

Extrathyroidal Benefits of Iodine

Donald W. Miller, Jr., M.D.

ABSTRACT

In addition to being an essential element in thyroid hormones, iodine has many biological functions. The recommended dietary intake of 100–150 mcg is perhaps 100 times too low. Potential benefits of higher amounts include enhancement of immune function and reducing the incidence of breast cancer. Older studies of therapeutic benefits, particularly with respect to fibrocystic breast disease, need to be updated and expanded.

Most physicians and surgeons view iodine from the narrow perspective of its use as an antiseptic that disinfects drinking water and prevents surgical wound infections, and its presence in thyroxine (T4) and triiodothyronine (T3). They consider iodine's sole function in the body is to be organically bound to the phenyl ring of tyrosine in thyroid hormones. The thyroid gland needs only a trace amount of iodine, 70 mcg/day, to synthesize the requisite amounts of T4 and T3 used to regulate metabolism and ensure normal growth and development.

Everyone agrees that a lack of iodine in the diet causes a spectrum of disorders that includes, in increasing order of severity, goiter and hypothyroidism, mental retardation, and cretinism.

In an effort to prevent these iodine deficiency disorders, which the World Health Organization estimates afflict 30 percent of the world's population,¹ health policymakers all subscribe to the same reference daily intake (RDI) for this element. First proposed in 1980, the RDI (formerly called the recommended dietary allowance) for iodine is 100–150 mcg/day, an amount considered sufficient to meet the requirements of nearly all, 97–98 percent of healthy individuals.^{2,3} Medical authorities consider an iodine intake greater than 750 mcg/day, an amount considerably more than that needed for production of thyroid hormones, to be "excessive." But there is growing evidence that iodine provides important extrathyroidal benefits when taken in milligram amounts, in doses 100 times more than its RDI.

Iodine Consumption in Japan and the United States

Seaweed is a potent source of iodine, and the Japanese eat a lot of it. More than 95 percent of the iodine mainland Japanese consume comes from seaweed, which includes kelp (brown algae), nori sheets (red algae) with sushi, and chlorella (green algae). The concentration of iodine in these marine plants ranges from 0.5–8.0 mg/g. Terrestrial plants, in contrast, contain only trace amounts of iodine, 0.001 mg/g. In 1964, the Nutrition Section of Japan's Bureau of Public Health found that people in Japan consumed a daily average of 4.5 g of seaweed with measured iodine content of 3.1 mg/g, or 13.8 mg of iodine.⁴ According to bureau officials, seaweed consumption in

Japan is now 14.5 g, providing 45 mg of iodine if its iodine content, which was not measured, has remained unchanged.⁵ Studies measuring urine concentration of iodine confirm that the Japanese consume iodine in milligram amounts.⁶ And researchers have determined that residents on the coast of Hokkaido eat a quantity of seaweed sufficient to provide a daily iodine intake of 200 mg/day.⁷ Saltwater fish and shellfish contain iodine, but one would have to eat 15–25 pounds of fish to get 13 mg of iodine.

The average daily intake of iodine in the U.S. is 240 mcg, well within the range that the International Council for the Control of Iodine Deficiency Disorders defines as an optimal iodine intake, 150 to 299 mcg/day.⁸ Though considered "iodine sufficient," this amount, 0.24 mg, is a small fraction of that consumed in Japan. Also, this is half the amount of iodine that Americans consumed 30 years ago, when iodine was used more widely in the dairy industry and as a dough conditioner in making bread. Now it is only added to table salt, and 45 percent of American households buy salt without iodine, which grocery stores also sell. And over the last 25 years those who do use iodized table salt have decreased their consumption of it by 65 percent. As a result, 15 percent of the U.S. adult female population, one in seven, suffers from iodine deficiency, as reflected in a urinary iodine concentration of less than 50 mcg/L.^{9,10} One in seven American women now also develop breast cancer during their lifetime (30 years ago it was 1 in 20).¹¹

Although one cannot draw cause-and-effect conclusions by looking at single factors in the context of general health statistics, the incidence of breast cancer in the U.S. is the highest in the world, and in Japan, until recently, it was the lowest. Japanese women who emigrate from Japan or adopt a Western-style diet have a higher rate of breast cancer compared with those who eat seaweed.^{12,13}

Life expectancy in Japan is 81.25 years, compared to 77.85 years in the U.S. Infant mortality rate in Japan is the lowest in the world, 3.5 deaths under age 1 per 1,000 live births, half the infant mortality rate in the United States.¹⁴ While no conclusions can be drawn from such figures concerning the benefits of iodine supplementation, they do suggest that iodine intake nearly 200 times greater than in the U.S. is unlikely to be toxic.

