The Historical Background of the Iodine Project

by Guy E. Abraham, MD

The goal of this article is to provide the background on the Iodine Project which started five years ago and reacquaint the reader with the concept of orthoiodosupplementation — the amount of iodine required for whole body sufficiency based on an iodine/iodide loading test recently developed by the author.[1]

During the first half of the 20th century, almost every US physician used Lugol solution for iodine supplementation in his/her practice for both hypo- and hyperthyroidism,[1] and for many other medical conditions.[2] In the old pharmacopeias, Lugol solution was called *Liquor Iodi Compositus*. The minimum dose, called minim, was one drop containing 6.25 mg of elemental iodine, with 40% iodine and 60% iodide as the potassium salt. The recommended daily intake for iodine supplementation was 2-6 minims (drops) containing 12.5-37.5 mg elemental iodine. During the second half of the 20th century, iodophobic misinformation, disseminated progressively and deceitfully among the medical profession, resulted in a decreased use of Lugol, with iodized salt becoming the standard for iodine supplementation.[1] The bioavailable iodide from iodized salt is only 10%, and the daily amount of iodide absorbed from iodized salt is 200-500 times less than the amount of iodine/iodide previously recommended by US physicians. After World War II, US physicians were educated early in their medical career to believe that inorganic, non-radioactive forms of iodine were toxic. Adverse reactions to radiographic contrast media and other iodine-containing drugs were blamed on iodine. If a patient told his/her physician that he/she could not tolerate seafood, the physician told him/her that he/she was allergic to iodine.

Several forms of iodine prescribed by US physicians are listed in Table 1. The manmade organic forms of iodine are extremely toxic, whereas the inorganic non-radioactive forms are extremely safe.[1] However, the safe, inorganic, non-radioactive forms were blamed for the severe side effects of the organic iodine-containing drugs. A new syndrome, medical iodophobia, was recently reported[1] with symptoms of split personality, double standards, amnesia, confusion and altered state of consciousness. Medical iodophobia has reached pandemic proportion, and it is highly contagious (iatrogenic iodophobia). A century ago, non-radioactive forms of inorganic iodine were considered a panacea for all human ills,[2] but today, they are avoided by physicians like leprosy. Who or what killed iodine?

The first nail in the iodine coffin was the publication by Wolff and Chaikoff from UC Berkley in 1948,[3] describing their finding in rats administered iodide in increasing amounts by intraperitoneal injection. When serum inorganic iodide levels reached 0.2 mg/L, that is 10^{-6}M, radioiodide uptake by the thyroid gland became undetectable. The correct interpretation would be: that iodide sufficiency of the thyroid gland was achieved when serum inorganic iodide levels reach 10^{-6}M, as we previously discussed.[4] But Wolff and Chaikoff concluded that serum inorganic iodide levels at a concentration of 10^{-6}M blocks the synthesis of thyroid hormones, resulting in hypothyroidism and goiter. These authors did not measure thyroid hormones in the rats studied. Hypothyroidism and goiter were not observed in those rats. This fictitious phenomenon became known as the Wolff-Chaikoff effect.[5] Because these law-abiding rats refused to become hypothyroid and instead followed their normal physiological response to the iodide load, they were unjustly accused of escaping from the law of the Wolff-Chaikoff effect. Labeling these innocent rats as fugitives was a great injustice against these rodents.

The second and final nail in the iodine coffin was hammered in by Dr. Wolff in 1969.[5] By 1969, Wolff had moved to the National Institute of Health from UC Berkley. Wolff arbitrarily defined four levels of "iodine excess." The first level of excess started with intake above 0.2 mg/day, and iodide intake of 2 mg or more was considered "excessive and potentially harmful." In the next issue of this journal, this author discusses the Wolff-Chaikoff effect and presents evidence that the data reported in the rats by Wolff and Chaikoff[3] did not justify the interpretation of these data as applied to rats. Even worse, extrapolation of these findings to human subjects by Wolff[5] was inappropriate, and unscientific. By the 1970s, physicians concluded that one must avoid inorganic, non-radioactive iodine like leprosy, unless it was incorporated into the toxic, organic iodine-containing drugs. Then iodine could be tolerated because iodine could be blamed for the toxicity of these drugs.

Against this background, a 1993 publication by Ghent, *et al*,[6] reported the beneficial effects of 5 mg iodine ingested daily for approximately one year in 1,368 patients

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Table 1
Various Forms of Iodine/Iodide Used in Clinical Medicine and Their Toxicity Levels

	FORMS	TOXICITY
INORGANIC	1) Non-radioactive A) Iodides (i.e., SSKI) B) Tincture of iodine C) Lugol solution	Extremely safe
INORGANIC	2) Radioactive iodides for diagnostic and therapeutic purposes	Carcinogenic, Cytotoxic
ORGANIC	1) Naturally occurring A) Thyroid hormones B) Thyroidal iodolipids	Safe within physiologic ranges
ORGANIC	2) Man-made A) Radiographic contrast media B) Iodine-containing drugs (i.e., amiodarone)	Extremely toxic

with fibrocystic disease of the breast (FDB). This author became aware of Ghent's publication in 1997. Ghent's study did not confirm Wolff's prediction that daily iodine intake of 2,000 µg (2 mg) was "excessive and potentially harmful." Based on academic credentials and reputation, the opinion of thyroidologist Wolff from the National Institute of Health, would prevail over the findings of Ghent, *et al*. However, being interested in facts only, not in preconceived opinions of famous thyroidologists, an extensive search of the literature on iodine in medicine was initiated seven years ago by the author, combined with some original clinical research.

