also releases portions of intact Tgb into blood that can be detected by sensitive analytical methods."**

Finally, Teng et al (4) point out that serum thyrotrophin/thyroglobulin ratio may be a better index of evaluating iodine status and Contempre et al (5) suggest that this ratio may be a good way to monitor response to iodine supplementation.

**Thyroxine, triiodothyronine, and thyroid stimulating hormone**

Of course, given that, these days, serum thyroxine ($T_4$), serum triiodothyronine ($T_3$), and thyroid stimulating hormone (TSH) are conveniently and routinely tested, it certainly would be ideal from a practicality standpoint that we might be able to learn more about iodine need from these tests. Fortunately, the Ristic-Medic et al paper (1) suggests that two of these tests have value in determining iodine need. Concerning thyroxine, the authors state the following:

> **"Overall, serum thyroxine appears to be a useful marker of iodine status in children and adolescents, adults, women, and those at moderate thyroxine status at baseline, where iodized oil, potassium iodate, or iodide are used for supplementation, where a single dose of <500 mg is given, and where either radioimmuno- or immunofluorimetric assays are used."**

In contrast, the authors note:

> **"It is not a useful biomarker in pregnant and lactating women or with moderate daily supplementation."**

What about $T_3$? Ristic-Medic et al (1) point out emphatically:

> **"Overall, there is not evidence that triiodothyronine is a useful biomarker for iodine status."**

Next, consider TSH. In contrast to $T_3$, the authors do have some positive comments:

> **"Overall, TSH appears to be a good marker of iodine status and to be useful in pregnant women and females; with intramuscular iodized oil, potassium iodide and iodate; with a moderate daily dose, and when using immunoradiometric and immunofluorimetric assays."**

However, this usefulness is not universal for all patient populations:

> **"It does not appear to be useful in children and adolescents, in persons with moderate TSH baseline status who take oral iodized oil supplements or a single dose of <500 mg iodine, and when using radioimmunoassay for sample analysis."**

As I mentioned, these findings by Ristic-Medic et al (1) provide hope that two very ubiquitous lab tests can be used to ascertain iodine status. Unfortunately, this opinion is not shared by all. Fitzgerald et al (3) take a much more negative view concerning the use of $T_4$ and TSH to determine iodine need:

> **"…mild to moderate iodine deficiency may not be reflected in TSH levels. Thus, clinically significant iodine deficiency could have detrimental mental and neurodevelopmental consequences without tell-tale high TSH and without clinical hypothyroidism. In rats, iodine deficiency resulted in a variety of adaptive mechanisms to ensure adequate T3 supply to skeletal muscle, heart, lung and ovary, whereas other tissues, such as the brain, were deprived of T3. Due to increasing rates of peripheral conversion, T3 may increase as iodine deficiency worsens, while T4 is still within normal ranges."**

## *URINARY IODINE MEASUREMENT*

Over the years, as you will see, urinary iodine measurement has been considered to be the modality of choice for determining iodine status. However, as I have noted in my previous discussions on the iodine loading test devised by Abraham and colleagues, there exists a great deal of controversy concerning the best test methodology to most accurately determine iodine need. Of course, with the above mind, it should come as no surprise that a large amount of papers have been published on the use of urinary iodine measurements to determine iodine need.

To fully appreciate the strengths and limitations of the methodologies to be discussed, though, I feel it is important to first review basic published information concerning iodine absorption and elimination.

First, consider absorption. As I mentioned in part VI of this series, dietary iodine is absorbed on an extremely efficient basis. Precisely, how efficient is iodine absorption? Rasmussen et al (6) state:

> **"Iodine from food is believed to be absorbed efficiently (about 90%)."**

What about excretion? Two references, Ristic-Medic et al (1) and Hurrell (7) both agree that 90% of ingested iodine is excreted in the urine. As you may recall, Abraham and colleagues maintain that this is the ideal level of iodine excretion that only occurs when all physiologic pathways that require iodine are fully repleted. However, Hurrell (7) goes

on to make a statement that is at odds with claims made by Abraham and colleagues:

> **"There is no general homeostatic mechanism to conserve iodine by increasing absorption or reducing excretion."**

Thus, even though research shows, as maintained by Hurrell (7), 90% of iodine will be excreted in the urine no matter what the dose or physiologic circumstances, Abraham and colleagues maintain that a 50 mg dose of iodine/iodide will only be excreted in the urine at the 90% level if all physiologic pathways requiring iodine are repleted. Can a common middle ground be found for this very significant difference in claims about iodine metabolism? I will address this question shortly.