Iodine as Antioxidant

Oxygen breeds reactive oxygen species, which include superoxide anion, hydrogen peroxide, and hydroxyl radical. The hydroxyl radical wreaks havoc by reacting with lipids in cellular membranes, nucleotides in DNA, and tyrosine and sulfhydryl groups in proteins. In *Laminariales*, a species of kelp, Kupper et al. show how inorganic iodine functions as an antioxidant. It neutralizes hydrogen peroxide in a two-step process, converting it first to hypoiodous acid and then water, thereby preventing it from becoming a hydroxyl radical. These investigators also found that this alga absorbs increased amounts of iodine when placed under oxidative stress.¹⁵

Other investigators have shown that iodide is a specific scavenger of hydroxyl radicals,¹⁶ and that it, like vitamin C, increases the antioxidant status of human serum.¹⁷ Iodine defends brain cells in rats from lipid peroxidation, attaching to the double bonds of polyunsaturated fatty acids in cellular membranes, rendering them less susceptible to free radicals.^{18,19}

As an interesting aside, cyanobacteria (blue-green algae), the most primitive organisms capable of photosynthesis, have an affinity for iodine, although it is present in seawater only in minute amounts, about 0.05 parts per million. Photosynthesis, with chlorophyll as a catalyst and sunlight as an energy source, converts six molecules of carbon dioxide and six molecules of water into one molecule of dextrose, with six molecules of oxygen as a waste product. In cyanobacteria, which are considered in large part the source of the oxygen in earth's atmosphere,²⁰ iodine probably serves as an antioxidant, while it is toxic to all other, non-photosynthesizing bacteria.²¹ Indeed, iodine's ability to neutralize reactive oxygen species apparently made photosynthesis possible.

Algae, which also photosynthesize, are a dietary source of organic iodinated molecules and thus serve as a primitive "thyroid gland" for some invertebrates.²²

Apoptosis and Cancer

Iodine induces apoptosis. This process of programmed cell death is essential to growth and development (fingers form in the fetus by apoptosis of the tissue between them) and for destroying cells that represent a threat to the integrity of the organism, like cancer cells and cells infected with viruses. It is hypothesized that anticancer function may well prove to be iodine's most important extrathyroidal benefit.

Zhang and coworkers spliced genes that enhance iodine uptake and iodination of proteins—the iodine pump (sodium-iodide symporter) and thyroperoxidase genes—into human lung cancer cells. Inorganic, nonradioactive iodine induced apoptosis in more than 95 percent of these genetically modified cancer cells in vitro. When implanted in mice, iodine effectively limited the growth of the genetically modified tumor xenografts, compared with unmodified tumors ($P < 0.001$).²³

Sekiya et al. have studied the effect of Mekabu, a kind of seaweed, on a cultured human breast cancer cell line. They have shown that it induces apoptosis by activating caspases 3, 6, and 8.²⁴ Shrivastava and coworkers have recently shown how molecular iodine (I_2) can also induce apoptosis in human breast cancer cell lines using a caspase-independent and mitochondrial-mediated apoptotic pathway.²⁵

Epidemiological studies show that a high intake of iodine is associated with a low incidence of breast cancer, and a low intake with a high incidence of breast cancer.^{26,27} Animal studies provide evidence that iodine reduces the incidence of breast cancer, arguing for a causal association to these epidemiological findings. Garcia-Solis and coworkers analyzed the effect of iodine on preventing breast cancer in rats given the carcinogen nitrosomethylurea. Molecular iodine (I_2) was more effective than potassium iodide, significantly reducing the cancer incidence to 30 percent, compared to 73 percent in controls ($P < 0.05$).²⁸ Another study, using DMBA as the carcinogen, showed the same effect ($P < 0.01$).²⁹