The literature search revealed that 60 million mainland Japanese consume a daily average of 13.8 mg of elemental iodine, and Japan is one of the healthiest nations, based on overall well-being and cancer statistics.[4] Japanese women do not stop consuming iodine-rich foods during pregnancy, and Japanese fetuses are exposed to maternal peripheral levels of iodide at concentrations of 10^{-5}M to 10^{-6}M.[1,4] Either the Japanese are mutants, capable of thriving on toxic levels of iodine or we have been grossly deceived, and the human body needs at least 100 times the RDA, which was established very recently in 1980 and confirmed in 1989![7]

The literature search also revealed that US physicians over the past century used Lugol solution extensively in their practice for both hypo- and hyperthyroidism.[1] The recommended daily amount for iodine supplementation, as previously mentioned, was from 2-6 drops containing 12.5-37.5 mg elemental iodine with 40% iodine and 60% iodide as the potassium salt. As late as 1995, it was still the recommended amount in the *19th Edition of Remington's Science and Practice of Pharmacy*. For hyperthyroidism, physicians then used Lugol solution in daily amounts ranging from 6-180 mg, with the most common dose of 90 mg resulting in success rates as high as 90%.[1] Radioiodide and goitrogens called antithyroid drugs were not available to US physicians until the late 1940s, after World War II.

With the advent of radioiodide and goitrogens as alternatives to Lugol solution in patients with hyperthyroidism, thyroidologists became very destructive, causing hypothyroidism in 90% of these unfortunate patients.[1] It is of interest to mention that both radioiodide and goitrogens were introduced by the same group of investigators as a replacement to Lugol in the treatment of hyperthyroidism, at about the same time iodophobic misinformation started appearing in the medical literature again authored by the same investigators.[1] How strange!

Thyroidologists suffer from selective iodophobia for the inorganic, non-radioactive forms of iodine combined with paradoxical iodophylia for radioactive iodide and the toxic, organic iodine-containing drugs. As an example, some thyroidologists recommend radioiodide ablation of the thyroid gland in order to allow the reintroduction of the organic iodine-containing drug amiodarone in patients with a prior history of amiodarone-induced thyrotoxicosis.[8] Amiodarone is a toxic form of sustained-release iodine. The author has previously discussed the interesting observation that this antiarrhythmic drug becomes effective when the body has accumulated approximately 1.5 g of iodine.[8] This is exactly the amount of iodine retained by the human body when iodine sufficiency is achieved following orthoiodosupplementation.[7] Whole body sufficiency for inorganic, non-radioactive iodine/iodide results in optimal cardiac functions. Inorganic, non-radioactive iodine was never tested in clinical conditions for which physicians prescribe amiodarone. However, inorganic iodide is blamed for the severe side effects of this drug. Unbelievable, but true!

A review of the iodine literature revealed that British physicians recommended a similar range of daily intake of iodine in the form of hydrogen iodide as the ranges of iodine recommended by US physicians in the form of Lugol solution. The recommended daily intake of hydriodic acid syrup was 2-4 ml.[9] The syrup is prepared by the British apothecary from a stock solution containing 10% hydrogen iodide (HI), which is diluted 10-fold with

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syrups of different flavors. The syrup would contain 1% hydrogen iodide. This would compute to 10 mg iodide per ml. So, the recommended daily amount of elemental iodine was 20-40 mg.

After overcoming the delusion that inorganic, non-radioactive forms of iodine are toxic and becoming aware that the inorganic, non-radioactive forms of iodine were extremely safe and used extensively by US physicians for many medical conditions, the author initiated the Iodine Project. Clinical studies were performed five years ago to confirm Ghent's findings,[6] combined with some original research. The clinical aspects of this research were performed under contract at the Flechas Family Practice Clinic in Hendersonville, North Carolina under the supervision of Jorge D. Flechas, MD, and funded with grants from Optimox Corporation. The author designed the protocols and monitored the progress and completion of each project. Informed consent was obtained from all subjects participating in these projects.

Because administration of iodine 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 of Lugol. To prevent gastric irritation, the iodine/iodide preparation was absorbed unto a colloidal silica excipient; to eliminate the unpleasant taste of iodine, the tablets were coated with a thin film of pharmaceutical glaze. John C. Hakala from Hakala Apothecaries, in Lakewood, Colorado, compounded the tablets.[10]

To confirm the safety of the Lugol tablets, pilot studies were performed with tablets of Lugol containing 1.0-12.5 mg of elemental iodine. Following the pilot studies, 10 female subjects, seven with breast symptomatology, were studied for three months at 12.5 mg/day. Pre- and post-supplementation evaluation of blood chemistry, hematology, thyroid function tests, and ultrasonometry of the thyroid gland were performed. The results obtained in these female subjects using a tablet form of Lugol solution (Iodoral®, Optimox Corporation, Torrance, CA) at 12.5 mg/day for three months confirmed Ghent's observations, and the safety of the Lugol tablets. This was reported in *The Original Internist* in 2002.[10]

In order to build a database that could be used to develop a protocol for the implementation of iodine supplementation in FDB and other clinical conditions, a long-term study of Lugol tablets in female patients with FDB, using Ghent's scoring of FDB, was initiated four years ago at Dr. Flechas' clinic, supported by grants from Optimox Corporation. Dr. Flechas will present a preliminary report of his results on the use of Lugol tablets in FDB, using daily amounts of 12.5-50.0 mg of elemental iodine (See page 89). In 2003, Dr. David Brownstein joined the Iodine Project and became a very efficient spokesman for the orthoiodosupplementation program. He wrote a booklet published in 2004,[11] describing his experiences with this approach in his practice. Dr. Brownstein was invited to outline some key recommendations for the benefit of other health care practitioners based on his and his partners' experience so far in 3,000 patients. His article will be in next month's issue.