**Conventional use of urinary iodine measurements to ascertain iodine status**

As I have suggested, the way Abraham and colleagues employ urinary iodine testing is contrary to that stated in all the peer reviewed, published papers on the subject that I have read. Of course, that alone does not make the position held by Abraham and colleagues incorrect. Therefore, before trying to formulate any conclusions, I would like to review the more traditional use of urinary iodine measurements as a tool to determine iodine status.

In the review of the literature discussed above by Ristic-Medic et al (1) the following is stated about general use of urinary iodine as a legitimate diagnostic tool:

> **"Overall, urinary iodine (UI) appears to be an effective biomarker of iodine status in children and adolescents, in those with low-to-moderate baseline iodine status, in those supplemented with iodized oil and potassium iodide or iodate, and those given a single dose of <500 mg iodine, whereas UI may not be a good marker of status in those given a higher (>500 mg) single doses of iodine."**

In addition, the following is generally accepted as the cut-off value for determining iodine deficiency, as noted by Fitzgerald et al (3):

> **"Iodine deficiency is indicated for individuals with UI concentrations <50 µg/L."**

However, beyond these commonly accepted aspects of urinary iodine measurement, there exists a fair amount of controversy about the best way to measure urinary iodine. Of course, as I mentioned, Abraham and colleagues have a very unique approach to urinary iodine measurement, which I will explore again shortly. Beyond the position held be Abraham and colleagues, though, authors in the published literature discuss three different ways to measure urinary iodine in order to gain the most accurate information on whole body status and need for supplementation.

***One time or "casual" urine sample*** – While this method is preferred by both practitioners and patients due to ease of collection, it is considered to be inaccurate. The following quotes give the reasons why. First consider this comment by Andersen et al (8):

> **"The relevance of determining individual iodine excretion is debated. The thyroid gland has the capacity to store large amounts of iodine, unaffected by short-term low iodine intake. In addition, iodine excretion in the individual reflects the iodine intake over a short period of time prior to collection, and urinary iodine excretion varies considerably. Thus, short-term estimation of individual iodine intake may likely be inaccurate."**

Rasmussen et al (6) offer the following on this issue:

> **"The individual iodine excreted varied considerably during the day. This means that it is not possible to classify an individual as a high or low iodine intaker from a casual urine sample. A subject classified as having a very low intake could, in a sample taken a few hours later, be classified as having a very high iodine intake."**

Of course, even with the daily variability mentioned above, if there were a definitive circadian rhythm to iodine excretion the situation could be remedied by doing a one-time urine collection at the same time each day. Unfortunately, according to Rasmussen et al (6), while there are certain trends in excretion there is no definitive circadian rhythm:

> **"…we did not find any clear circadian rhythm in iodine excretion although the iodine excretion seems to be lowest in the morning."**

Therefore, even though it is the most convenient of all the urine tests for iodine, one-time tests have no real value in ascertaining iodine status or need for supplementation.

***24-hour urine samples*** – While we all realize that it is difficult to gain patient compliance in terms of collecting urine for 24 hours, the literature, as you will see, concurs with Abraham and colleagues that examination of a 24 hour accumulation of urine will

give the most reliable information. Andersen et al (8) state:

> **"Estimated 24 h urinary iodine excretion has been preferred to crude urinary iodine excretion by some authors as this was more precise in determining the 24-h urinary iodine excretion."**

According to Fitzgerald et al (3), the normal values for iodine content in a 24 hour catch are 100 to 460 μg/d. Of course, as you are well aware, Abraham and colleagues have been very vocal in their disagreement with this statement. Again, I will address the position held by Abraham and colleagues on urinary iodine testing shortly.