Other evidence, adding biologic plausibility to the hypothesis that iodine prevents breast cancer, includes the finding that the

ductal cells in the breast, the ones most likely to become cancerous, are equipped with an iodine pump, the sodium-iodide symporter, the same one the thyroid gland has, to absorb this element.³⁰ And people with goiters resulting from iodine deficiency have a three times greater incidence of breast cancer.³¹

Other Functions of Inorganic Iodine

Extrathyroidal iodine also has other functions, which warrant further study. It removes toxic chemicals and biological toxins;³² suppresses autoimmunity;³³ strengthens the T-cell adaptive immune system;^{34,35} and protects against abnormal growth of bacteria in the stomach, *Helicobacter pylori* in particular.³⁶

Organs with Iodine-Concentrating Ability

In addition to the thyroid, other organs have a sodium-iodide symporter pump. Total-body scintiscans taken after administration of radioactive iodine (^{125}I) show that stomach mucosa absorbs intravenously injected iodine. Lactating mammary glands and the three paired salivary glands concentrate iodine almost to the same degree as does the thyroid, in a 40-fold increase over serum levels. The thymus, seat of the T-cell adaptive immune system, absorbs inorganic iodine. Scintiscans also show an increased uptake of iodine by the choroid plexus, which makes cerebrospinal fluid; in skin; and by joints, arteries, and bone.³⁷

"Expert Opinion" and Iodine

These data call into question the accepted view that the thyroid gland is the only organ that needs iodine. The following statement applies to "accepted views" in general and to those about iodine in particular: "When you seek a new path to truth, you must expect to find it blocked by expert opinion."³⁸

Expert opinion on iodine is now the purview of thyroidologists, and they often discount or ignore extrathyroidal actions of iodine. Many thyroidologists consider an iodine intake greater than 1 to 2 mg to be potentially harmful, citing the Wolff-Chaikoff effect³⁹ and an increase in TSH (thyroid stimulating hormone) concentration with intakes greater than this amount.²

The Wolff-Chaikoff effect, a temporary inhibition of thyroid hormone synthesis that supposedly occurs with increased iodine intake, is of no clinical significance.⁴⁰ And an elevated TSH, when present, is "subclinical"; i.e., it is not accompanied by any signs or symptoms of hypothyroidism.² Some people taking milligram doses of iodine, usually more than 50 mg/day, develop mild swelling of the thyroid without symptoms of hypothyroidism.⁴¹ The vast majority of people without thyroid disease can take iodine in doses ranging from 10 mg/day to 200 mg/day without any clinically adverse effects on thyroid function.⁴²

The truth is that the 26-year-old RDI for iodine is far too low—perhaps, citing the Japanese example, two orders of magnitude too low.

Therapeutic Use of Iodine in the Past

Iodine was first used to treat goiters. In 1779 the Coventry Remedy for goiter, which was very effective in treating this disease and long held secret, was published. The remedy turned out to be burnt sea sponge.

Then in 1811 Bernard Courtois, brewing soda to make saltpeter for gunpowder, discovered iodine. Andrew Fyfe, in 1816, found that sea sponge contains high quantities of iodine. Following this chain of evidence, a French physician, Jean Coindet, showed that tincture of iodine shrinks goiters.⁴³

The first controlled study using iodine to prevent goiters was done 85 years ago in school-aged children in Akron, Ohio. The treatment group received an average of 11 mg/day of sodium iodide and the control group nothing. The iodine treatment group, 2.5 years later, had a 0.2 percent incidence of goiter, whereas the control group had a 22 percent incidence of goiter—a 110-fold difference.⁴⁴

Iodine was used for a wide variety of ailments in the 19th and early part of the 20th centuries, especially for syphilis and chronic lung disease.⁴⁵ For many years physicians used potassium iodide in doses starting at 1.5 to 3 g increasing up to more than 10 g/day for weeks at a time to treat bronchial asthma and chronic obstructive pulmonary disease, reportedly with good results and surprisingly few side effects.⁴⁶ The Nobel laureate Albert Szent Györgi (1893–1986), the physician who discovered vitamin C, writes:⁴⁷ “When I was a medical student, iodine in the form of KI [potassium iodide] was the universal medicine. Nobody knew what it did, but it did something and did something good.” The standard dose was 1 g, which contains 770 mg of iodine.