Five years ago, urine samples were sent to local laboratories for the measurement of iodide levels before and after orthoiodosupplementation. The iodophobic mentality became evident immediately. The reports came back with statements like "Greater than 500 µg iodide/24 hr., check for contamination." The author then switched to a large commercial laboratory catering to some 30,000 health care practitioners. The normal range of urine iodide levels for that laboratory was: 0.02-0.50 mg/24 hr. Together with urine iodide levels, this laboratory also performed urine levels of minerals, trace elements, and toxic metals.

The bioavailability of a Lugol tablet (Iodoral®) containing 12.5 mg elemental iodine was evaluated by measuring 24-hour urine levels of iodide together with the minerals, trace elements, and toxic metals before and after administration of this preparation. The results obtained following iodine supplementation revealed that in some subjects, the urine levels of mercury, lead, and cadmium increased by several times after just one day of supplementation. For aluminum, this increased excretion was not observed usually until after one month or more on the iodine supplementation.

Based on data available in the medical literature, urinary iodide levels are considered the best index of iodine intake.[12] The initial results of the bioavailability study suggested that the Lugol tablets were not well absorbed since only 20-30% of the administered amount was recovered in the 24-hour urine collection of five subjects tested.[12] Just in case medical textbooks were wrong, and the explanation for the low recovery of iodide is body retention of iodine/iodide, the supplementation was continued for one month and then urine iodide levels were measured again in the 24-hour urine collection. Medical textbooks were wrong. The subjects excreted a mean of 50% of the amount ingested, with one subject excreting 96% of the ingested amount.[12]

The implication of such observation was that an iodine/iodide-loading test could be developed to assess not just thyroid sufficiency for iodine but requirement of the

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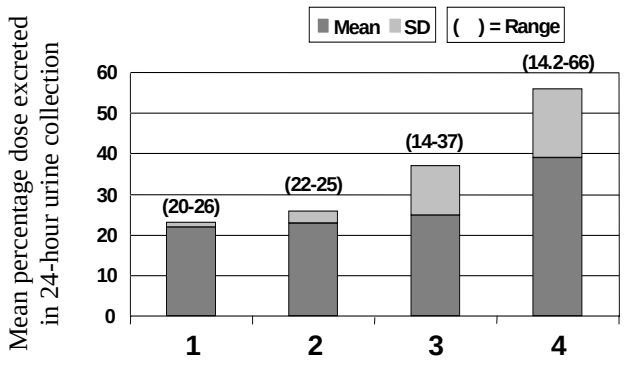
Figure 1

Effect of Increasing Intake of Iodine/Iodide on Percentage Urinary Excretion of Ingested Amounts



Quantity of Iodoral® tablets used in loading test

(From Abraham reference 1)

whole human body for that essential element. However, instead of a one-month loading test, further studies were performed to shorten this test to a single ingestion of the preparation. Another group of six subjects, (three male and three female) were evaluated with 24-hour urinary iodide levels after ingesting one, two, and three tablets of the same preparation. The mean percentage excretions (± SD) were 22±1.2% for one tablet, 23±2.8% for two tablets, and 25±12.3% for three tablets. In a third group of six subjects, urine iodide levels were evaluated following four tablets of the same preparation. The mean pecentage excretion was 39±17.2%. (See Figure 1.) For the loading test, a single ingestion of four tablets was chosen, because this dose resulted in the highest mean percentage iodide excreted with the widest interindividual variations.

Because of the improved overall well-being reported by the subjects who achieved 90% or more iodide excreted, sufficiency was arbitrarily set as 90%. Implementation of orthoiodosupplementation based on the loading test revealed that sufficiency was not achieved in some subjects even after two years of iodine supplementation at 1-2 tablets/day. To achieve sufficiency within three months, most subjects required 3-4 tablets/day (37.5-50.0 mg), and some obese and diabetic subjects required even more than 50 mg/day to achieve and maintain sufficiency.

Six normal subjects with normal body weight (three men and three women) ingested four tablets of Iodoral® (50mg)/day for three months and were followed with monthly loading tests. After three months on orthoiodosupplementation, only one female subject did not reach sufficiency. Following one month off orthoiodosupplementation, the loading test was repeated. All six subjects showed a significant drop of the iodide concentration in the 24-hour urine collection. In all five subjects who had reached sufficiency, the percentage of the oral amount excreted in the 24-hour urine collection was below 90%, ranging from 64-82%. This drop in percentage excretion has been observed in some subjects after they have achieved whole body sufficiency for iodine, even though they continued to ingest 50 mg iodine/day regularly. Increased exposure to goitrogens may be the explanation. In some of these cases, the author has observed increased urine bromide excretion as high as 20-fold baseline levels following the loading test, concomitant with a drop in percentage iodide excreted.