Beyond the objections of Abraham and colleagues, is it generally accepted in the medical literature that a one-time 24 hour catch will provide optimal information concerning iodine status? Rasmussen et al (6), in one of the most definitive studies on the subject, say no:

> **"This study shows that iodine excretion in one 24-h urine sample is insufficient to determine iodine status in an individual because of the great variation from one day to another."**

***24-hour urinary iodine/creatinine (Cr) ratio*** – It has been suggested that the problem of day-to-day variation can be obviated by calculating the ratio between iodine and creatinine in a 24-hour sample. Fitzgerald et al (3) state;

> **"…24-hour UI/creatinine eliminates within-day and day-to-day variations in iodine excretion…"**

However, they also point out this ratio can be misleading with certain patients because creatinine can be affected by diet and lifestyle. The authors point out:

> **"…creatinine is affected by poor nutrition, advancing age and sedentary lifestyle. Large inter- and intraindividual variations have been reported for creatinine, so the creatinine normalization method may give inaccurate results for iodine levels, misrepresenting iodine deficiency as iodine sufficiency."**

Rasmussen et al (6) go into more detail on the limitations of the 24 hour UI/Cr ratio:

> **"Others have come to the conclusion that the I/Cr ratio is not a suitable index for assessing iodine status. One reason is that in populations with protein malnutrition the creatinine excretion will be below normal values leading to an overestimation of the iodine intake. However, this argument cannot be used in a well-nourished population like the Danish. Another argument is that the I/Cr ratio in general underestimates iodine status compared to 24-h urinary iodine and that women's iodine status is overestimated compared to men's. These problems could be overcome by multiplying the I/Cr ratio with the age- and sex-adjusted 24-h creatinine excretion. Without this correction the I/Cr measure is not usable to determine the iodine status in a population but can only be used if similar groups are compared. Moreover, the 24-h creatinine excretion shows inter- and intra-individual variation. Finally, the creatinine excretion has been found to vary throughout the day."**

With the above in mind, the authors conclude:

> **"We conclude that the I/Cr ratio is usable in a healthy, well-nourished adult population if corrected for the age- and sex-adjusted 24-h creatinine excretion."**

Finally, Rasmussen et al (6) again emphasize in their conclusion:

> **"For determination of iodine status in an individual more than one 24-h urine must be used."**

***The iodine loading test using 24-hour urine*** - As I expect you can see, while helpful, all the diagnostic modalities discussed above have their limitations in terms of providing highly reliable information that we can use to determine need for iodine supplementation or progress from an iodine supplementation program. Interestingly, there is another reason, as suggested repeatedly by Abraham and colleagues, why the methodologies discussed above will be suboptimal in terms of determining iodine need. All of these diagnostic modalities are primarily designed to determine the amount of iodine needed to promote optimal thyroid function. Why is this a problem? As I have noted throughout this series, Abraham and colleagues were very correct in pointing out that a large body of research makes it clear that iodine is required for proper function of many other parts of the body besides the thyroid, particularly the breast. In turn, any diagnostic modality for iodine need that is based solely on the iodine requirements of the thyroid will tend to under estimate total iodine need. Given that every diagnostic method I discussed above, according to the published literature on them, revolve around thyroid requirements, Abraham and colleagues were certainly justified in making the assumption that a whole new method of diagnosis

was required. In "The safe and effective implementation of orthoiodosupplementation in medical practice" Abraham (9) states:

> **"The concept of orthoiodosupplementation is based on the self-evident fact that the whole body, not just the thyroid gland, needs iodine. The whole body needs this essential trace element, which plays different roles in different organs and tissues. In order to assess whole body sufficiency for iodine/iodide, a simple loading test was developed, based on the concept that the more deficient a patient is in this nutrient, the greater the percentage of ingested iodine/iodide that will be retained, the smaller percentage excreted in the urine."**

What were the goals being considered in devising the loading test? Abraham (9) points out:

> **"We were interested in a loading test that would result in 40-50% of the ingested dose excreted in the 24-hour urine and also with a wide range of values in different subjects."**

In turn, studies were conducted by Abraham and colleagues using differing doses of a tablet containing 12.5 mg of iodine/iodide:

> **"For six subjects tested, the following percent dose excreted was obtained, expressed as mean ±SD (range): one tablet = 22 ± 1.2 (20-26); two tablets = 23±2.8 (22-25); three tablets = 25±12.3 (14-37). Another group of six normal subjects on a similar Western diet was tested with four tablets and the values were = 39±17.2 (14.2-66.0)."**

Since four tablets yielded approximately 40% excretion, Abraham and colleagues chose four tablets (50 mg of iodine/iodide) as the loading dose. Why was 40% chosen as an acceptable cut-off point in this study? Unfortunately, I could find no definitive, referenced statements in any of the papers by Abraham and colleagues that make their reasoning clear that the decision process was more than arbitrary.

Of course, there is another important question that needs to be asked about the loading test. In the quote above it is pointed out that six normal subjects excreted approximately 40% of a four tablet loading dose over 24 hours. In turn, it might be assumed that 40% would be used as the indicator for sufficiency. In contrast, Abraham and colleagues chose 90%. Why? Beyond an arbitrary, subjective rationale, no reason is given. Abraham (9) states:

> **"We chose four tablets for the loading test. Sufficiency of whole human body for iodine/iodide was arbitrarily defined as 90% or more of the ingested amount excreted in the 24-hour urine collection, using 50 mg of the iodine/iodide preparation (four tablets)."**

The only other rationale I could find in the papers by Abraham and colleagues is the following that comes from "The concept of orthoiodosupplementation and its clinical implications" (10):

> **"Because of the improved overall well-being reported by the subjects who achieved 90% or more iodide excreted, sufficiency was arbitrarily defined as 90%."**

As you might expect, with so many of the parameters being based on arbitrary or subjective indicators, other important questions also need to be asked:

1. *Since anecdotal reports and the research discussed above by Abraham and colleagues suggest that no one has ever tested at 90% or above excretion rate without prior use of iodine/iodide supplementation, why run the test? This is an important question to ask since it is generally assumed that the main reason clinicians order laboratory tests is that some patients will actually demonstrate baseline values that are within the normal and/or optimal ranges.*
2. *If no reliable data exists that suggest patients or healthy individuals will demonstrate excretion rates of 90% or more without supplementation, does the 90% value truly reflect an optimally healthy situation?*
3. *Why have no other researchers working with iodine confirmed the findings of Abraham and colleagues concerning the loading test?*
4. *If research, as noted above by Hurrell (7) on page 3 of this monograph, suggests that all dietary iodine will be excreted at a 90% rate in the urine, why are excretion rates considerably lower than this typically noted for the iodine loading test?*

Unfortunately, after over two years of examination of as much literature on iodine as I could find, I cannot locate definitive answers to any of these questions. However, as suggested in part I of this series, one individual who is generally recognized as an expert in clinical nutrition has offered some theories to answer at least some of these questions. In the August/September 2005 edition of *Townsend Letter for Doctors and Patients* Alan Gaby, MD commented on many aspects of the approach to iodine biochemistry and physiology taken by Abraham and colleagues in "Editorial: Iodine: A lot to swallow." What follows are quotes from this

commentary that relate to the above mentioned concerns:

> **"…the validity of the test depends on the assumption that the average person can absorb at least 90% of a 50-mg dose. It may be that people are failing to excrete 90% of the iodine in the urine not because their tissues are soaking it up, but because a lot of the iodine is coming out in the feces. There is no reason to assume that a 50-mg dose of iodine, which is at least 250 times the typical daily intake, can be almost completely absorbed by the average person. While this issue has not apparently been studied in humans, cows fed supraphysiological doses of iodine (72 to 161 mg per day) excreted approximately 50% of the administered dose in the feces."**

With the above in mind, why has it been observed by many, including Abraham and colleagues, that excretion rates will increase over time with milligram dosing of supplemental iodine? Gaby states:

> **"Proponents of the iodine-load test argue that the less-than-90% urinary excretion seen in most patients is probably not due to incomplete intestinal absorption. They point out that the percent urinary excretion increases progressively (usually over a period of months) with continued high-dose iodine administration, and that this increase occurs because the body retains less of each successive dose as it becomes more saturated with iodine. However, an alternative explanation for the progressive increase in urinary iodine excretion is that repeated dosing leads to increases in the percent absorbed. That could conceivably occur in a number of different ways. As an antimicrobial agent, iodine might enhance overall nutrient absorption by killing certain pathogens in the gastrointestinal tract. Supplementing with large doses of iodine might also induce the proliferation of an intestinal iodine-transporter molecule, thereby increasing iodine absorption capacity. A third possibility is that an enterohepatic circulation exists for iodine. Repeated dosing with 50 mg of iodine might overload the enterohepatic circulation system, resulting in less iodine being dumped back into the intestine to be excreted in the feces, and more excreted in the urine."**

With these considerations in mind, Gaby makes the following overall statement about the iodine loading test:

> **"Before the iodine-load test can be considered a reliable indicator of tissue iodine levels, it needs to be demonstrated that only negligible amounts of iodine are excreted in the feces after an oral iodine load."**

Abraham and Browstein rebutted Gaby's editorial in the October 2005 edition of *Townsend Letter for Doctors & Patients* in a letter to the editor entitled "A rebuttal of Dr. Gaby's Editorial on Iodine." Concerning Gaby's claim that a 50 mg dose of iodine/iodide may not be completely absorbed, as evidenced by research performed on cows, Abraham and Brownstein reference a 1950 study performed on patients with exophthalmic goiter (11). In this study, even though GI absorption was not directly studied, it was obvious from renal clearance measurements that doses up to 500 mg of sodium iodide were highly absorbable. However, other than discussing the issue of thyroid uptake of iodine, the study offers no information to confirm the hypothesis offered by Abraham and colleagues that renal clearance is initially low in the iodine loading test because organs depleted of iodine are increasing uptake. To support this claim, Abraham and Brownstein offer a study by Broekhuysen et al (12). While I could not read the study since it was published in French, Abraham and Brownstein review key points that suggest administration of amiodarone, an antiarrhythmic agent containing large amounts of iodine, will vary based on time in terms of urinary iodine. Specifically, in support of the claim by Abraham and colleagues, the study initially demonstrated low levels of iodine in the urine with significantly higher levels approximately one month later. With these findings in mind, Abraham and Brownstein offer the following quote from the study:

> **"'These results suggest that iodine is retained in the body until a mechanism is triggered that adjusts the excretion of iodine to balance completely the intake.'"**

Following this quote, Abraham and Brownstein state:

> **"They estimated that the body retained 1.5 gm of iodine before the ingested iodine in amiodarone is completely excreted, and before therapeutic efficacy."**

According to Abraham and Brownstein, the Broekhuysen et al (12) study also suggests what happened to the iodine that was not excreted:

**"In 3 patients who eventually died following long-term treatment with amiodarone, the levels of inorganic iodine (not amiodarone) present in various organs and tissues were measured. The total body non-amiodarone iodine content was estimated at approximately 2 gm with the greatest amount found in fat tissues (700 mg) and striated muscle (650 mg). Iodine was present in every tissue examined. The highest concentrations of non-amiodarone iodine were found in descending order: thyroid gland, liver, lung, fat tissues, adrenal glands and the heart."**

Finally, Abraham and Brownstein note that Broekhuysen et al (12) found no inorganic iodine from amiodarone in the feces, thus negating Gaby's hypothesis that much of the 50 mg dose of iodine/iodide used in the loading test is not absorbed.

While I must admit that, assuming Abraham and Brownstein have translated the French study by Broekhuysen et al (12) correctly, the rebuttal is very compelling, questions still remain in my mind:

1. *Even though amiodarone contains inorganic iodine, can we absolutely conclude that its metabolism can be directly extrapolated to supplemental inorganic iodine? Abraham and colleagues, as far as I know, provide no conclusive data to answer this question.*
2. *Assuming the body does initially retain a significant portion of a large dose of supplemental iodine, what is the mechanism? Broekhuysen et al (12) suggest no mechanism. Furthermore, they do not suggest the rationale offered by Abraham and colleagues that the body is repleting deficiencies.*
3. *Given that Broekhuysen et al (12) suggest no mechanism or rationale, still another question needs to asked. Is the inorganic iodine retention by various organs in the body, as noted in the above quote, a good thing or a bad thing? Given that the patients died, I'm not entirely convinced that it is good.*