Iodine in Dermatology

This 19th century medicine continues to be used in gram amounts in the 21st century, by dermatologists. They treat inflammatory dermatoses, like nodular vasculitis and pyoderma gangrenosum, with SSKI (supersaturated potassium iodide), beginning with an iodine dose of 900 mg/day, followed by weekly increases of up to 6 g/day as tolerated. Fungal eruptions, like sporotrichosis, are treated initially in gram amounts with great effect.⁴⁸

Iodine Toxicity

A 54-year-old man, thinking it was iced tea, drank a “home preparation” of SSKI in water that his aunt kept in the refrigerator for her rheumatism. Over a short period of time he consumed 600 ml containing 15 g of iodide, an amount 100,000 times greater than the RDI for iodine. Twelve hours later he developed swelling of the face, neck, and mouth, and had transient cardiac arrhythmias, but made an uneventful recovery.⁴⁹

High doses of iodine are remarkably well tolerated. Herxheimer gave 5 g of KI, four days on, three days off, to 2,400 asthmatic patients and had 12 cases of myxedema and only four patients who had swelling of the thyroid gland.⁵⁰

It is important to remember, however, that some individuals are oversensitive to iodine, particularly in SSKI and topical skin preparations, and may experience severe adverse allergic reactions to organic iodinated contrast materials. Reportedly, iodide exposure has caused iodide-induced autoimmune thyroiditis as well as both hypo- and hyperthyroidism in a small number of patients. Thus, caution, with appropriate patient monitoring, is needed.

Forms of Iodine

Inorganic, nonradioactive iodine, as molecular iodine (I₂) and iodide (I⁻), provides the extrathyroidal benefits addressed here. In addition to seaweed, four commercially available forms of orally

administered inorganic iodine are potassium iodide tablets (in 0.23, 32.5, 65, and 130 mg amounts), SSKI (19–50 mg of iodide per drop), Lugol’s solution (6.3 mg of molecular iodine/iodide per drop), and Iodoral tablets (12.5 mg iodine/iodide). Lugol’s solution is 5 percent iodine (I₂) and 10 percent potassium iodide (I⁻) in water. Iodoral is a tablet form of Lugol’s solution, in which one tablet equals two drops of Lugol’s.

Iodine in a manufactured organic form, in the antiarrhythmic drug amiodarone and in various radiocontrast media, plays other extrathyroidal roles. Four radioactive isotopes of iodine, three of which are made in cyclotrons and one by nuclear fission (¹³¹I), are used as radiotracers and in radiotherapy—¹²³I (half life 13 hours), ¹²⁴I (4.2 days), ¹²⁵I (60 days), and ¹³¹I (8 days).

Fibrocystic Breast Disease

In animal studies, female rats fed an iodine-free diet develop fibrocystic changes in their breasts,^{51,52} and iodine in its elemental form as I₂ cures it.⁵³

The incidence of fibrocystic breast disease in American women was 3 percent in the 1920s. Today, 90 percent of women have this disorder, manifested by epithelial hyperplasia, apocrine gland metaplasia, fluid-filled cysts, and fibrosis. Six million American women with fibrocystic breast disease have moderate to severe breast pain and tenderness that lasts more than six days during the menstrual cycle.⁵⁴

In 1966 Russian researchers first showed that iodine effectively relieves signs and symptoms of fibrocystic breast disease. Vishniakova and Murav’eva treated 167 women suffering from this disorder with 50 mg KI during the intermenstrual period and obtained a beneficial healing effect in 71 percent.⁵⁵

Ghent and colleagues also reported a 70 percent success rate using iodine to treat fibrocystic breast disease. Their 1993 report is a composite of three clinical studies: two case series done in Canada treating 696 women with various types of iodine, and one in Seattle. The Seattle study, done at the Virginia Mason Clinic, is a randomized, double-blind, placebo-controlled trial of 56 women designed to compare 3–5 mg of elemental iodine, I₂, to a placebo (an aqueous mixture of brown vegetable dye with quinine). The women were followed for 6 months and subjective and objective changes in their fibrocystic disease tracked.⁵⁴