Whole body sufficiency for iodine correlated well with overall well-being, and some subjects could tell when they achieved sufficiency even before knowing the results of the test. Iodine sufficiency was associated with a sense of overall well-being, lifting of a brain fog, feeling warmer in cold environments, increased energy, needing less sleep, achieving more in less time, experiencing regular bowel movements and improved skin complexion. In some subjects with overweight or obesity, orthoiodosupplementation resulted in weight loss, decreased percentage body fat and increased muscle mass. Following orthoiodosupplementation, increased urinary excretion of the goitrogens fluoride and bromide and the toxic metals mercury, lead, cadium, and aluminum was observed; marked improvement of fibrocystic disease of the breast occurred following three months of iodine supplementation at 50 mg/day. In three patients with polycystic ovary syndrome with olygomenorrhea, orthoiodosupplementation resulted in regularization of the menstrual cycle. In patients on thyroid hormones, orthoiodosupplementation resulted in a decreased requirement to much lower levels of thyroxine and in some cases, resulted in the complete discontinuation of this hormone. This decreased requirement for thyroid hormones following orthoiodosupplementation was observed in a female patient with total thyroidectomy, suggesting that iodine not only improves thyroid function but also has an effect at the target organ level. In diabetic patients on insulin, orthoiodosupplementation resulted in better control of this condition, and in some cases alleviated this condition without the need for insulin. In hypertensive patients, whole body iodine sufficiency resulted in normalization of blood pressure without medications. Similar observations were reported by other physicians using this program. Best results were achieved when orthoiodosupplementation was combined with a complete nutritional program emphasizing magnesium instead of calcium.[1] The occurrence of side ef-

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fects was rare and this topic will be discussed by Drs. Flechas and Brownstein in other articles. The Wolff-Chaikoff effect was not observed in some 4,000 patients on orthoiodosupplementation for as long as three years with daily intake ranging from 12.5-50.0 mg. This is the combined experience of Drs. Flechas and Brownstein.

The serum level of inorganic iodide supposedly causing hypothyroidism and simple goiter by the Wolff-Chaikoff effect is 0.2 mg/L.[3] The author previously calculated that in an adult, this level would be achieved with a daily ingestion of 12.5 mg elemental iodine.[1] Since this amount of Lugol solution was used safely by three generations of US physicians for iodine supplementation, and since we have observed that patients reported optimal mental and physical performances on 3-4 times that amount, we would like to propose a redefinition of the Wolff-Chaikoff effect as optimal mental and physical performances. This seems to be the most congenial solution to the Wolff-Chaikoff forgery. In this way, the names of Wolff and Chaikoff would continue to be mentioned in the medical literature, but associated with the real and pleasant outcome of orthoiodosupplementation, that is optimal mental and physical performances, not the gloomy, fictitious outcome proposed by Wolff,[5] that is goiter and hypothyroidism.

Three years ago, the author decided to set up the iodide assay *in situ*, using the ion-selective electrode procedure. To improve specificity, chromatography separation of the halides was performed on anion-exchange resins.[12] Halides and other substances interfered in the assay of iodide (Table 2). One full year was required to optimize the assay for iodide. In January 2003, Dr. Flechas and John C. Hakala were invited as guests of Optimox Corporation to attend a two-day workshop in order to learn this technology. Dr. Flechas quickly learned this procedure and set it up in his own clinical laboratory. At first, the loading test was performed on his patients only, but eventually, he made this service available to other clinicians. Packets containing four tablets of Iodoral® were made available for the loading test. In another article in this issue, Dr. Flechas will present the results of the loading tests he gathered during the previous two years and his experience with the implementation of orthoiodosupplementation in his practice.

In order to test the reliability of commercial laboratories in the performance of urine iodide assay at the levels observed following the loading test, Optimox Corporation financed a pilot study on five subjects who underwent the loading test. Samples were sent to two commercial laboratories for iodide measurement. These laboratories used the ICP-MS method. The same samples were also measured by the author *in situ* (Table 3). Lab #1 consistently underestimated and Lab #2 consistently overestimated the levels measured in the potentiometric laboratory of the author. Physicians using the iodine/iodide loading test to follow their patients on orthoiodosupplementation will depend on the results of these tests for evaluation of whole body iodine sufficiency and clinical response. Therefore, the measurement of urine iodide levels must be accurate at concentrations two orders of magnitude greater than the normal range of these laboratories, that is 0.02-0.50 mg/24 hr.

The supervisor of Lab #1 was contacted. He was very helpful and explained that his equipment was calibrated to measure the range of urine iodide levels expected in the US population, that is 0.02-0.50 mg/24 hr, and therefore, it would not be reliable at levels 100 times higher. He performed recovery experiments and confirmed that his equipment underestimated the true value by 50%

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Table 2

Interferences in the Ion-Selective Electrode Assay of Halides and Procedures for Preventing These Interferences

Halides	Interferences*	Procedures for preventing interference
Chloride	$OH^- = 80$ $Br^- = 3 \times 10^{-3}$ $I^- = 5 \times 10^{-7}$	1) Acidification 2) Chromatographic separation from other halides
Fluoride	OH^-	Acidification with Orion spcial ISA: TISAB, added to urine samples at equal volumes
Bromide	$OH^- = 3 \times 10^4$ $Cl^- = 400$ $I^- = 2 \times 10^{-4}$	Chromatographic separation from other halides
Iodide	$Cl^- = 10^{-6}$ $Br^- = 5 \times 10^3$	Chromatographic separation from other halides

* The maximum allowable concentrations of interfering substances express as the molar ratio of the interfering ion concentration to the sample halide concentration. If the ratio is exceeded, the data generated by electrode will become unreliable. Information supplied by Thermo Orion Corporation.

within the range of iodide levels expected for the loading test. He showed great interest in offering this service to his clients, and the author supplied him with the details of the technique using ion-selective electrode, following chromatography on strong anion exchangers.