To conclude my review of the literature of this highly controversial aspect of the world view of iodine as held by Abraham and colleagues, I must admit that the anecdotal and research data they provide to support the iodine loading test is very compelling. However, because of the limited research and heavy reliance on subjective information and arbitrary conclusions, I must regard it as preliminary at this time. For me to be totally convinced of its efficacy and safety, I would need to see much more confirmatory objective research, particularly by researchers not connected with Abraham and colleagues.

***Iodine skin test*** – Before leaving this discussion on diagnostic modalities to determine need for supplemental iodine, I would like to briefly comment on the iodine skin test. According to Gulland (13) the test is conducted in the following manner:

**"Simply put 1-2 drops of 5% Lugol's solution (aqueous $I_2$ and iodide) on a patient's wrist, ideally early in the morning. The solution will create a yellow stain about the size of a half-dollar. Then simply have the patient monitor how fast the stain disappears.**

**The faster it fades the more iodine-deficient he or she is. In a healthy patient with optimal iodine levels, the stain will be visible for 14-16 hours or even longer. If it's gone in 2-3 hours, she's got a significant deficiency. In essence, the test is showing to what degree the patient's system is 'hungry' for iodine."**

Is this a valid way to determine iodine need? Fitzgerald et al (3) provide the following answer to this question:

**"There are no accepted norms for the time for fading, and the observation is complicated by dark skin color."**

Abraham (14) also has an opinion on the validity of the iodine skin test:

**"…the skin iodine patch test is not a reliable method to assess whole body sufficiency for iodine. Many factors play a role in the disappearance of the yellow color of iodine from the surface of the skin. For example, if iodine is reduced to iodide by the skin, the yellow color of iodine will disappear because iodide is white. In order to regenerate iodine on the skin, one needs to apply an oxidant such as hydrogen peroxide, complicating the test further. The evaporation of iodine from the skin increases with increased ambient temperatures and decreased atmospheric pressure. For example, the yellow color of iodine will disappear much faster in Denver, Colorado at 5,000 feet above sea level than in Los Angeles, California at sea level, irrespective of the amount of bioavailable iodine."**

Please note that none of the claims in the above quotes on the iodine skin test are referenced with peer reviewed studies.

The conflicting information presented above is certainly in line with the anecdotal reports from you that have been highly variable in terms of suggesting

reliability of the iodine skin test in determining need for milligram doses of supplemental iodine. Therefore, I find it difficult to give this method of determining iodine need any credence at this time.

### *OVERALL CONCLUSIONS ON TESTS TO DETERMINE NEED FOR SUPPLEMENTAL IODINE*

As I hope you could see, most of the tests described above were designed to determine iodine need only in relation to thyroid function. However, even with this limited perspective, as I hope you could also see, many questions remain as to their accuracy and reliability. But, of course, as I have mentioned, there is another perspective that virtually all of them ignore. As Abraham and colleagues have brilliantly pointed out, iodine is required by many more physiologic systems beyond thyroid function. While the iodine loading test and iodine skin test were designed to ascertain whole-body need, unfortunately, in my opinion, not enough conclusive data exists at this time to wholeheartedly endorse their routine use in clinical practice.

Do I have a feel-good, parting sound-byte that states what you can very confidently do in terms of diagnosing iodine need? Unfortunately no. That is why I waited until the end of this series to explore this subject. Over the 2-3 three years I have been researching and writing about iodine, I had high hopes that I would arrive at definitive answers. Regretfully, those answers are yet to come to me. Because of this, many practitioners I know who routinely provide milligram doses of supplemental iodine to their patients, even with any of the above mentioned lab tests in hand, will proceed very cautiously with supplementation, starting with 1-2 mg per day and increasing slowly, if necessary, based on follow up TSH measurements and clinical signs and symptoms of improvement or lack thereof.