The randomized study in the Ghent paper was reported without tests for statistical significance. Two years later, however, a sponsor, Mimetix, Inc., did a statistical analysis of the Seattle study, increased to 92 women followed for seven months. The company submitted a Special Report on “Iodine’s Efficacy and Safety” to the FDA, seeking its approval to mount a larger clinical trial. Approval was denied. This 38-page report, now available online, shows that iodine exerts a highly statistically significant beneficial effect on fibrocystic disease (*P* < .001). Iodine reduced breast tenderness, nodularity, fibrosis, turgidity, and number of macrocysts—the five parameters in a total breast examination score that an investigator measured who was blinded to what treatment the woman was taking, iodine or placebo.⁵⁶

The FDA has now approved a randomized controlled trial on the benefits of molecular iodine for fibrocystic disease sponsored by Sybion Pharmaceuticals. A phase III trial enrolling 175 women is underway.^{57,58}

Presented with the evidence on fibrocystic disease and on breast cancer, it is reasonable to hypothesize that fibrocystic disease of the

breast and breast cancer may, like goiter and cretinism, be iodine-deficiency disorders.^{59,60} But as of 2003, after most of these studies had been published, a leading textbook on breast diseases, Bland and Copeland's *The Breast: Comprehensive Management of Benign and Malignant Disorders*, fails to mention iodine anywhere in its 1,766 pages.¹¹

The Iodine Project: Milligram Doses of Iodine

In 1997, after reading the Ghent paper in the *Canadian Journal of Surgery*, Guy Abraham, M.D., a former professor of obstetrics and gynecology at UCLA, decided to study iodine and mounted the Iodine Project. He had his company, Optimox Corp., manufacture Iodoral, and in 2000 engaged Jorge Flechas, M.D., to do clinical studies with it to confirm the findings of Ghent et al. David Brownstein, M.D., joined the project in 2003.

The Iodine Project's hypothesis is that whole body sufficiency of iodine requires a daily intake of 12.5 mg. The accepted view is that the body contains about 50 mg of iodine, of which 70–80 percent resides in the thyroid gland. Abraham concluded that whole body sufficiency exists when a person excretes 90 percent of the amount of iodine ingested. He devised a loading test in which one takes 50 mg of iodine and measures the amount excreted in the urine over the next 24 hours. He found that the vast majority of people tested retain a substantial amount of the 50 mg dose. Many require 50 mg/day of iodine for several months before they will excrete 90 percent of it. His studies indicate that given a sufficient amount the body will retain 1,500 mg of iodine, 30 times more than the presumed 50 mg, with only 3 percent of that 1.5 g amount residing in the thyroid gland.⁶¹

More than 4,000 patients in this project take iodine in daily doses ranging from 12.5 to 50 mg, and those with diabetes can take up to 100 mg /day. These investigators have found that iodine reverses fibrocystic disease; their diabetic patients require less insulin; hypothyroid patients need less thyroid medication; symptoms of fibromyalgia resolve; and patients with migraine headaches stop having them. To paraphrase Dr. Szent-Györgyi, these investigators aren't sure how iodine does it, but they see that it does something good.⁶²

Thyroid function has remained unchanged in 99 percent of their patients. Untoward effects of iodine—allergies, swelling of the salivary glands and thyroid, and iodism—occur rarely, in less than 1 percent. Iodine removes fluoride and bromide from the body. Iodism, an unpleasant brassy taste, runny nose, and acne-like skin lesions, is caused by the bromide that iodine extracts from the tissues, and it subsides on a lesser dose of iodine.⁶³

Consumption of iodine in milligram doses should be coupled with a complete nutritional program that includes, in particular, adequate amounts of selenium, magnesium, and omega-3 fatty acids. So done, Dr. Abraham believes that taking 12.5 mg/day of iodine is “the simplest, safest, most effective and least expensive way” to help solve many medical problems.

Many subjective benefits have been claimed for milligram-dose iodine: a greater sense of well being, increased energy, and a lifting of brain fog. Patients also report that they feel warmer in cold environments, need somewhat less sleep, have improved skin complexion, and have more regular bowel movements.⁶¹⁻⁶⁴ These are in addition to the improvements in fibrocystic disease of the breast and a possibly reduced incidence of breast cancer noted above.^{51-60,65}

Conclusion

The extrathyroidal health effects of iodine are worthy of thorough investigation, especially in view of the high incidence of breast cancer in American women. Such research deserves the support of public and private funding agencies.