The chromatographic system was modified in order to measure accurately the other halides: chloride, fluoride, and bromide, using a positive displacement manifold designed by the author.[8] The flowchart for this chromatographic separation is displayed in Figure 2. Comparison of results obtained before and after chromatographic purification of the halides chloride, fluoride, bromide, and iodide revealed the following. In 24 urine samples analyzed, the values obtained for chloride and fluoride by the direct assay, using Thermo Orion reagents and the values obtained after chromatography were not significantly different. However, for bromide and iodide, the direct assay overestimated significantly the values obtained following chromatography. For iodide, the direct assay overestimated by two-fold on the average, the levels obtained following chromatography in urine samples obtained prior to iodine supplementation. Even after iodine supplementation, significant differences were observed in the iodide levels of some samples measured by these two procedures. It was decided to perform chromatography on all samples prior to analysis by the iodide-selective electrode, no matter the expected iodide levels.

Orthoiodosupplementation resulted in marked increase in bromide excretion, and to a lesser extent in fluoride also. The results obtained in the first five subjects studied are displayed in Table 4. The results observed for bromide in subject #5 were so surprising that they were published as a letter to the editor of *Townsend Letter*.[13] These findings have since been replicated in a large number of tests. Female patients with breast cancer seem to retain more iodine on the loading test than normal subjects and excrete more bromide than normal subjects. This needs to be confirmed using a well-designed protocol since this observation is anecdotal on a small number of patients.

Recently, the author extended the ion-selective electrode assay to serum samples.[8] Evidence for an enterohepatic circulation of inorganic iodine was observed for the first time. Serum iodide levels reached peak values of 1.5-2.2 mg/L between two and four hours post ingestion of Iodoral® in subjects ingesting 3-4 tab/day. A second peak of serum iodide after eight hours following the first peak was observed in some subjects suggesting that serum iodide undergoes an enterohepatic circulation. Se-

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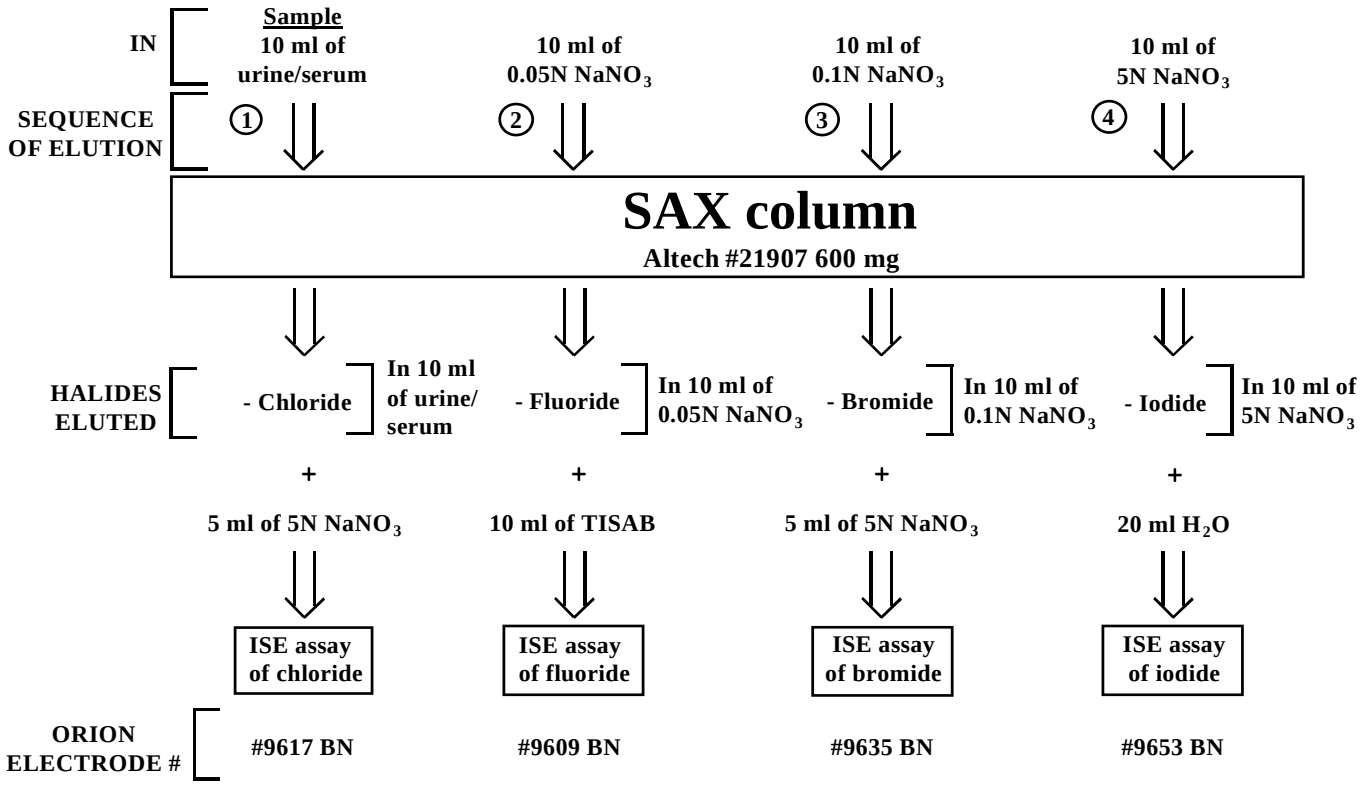
Figure 2