### *SOME FINAL THOUGHTS TO CONCLUDE THIS SERIES*

Given that this series has occupied over two years of my life, how do I feel about it coming to an end? Interestingly, my feelings are mixed. On one hand I have gained tremendous understanding and appreciation for one of the most important, complex, under-appreciated, and misunderstood nutrients in all of clinical nutrition. For that I am grateful I spent all this time. On the other hand, I initially had a goal over two years ago to find research that would allow me to present more definitive conclusions to you on the use of milligram doses of iodine clinically than what I actually did. While I feel I performed a fairly good job on issues such as those relating to extrathyroidal need for iodine, the dangers to certain patient populations of milligram dosing, and the Japanese experience concerning dietary intake, I regret that in many other areas I left you with more unanswered questions than what I anticipated. However, there is one overriding reason that leaves me with very positive feelings about this two year odyssey. Its publication has led to many wonderful and highly informative conversations with many of you where I was able to both inform you and learn from you. Because of this, my regrets are vastly minimized by the many good feelings I have about this experience.

In conclusion, please note my following parting thoughts on the various controversies addressed in this series:

**Overall thoughts on Abraham and colleagues:**

While, as you know, I have significant disagreements with Abraham and colleagues on several issues, overall I have tremendous respect, gratitude and admiration. Why? Without their research and publications I, like many others in the clinical nutrition community, would still regard iodine as a side bar in clinical practice worthy of attention only in those rare instances where patients with low thyroid function were not ingesting 150 mcg per day. In contrast, because of the work of these researchers and clinicians, many, including myself, now recognize and appreciate the major role iodine plays, not only in relation to thyroid function, but in relationship to many of the most pressing issues we face today in trying to meet the needs of chronically ill patients. Yes, the research on much of what I have discussed in this series occurred independently of the efforts of Abraham and colleagues. However, without their efforts, I can say with a high degree of certainty that I would have never become aware of it. For these reasons, as I am eternally grateful to Dr. Bland for exposing detoxification research and Dr. Hollick for exposing vitamin D research to the clinical nutrition community, I will be eternally grateful to Abraham and colleagues for exposing to the clinical nutrition community so much iodine research that had been sitting almost completely ignored in the country's medical libraries for years.

**Overall thoughts on attitudes held by Abraham and colleagues concerning those with whom they disagree**

With the above being stated, please do not assume that I agree with all positions taken by Abraham and colleagues. As you may recall, I started this series with probably my most vehement disagreement, which continues to this day. While I realize, as seen in politics and the 24 hour news networks, that it is fashionable right now to portray those with whom you have disagreements as enemies and conspirators

who need to be vanquished, I strongly feel that this "Those who do not agree with me are my enemies" attitude has no place in the clinical nutrition community nor the scientific community at large. Unfortunately, I have observed increased incidents where those in the clinical nutrition community see enemies and conspirators whenever a negative study or article is published, whether it is the drug companies, the FDA, Codex, etc. While I do not deny that there are those in our midst who have made an a priori assumption that everyone in clinical nutrition is a quack who should be wiped clean from the face of the earth, I saw none of this in my two to three years of research on iodine. Rather, I saw very human, very real researchers doing their best to interpret intelligently data from animal and human research plus clinical and anecdotal experiences. Granted, sometimes they came up with conclusions that were not only at odds with those derived by Abraham and colleagues but seemed inconsistent with what we know today from an overall standpoint. However, this does not mean they are bad people. Furthermore, knowing that some of these researchers worked decades ago without computers and the Internet and with technology and methodologies we now often regard as primitive, I feel we should give them even more benefit of the doubt when contemplating accusations of conspiracy and outright name-calling. In turn, I continue to maintain the strong position I took in part I of this series. I know of no one involved in iodine research, including Dr. Wolff or any of the other high profile "players," who deserves to be accused of conspiracy or deserves the moniker "medical iodophobe."

**Overall thoughts on the presence of iodine deficiency on a large scale**

I am in total agreement with Abraham and colleagues that iodine deficiency is a major under-appreciated problem not only in this country but worldwide.

**Overall thoughts on the belief that iodine is only a thyroid nutrient**

As I have mentioned, I will be forever grateful to Abraham and colleagues for bringing to light the large body of research that makes it clear that iodine has important functions outside of the thyroid, particularly in relation to breast health.