Donald Miller, M.D. is professor of surgery, Division of Cardiothoracic Surgery, University of Washington School of Medicine. Contact: dwm@u.washington.edu.

Potential conflicts of interest: none.

REFERENCES

- 1 World Health Organization. Iodine deficiency disorders. Fact Sheet No. 121. Geneva, Switzerland: WHO; 1996.
- 2 FNB-IOM. Iodine. In: *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc: A Report of the Panel on Micronutrients*. Washington, D.C.: National Academy Press; 2001:258-289.
- 3 WHO-FAO-IAEA. Iodine. In: *Trace Elements in Human Nutrition and Health*. Geneva, Switzerland: WHO; 1996:49.
- 4 Nutrition Section, Bureau of Public Health. *Nutrition in Japan, 1964*. Tokyo, Japan: Ministry of Health and Welfare; 1965.
- 5 Abraham GE, Brownstein D. Validation of the orthoiodosupplementation program: a rebuttal of Dr. Gaby's editorial on iodine. *The Original Internist* 2005;12(4):184-194. Available at: http://optimox.com/pics/Iodine/IOD-12/IOD_12.htm. Accessed Jul 24, 2006.
- 6 Konno N, Yuri K, Miura I, et al. Clinical evaluation of the iodide/creatinine ratio of casual urine samples as an index of daily iodide excretion in a population study. *Endocr J* 1993;40:163-169.
- 7 Suzuki H, Higuchi T, Sawa K, et al. Endemic coast goiter in Hokkaido, Japan. *Acta Endocr* 1965;50:161-176.
- 8 International Council for the Control of Iodine Deficiency Disorders. Current IDD Status Database, 2003. Available at: <http://indorgs.virginia.edu/iccidd/mi/cidds.html>. Accessed Jul 3, 2006.
- 9 Hollowell JG, Staehling NW, Hannon WH, et al. Iodide nutrition in the United States. Trends and public health implications: iodide excretion data from National Health and Nutrition Examination Surveys I and III (1971–1974 and 1988–1994). *J Clin Endocrinol Metab* 1998;83:3401-3408.
- 10 Caldwell KL, Jones R, Hollowell JG. Urinary iodine concentration: United States National Health and Nutrition Examination Survey 2001-2002. *Thyroid* 2005;15:692-699.
- 11 Bland K, Copeland FM (eds). *The Breast: Comprehensive Management of Benign and Malignant Disorders*, Vol 1, 2. 3rd ed. Philadelphia, Pa.: Saunders; 2003.
- 12 Le Marchand L, Kolonel LN, Nomura AM. Breast cancer survival among Hawaiian Japanese and Caucasian women: ten-year rates and survival by place of birth. *Am J Epidemiol* 1985;122:571-578.
- 13 Nagata C, Shimizu H. Risk factors for breast cancer: Findings from comparative studies on Japanese in Japan, Japanese and whites in the United States. *Gann Monograph on Cancer Research* 1996;44:51-57.
- 14 Central Intelligence Agency. *The World Factbook*. Springfield, Va.: National Technical Information Service; 2006. Available at: www.cia.gov/cia/publications/factbook/index.html. Accessed Jul 27, 2006.
- 15 Küpper FC, Schweigert N, Ar Gall E, et al. Iodine uptake in *Laminariales* involves extracellular, haloperoxidase-mediated oxidation of iodide. *Planta* 1998;207:163-171.
- 16 Murata A, Suenaga H, Hideshima S, et al. Hydroxyl radical as the reactive species in the inactivation of phages by ascorbic acid. *Agric Biol Chem* 1986;50:1481-1487.
- 17 Winkler R, Griebenow S, Wonisch W. Effect of iodide on total antioxidant status of human serum. *Cell Biochem Funct* 2000;18:143-146.