Flowchart Describing the Combined Measurement of Chloride, Fluoride, Bromide, and Iodide in the Same Urine or Serum Sample by Prior Chromatography on Anion-Exchange Resin Cartridges Fitted with the 10 ml Plastic Syringes in a Positive Displacement Manifold (PMD).[11]



rum iodide levels were still elevated 24 hours after the loading dose, ranging from 0.3-0.6 mg/L.[3,7]

In order to assess the presence of iodine and iodate (the oxidized forms) in serum following orthoiodosupplementation, serum iodide levels (the reduced form) were measured by ion-selective electrode before and after reduction with sodium metabisulfate. The three inorganic forms of the element iodine consumed by human subjects are 1) the negatively charged reduced iodide; 2) the negatively charged highly oxidized iodate IO^-_3; and 3) the neutral oxidized iodine I_2. The iodide selective electrode is influenced only by negatively charged forms of this element, that is, iodide I^- and iodate IO^-_3. Experiments performed by the author with sodium iodate revealed that the iodate molecule, because it is larger in size than iodide, did not have any appreciable effect on the electromotive force (EMF) of the electrode, even at concentrations 10,000 times higher than the amount of iodide influencing significantly the EMF of the selective electrode.

Pilot studies were performed in order to quantify the amount of the reductant needed for the reduction of iodine and iodate to iodide. Almost 10 times more reductant was required for the reduction of iodate to iodide than iodine to iodide. The reduction of iodate resulted in the formation of iodine first, then iodide. When this procedure was applied to urine samples, no significant difference was observed between pre- and post-reduction levels, suggesting that only iodide, the reduced form, was present in urine. However, serial serum samples obtained for 24 hours following the loading test, showed a significant difference in the serum iodide levels between pre- and post-reduced samples within the first two hours in a female subject, with post-reduction levels 5-10% higher. This suggests the presence of serum iodine early after ingestion of the Lugol tablets. Iodine obviously is not completely reduced to iodide in the intestinal tract during absorption as mentioned in medical textbooks. In another female subject post-orthoiodosupplementation for one month, a second peak of serum iodine was observed eight hours after the first peak. Apparently, iodine is not reduced to iodide by the liver during enterohepatic circulation. There was no significant difference in the iodide measured following the addition of reductant to serum for the conversion of iodine to iodide or following the addition of 10 times more reductant for the conversion of iodate to iodide. Therefore, there was no evidence of iodate in the serum samples analyzed. The oxidation of iodine to iodate in biological systems has not been reported and this metabolic pathway of iodine probably does not occur *in vivo*. The only source of peripheral iodates would be from ingested food and drink. The author has not been able to locate a publication dealing with the measurements of serum iodate following ingestion of iodate. It is an easy experiment to carry out.

Table 3

Iodide Levels Measured in 24-hour Urine Collections of 5 Subjects Following the Iodine/Iodide Loading Test: A Comparison of Results Obtained from 3 Different Laboratories

Subject	Sex	Commercial Lab 1 (mg/24h)	Commercial Lab 2 (mg/24h)	Optimox R&D Lab (mg/24h)
1	F	14.0	37.8	23.1
2	F	12.0	20.8	19.0
3	M	7.0	23.8	12.5
4	M	11.0	99.0	34.7
5	M	12.0	41.9	19.0

* Urine iodide levels measured by Induction-Coupled Plasma — Mass Spectrometry.
** Urine iodide levels measured by Ion Selective Electrode Assay.

Serum inorganic iodide levels are a good index of the bioavailability of ingested iodine/iodide. Serum inorganic iodide is cleared rapidly by the kidneys with a daily clearance rate of 43.5 L.[7] At steady state condition, the serum iodide levels expected for patients receiving 50 mg iodine/day should be approximately: serum iodide (mg/L) = daily intake (mg)/43.5 L = 50 mg/43.5 = 1.15 mg/L.[7] If patients continue to excrete low levels of iodide after orthoiodosupplementation for three months, serum inorganic iodide levels are indicated to assess whether this is due to decreased absorption or increased demand. Malabsorption of iodine/iodide would result in very low serum inorganic iodide levels (10^{-8}M) in the presence of low urinary excretion. We have not observed a case of malabsorption of iodine yet, when iodine supplementation was in the range of 12.5-50.0 mg/day. However, the author has previously reported low absorption of sodium iodide from salt.[7] On a molar basis, there is 30,000 times more chloride than iodide in iodized salt. Due to competition for absorption by the halide chloride, only 10% of iodide in iodized salt is absorbed.