**Overall thoughts on the Japanese experience with iodine**

Based on a large body of research I presented in this series, I believe there is little doubt that Abraham and colleagues are incorrect in their assumption that the Japanese ingest approximately 13 mg of iodine per day with no ill-effects. In contrast, research, to me, clearly demonstrates that the average intake in Japan is approximately 2 mg per day with ill-effects seen at larger doses in certain populations.

**Overall thoughts on the safety of milligram dosing of supplemental iodine**

On this most heated controversy in relationship to the world view of iodine held by Abraham and colleagues, I feel there is little doubt, based on a very large body of research, clinical and anecdotal data, that the viewpoint adamantly maintained by Abraham and colleagues that supplemental iodine is totally and completely safe and without side effects of any kind for anyone at doses up to several dozen milligrams per day is completely incorrect. As I demonstrated, it does appear that up to several dozen milligrams is quite safe for the majority of people. However, a small but significant population of patients will demonstrate sometimes severe reactions, mostly thyroid related, to large and sometimes doses as low as 1-2 mg per day or even lower.

The most recent proof of this was demonstrated in the recently published study by Cerqueira et al (15) entitled "Association of iodine fortification with incident use of antithyroid medication – A Danish nationwide study." As the title suggests, the authors used a somewhat novel way of determining the incidence of side effects of iodine administration, an increase in the use of antithyroid medication. The impetus for the study was the initiation of an iodine fortification program in Denmark that started in 1998 where 8 ppm potassium iodide was added to all salt on a voluntary basis. The program was modified in 2000 when mandatory fortification of household salt and salt used for commercial production of bread was instituted. This mandatory fortification consisted of 13 ppm potassium iodide. According to the authors, the primary goals of fortification were the following:

> **"…1) to increase the iodine intake of the average Dane by 50 μg/d; 2) to lower the incidence of goiter; and 3) to lower the incidence of hyperthyroidism."**

How successful was the program in relation to these goals?

> **"Studies have demonstrated the program to be successful with respect to the first two aims."**

More specifically, what were the findings of this study? Cerqueira et al (15) state:

> **"In the region with moderate iodine deficiency, the number of incident users of antithyroid medication increased 46% in the first 4 yr of iodine fortification. The**

**use increased the most among the youngest age group (younger than 40 yr) and the oldest age group (older than 75 yr). In the mildly iodine-deficient region, the number of incident users increased only 18%, and only in the youngest groups (below 40 and 40-59 yr). After 4 yr of fortification, the incidence rates started to fall and reached baseline, for most groups, 6 yr after onset of fortification."**

The above findings led the authors to conclude:

**"This study shows that iodine fortification induced a temporary, modest increase in the incidence of hyperthyroidism as measured by use of antithyroid medication. A new steady state has not yet evolved."**

Thus, as you can see, ongoing research up to the present time suggests that certain populations, albeit small in numbers, will experience adverse, thyroid-related reactions to even small amounts of iodine supplementation.

**Overall thoughts on diagnosis of need and dosing**

Contrary to the strongly held position of Abraham and colleagues, none of the research, clinical, or anecdotal information I have seen suggests there is currently in existence a laboratory or clinical modality that will enable us to determine, with absolute certainty, which patients will benefit from any amount of milligram dosing of supplemental iodine without experiencing adverse reactions. In turn, all the information presented to me over the last two to three years leads me to agree with several clinicians who maintain the following is (1) the best method of determining need and (2) assuming need exists, the best method of administration:

***Based on overall impressions gained from several diagnostic modalities, start dosing iodine at levels of 1-2 mg per day with patients who demonstrate need. Then, based on subsequent signs, symptoms, and follow lab tests such as TSH, adjust the dose up or down gradually over a period of several weeks.***

One final parting thought. I want to thank all of you who have patiently stayed with my journey all of this time through the world of iodine. Your comments and feedback has been invaluable. Hopefully, even though I have ended this series on iodine, given that I left it with so many unanswered questions, you will continue to provide me with information on your ongoing thoughts and experiences with iodine so that, at sometime in the future, there will be much fewer questions and many more answers.

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