Obesity increases the requirement for iodine[7] and up to 100 mg elemental iodine/day may be required to achieve and maintain sufficiency. Another factor in-

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volved in the increased demand for iodine is the presence of excessive amounts of goitrogens from the diet and lifestyle. For example, smoking increases serum thiocyanate levels, interfering with the sodium/iodide symporter function. Sources of goitrogens are available from medical textbooks,[14] although the halides fluoride and bromide are not listed as goitrogens. Fluoride interferes with the uptake of iodide by the thyroid gland symporter system, but it is itself not transported inside the thyrocyte,[15] suggesting that fluoride causes oxidative damage to the halide-binding site of the symporter. The author previously discussed the goitrogenic effect of bromide even at low concentrations.[1] Patients who used water from wells and municipal plants may be exposed to potassium perchlorate, a very powerful goitrogen that behaves like fluoride, binding to the halide-binding site of the symporter without itself being symported. A recent Internet publication by Kirk, *et al*,[16] reported the presence of high concentrations of perchlorate in dairy milk sold in grocery stores and in human milk. The mean levels of perchlorate were five times higher in breast milk than dairy milk. Perchlorate has a selectivity factor of at least 30 over iodide. To compete effectively against this goitrogen, the peripheral concentration of inorganic iodide must be at least 100 times higher than the concentration of perchlorate. Kirk, *et al*,[16] observed that breast and dairy iodide levels were inversely correlated with the levels of perchlorate. Perchlorate and fluoride, due to their high redox potential, may cause oxidative damage to the halide-binding site, decreasing its efficiency for iodide transport.

If the pre-orthoiodosupplementation loading test report shows 90% or more of the ingested iodine in the 24-hour urine collection of patients on a Western diet, serum inorganic iodide levels are indicated to rule out an iodide transport defect or damage not just in the thyroid gland but throughout the whole body. In our experience, this is very rare and was observed in only two cases. The intestinal absorption of iodine/iodide involves a different mechanism than the uptake of iodide by target cells via the sodium/iodide symporter. For example, chloride competes with iodide in the intestinal tract[7] but chloride has no detectable effect on the iodide symporter system.[17] This explains why a patient with iodide transport damage is able to absorb iodine/iodide efficiently but unable to transfer peripheral iodine/iodide into the cells. Peripheral iodide is cleared very rapidly by the kidneys, resulting in quantitative recovery of ingested iodine/iodide in the urine in a patient who is very iodine-deficient, if the cellular transport system is defective. In those cases, serum inorganic iodide levels 24 hours after the loading test will be low, even though the loading test suggests whole body sufficiency for iodine. In two obese female patients with poor clinical response to orthoiodosupplementation, high urinary iodide excretion was associated with serum inorganic iodide levels below 10^{-6}M (0.13 mg/L). The expected serum levels associated with high urinary iodide excretion should be between 5×10^{-6}M to 10^{-5}M.[7]

Although congenital hypothyroidism due to sodium/iodide symporter defect is extremely rare, milder forms of iodine/iodide transport defect/damage throughout the whole body may be more common and undetected. As of 1997, only 38 cases of congenital hypothyroidism due to sodium/iodide symporter defect were reported. Of interest is that in one of these cases,[18] a male Japanese subject, the diagnosis was not made until he was 30 years old. At the time of evaluation, he was euthyroid with a goiter while on the high iodine Japanese diet, but he got hypothyroidism on a Western diet. Administration of 50 mg iodide restored euthyroidism. An active transport system for iodide by a sodium/iodide symporter has been demonstrated in several organs besides the thyroid gland, capable of concentrating peripheral inorganic iodide 20- to 40-fold against a gradient.[19] The cellular uptake of iodide in some tissues may involve other mechanisms than the symporter system. Inorganic iodine/iodide has been detected in every organ and tissue examined, with relatively high levels in the thyroid gland, liver, lung, heart, and adrenal glands. The highest quantity of iodine was found in fat tissue and muscle.[8] Exposure to fluoride and perchlorate can cause oxidative damage to the halide-binding site of the sodium/iodide symport system, due to their high redox potential. In such cases, more than 50 mg iodine/day may be required to overcome the low efficiency of the iodine transport system. If the high iodide excretion prior to orthoiodosupplementation is due to significant amount of iodine in the diet of the patient, such as the diet of mainland Japanese, or if due to ingestion of medications containing iodine, fasting serum inorganic iodide levels will be between 5×10^{-6} and 10^{-5}M (0.65-1.30 mg/L). This is the range of serum iodide levels observed by the author when sufficiency is achieved.[7]

As mentioned previously, medical iodophobia has reached pandemic proportion, is highly contagious, and has wreaked havoc in the practice of medicine and on the US population. More misery and death in the US may have resulted from the Wolff-Chaikoff effect than both World Wars combined. Due to thyroid fixation, thyroidologists dictate the need for iodine. However, thyroidologists suffer from selective iodophobia for the inorganic, non-radioactive forms of iodine combined with a paradoxical iodophylia for radioiodide. In a sur-

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vey of US thyroidologists, some 70% used radioiodide to treat hyperthyroidism[1] instead of the Lugol solution used previously to treat this condition safely and effectively with a success rate as high as 90%, compared to a thyroid destruction rate of 90% with radioiodide. The love affair of thyroidologist for radioiodide is not limited to its therapeutic application. Radioiodide is used extensively for diagnostic purposes although safer methods exist to obtain the same information. Fluorescence scanning of the thyroid gland gives more useful information than isotope scanning.[19] Okerlund commented, "The types of images obtained from fluorescent thyroid scanning are indistinguishable from those of isotope scanning, since the same electronics and data presentation systems are used. The size, shape, and positional relationships of the thyroid lobes are therefore comparable to isotope scanning, with the right lobe larger in the majority of normal cases, the two lobes of equal size in a smaller number, and the presence of a larger left lobe in a still smaller number." Fluorescent scanning gives additional information on the amount of stable iodine in the thyroid gland.

Okerlund[20] reported that thyroid hormone therapy and irradiation of the thyroid gland cause a depletion of iodine from the thyroid gland. Ingestion of thyroid hormones for three months or more resulted in very low levels of thyroidal stable iodine reaching the detection limit of the equipment. "The finding that previously irradiated thyroid glands are sometimes iodide depleted, coupled with the observation that the iodide depleted gland in experimental animals is physiologically more sensitive to the effects of pituitary thyrotropin (TSH), may lead to changes in the understanding of radiation-induced thyroid disease and to changes in the clinical management of at least some of these patients, who are known to be at high risk for thyroid tumor development." Okerlund[20] is suggesting that patients on thyroid hormones and receiving radioiodide or radiation therapy should be supplemented with iodine as a preventative measure against the carcinogenic effect of these interventions in iodine depleted thyroid glands.

For the US population, Okerlund[20] reported a mean value of around 10 mg iodine/thyroid, with a range of 4-19 mg. In 56 patients suffering from autoimmune thyroiditis, but with normal thyroid function, a mean value of 4.8 mg/thyroid was reported. In 13 patients with autoimmune thyroiditis and hypothyroidism, the mean value was 2.3 mg/thyroid. In 12 patients treated with amiodarone, a toxic form of sustained-release iodine, Jonckheer[21] reported a mean ± SD of 30.5±9.2 mg/thyroid. In five patients who experienced thyroid dysfunction during amiodarone therapy, (three with hypo- and two with hyperthyroidism), the iodine content of the thyroid gland was very low, being 4-10 times lower. The author previously calculated that the theoretical maximum of thyroidal iodine in the adult is 50 mg.[7] In the 12 patients on amiodarone therapy, the mean ± SD was 30.5±9.2 mg, giving a 95% confidence limit ranging from 12.0-48.9 mg/thyroid. The upper limit of measured iodine in the thyroid gland of these patients, 48.9 mg is very close to the theoretical maximum of 50 mg/thyroid.

Why don't thyroidologists use fluorescent scanning of the thyroid instead of isotope scanning? One possible reason is the fact that this procedure exposed the harmful effect of thyroid hormone therapy and radioiodide in depleting the thyroid gland of iodine. Low thyroid iodine is associated with thyroid hyperplasia and cancer.[1] Could thyroid hormones cause the same iodine depletion in breast tissue? The prevalence of breast cancer is higher in women on thyroid hormones.[4] Thyroidologists use thyroid hormones extensively in their practice without supplementing their patients with iodine. Fluorescence scanning of the thyroid gland should be implemented. Thyroidologists would then have to face the damages they are causing to the thyroid gland and consequently to their patients.

Medical iodophobia resulted in the removal of iodate from bread 20 years ago, replacing it with the goitrogen bromate. This was associated with an increased prevalence of obesity, diabetes, and hypertension, as well as thyroid and breast cancer.[1] A recent publication reported an association between low iodine intake in women during pregnancy and attention deficit and hyperactivity disorder (ADHD) in their offspring.[22] However, children diagnosed with ADHD do not demonstrate prenatal thyroid dysfunction, reflected in the newborn serum thyroxine levels.[23] The most plausible explanation is a decreased sensitivity of the nuclear thyroid hormone receptor to thyroid hormones. We previously reported evidence for improved receptor response to thyroid hormones following orthoiodosupplementation.[1,4] Therefore, iodine is not only necessary for the synthesis of thyroid hormones but also for their effect on target cells. This effect is probably due to iodination of the thyroid hormone receptor.[1,4] The essential element iodine, which is the inorganic, non-radioactive forms, deserves more attention from researchers and clinicians. It may be the missing link in patients currently resistant to conventional hormonal therapy.

About the Author

Guy E. Abraham, MD, is a former Professor of Obstetrics, Gynecology, and Endocrinology at the UCLA

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School of Medicine. Some 35 years ago, he pioneered the development of assays to measure minute quantities of steroid hormones in biological fluids. He has been honored as follows: General Diagnostic Award from the Canadian Association of Clinical Chemists, 1974; the Medaille d'Honneur from the University of Liege, Belgium, 1976; the Senior Investigator Award of Pharmacia, Sweden, 1980. The applications of Dr. Abraham's techniques to a variety of female disorders have brought a notable improvement to the understanding and management of these disorders. Twenty-five years ago, Dr. Abraham developed nutritional programs for women with premenstrual tension syndrome and postmenopausal osteoporosis. They are now the most commonly used dietary programs by American obstetricians and gynecologists. Dr. Abraham's current research interests include the development of assays for the measurement of iodide and the other halides in biological fluids and their applications to the implementation of orthoiodosupplementation in medical practice.

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Table 4

Fluoride and Bromide Levels Measured in 24-hour Urine Collections of 5 Subjects Following the Iodine/Iodide Loading Test Before and After 1 Month on Iodoral® at 3 Tab/Day

		Fluoride (mg/24)			Bromide (mg/24h)		
Subject	**Sex**	**Control**	**Before Iodoral®**	**After 1 Month of Iodoral®**	**Control**	**Before Iodoral®**	**After 1 Month of Iodoral®**
1	F	0.40	0.80	0.60	6.8	24.2	18.6
2	F	0.065	1.20	0.80	12.5	36.4	34.0
3	F	0.62	1.80	—	4.8	5.2	—
4	M	0.35	0.62	0.44	6.8	34.8	32.0
5	M	0.05	0.93	0.79	18.4	336.0	288.0
6	M	1.20	1.40	1.20	12.2	24.5	24.0