- ¹⁸ Katamine S, Hoshino N, Totsuka K, Suzuki M. Effects of the long-term feeding of high-iodine eggs on lipid metabolism and thyroid function in rats. *J Nutr Sci Vitaminol* (Tokyo) 1985;31:339-353.
- ¹⁹ Cocchi M, Venturi S. Iodide, antioxidant function and omega-6 and omega-3 fatty acids: a new hypothesis of biochemical cooperation? *Prog Nutr* 2000;2:15-19.
- ²⁰ DeMarais DJ. Evolution: when did photosynthesis emerge on earth? *Science* 2000;289:1703-1705.
- ²¹ Venturi S, Venturi M. Iodide, thyroid and stomach carcinogenesis: evolutionary story of a primitive antioxidant? *Eur J Endocrinol* 1999;140:371-372.
- ²² Johnson LG. Thyroxine's evolutionary roots. *Perspect Biol Med* 1997;40:529-536.
- ²³ Zhang L, Sharma S, Zhu LX, et al. Nonradioactive iodide effectively induces apoptosis in genetically modified lung cancer cells. *Cancer Res* 2003;63:5065-5072.
- ²⁴ Sekiya M, Funahashi H, Tsukamura K, et al. Intracellular signaling in the induction of apoptosis in a human breast cancer cell line by water extract of Mekabu. *Int J Clin Oncol* 2005;10:122-126.
- ²⁵ Shrivastava A, Meenakshi T, Sinha RA, et al. Molecular iodine induces caspase-independent apoptosis in human breast carcinoma cells involving the mitochondria-mediated pathway. *J Biol Chem* 2006;281:19761-19771.
- ²⁶ Cann SA, van Netten JP, van Netten C. Hypothesis: iodine, selenium and the development of breast cancer. *Cancer Causes Control* 2000;11:121-127.
- ²⁷ Eskin BA, Anjum W, Abraham GE, et al. Identification of breast cancer by differences in urinary iodine. *Proc Am Assoc Cancer Res* 2005;46:504.
- ²⁸ Garcia-Solis P, Alfaro Y, Anguiano B, et al. Inhibition of *N*-methyl-*N*-nitrosourea-induced mammary carcinogenesis by molecular iodine (I₂) but not by iodide (I⁻) treatment: evidence that I₂ prevents cancer promotion. *Mol Cell Endocrinol* 2005;236:49-57.
- ²⁹ Funahashi H, Imai T, Tanaka Y, et al. Suppressive effect of iodine on DMBA-induced breast tumor growth in the rat. *J Surg Oncol* 1996;61:209-213.
- ³⁰ Russo J, Russo I. Differentiation and breast cancer. *Medicina* (Buenos Aires) 1997;57(Suppl 2):81-91.
- ³¹ Giani C, Fierabracci P, Bonacci R, et al. Relationship between breast cancer and thyroid disease: relevance of autoimmune thyroid disorders in breast malignancy. *J Clin Endocrinol Metab* 1996;81:990-994.
- ³² Abraham GE. The historical background of the Iodine Project. *The Original Internist* 2005;12(2):57-66. Available at: www.optimox.com/pics/Iodine/IOD-08/IOD_08.htm. Accessed Jul 28, 2006.
- ³³ Schuppert F, Taniguchi SI, Schröder S, et al. In vivo and in vitro evidence for iodide regulation of major histocompatibility complex class I and class II expression in Graves' disease. *J Clin Endocrinol Metab* 1996;81:3622-3628.
- ³⁴ Marani L, Venturi S, Masala R. Role of iodine in delayed immune response. *Isr J Med Sci* 1985;21:864.
- ³⁵ Marani L, Venturi S. [Iodine and delayed immunity] [Italian]. *Minerva Med* 1986;77:805-809. Abstract [English] available at: <http://web.tiscali.it/iodio/>. Accessed Jul 27, 2006.
- ³⁶ Ma F, Zhao W, Kudo M, et al. Inhibition of vacuolation toxin activity of *Helicobacter pylori* by iodine, nitrite and potentiation by sodium chloride, sterigmatocystin and fluoride. *Toxicol in Vitro* 2002;16:531-537.
- ³⁷ Venturi S, Donati FM, Venturi M, et al. Role of iodine in evolution and carcinogenesis of thyroid, breast and stomach. *Adv Clin Pathol* 2000;4:11-17.
- ³⁸ Guérard AL. *Education of a Humanist*. Cambridge, Mass.: Harvard University Press; 1949.
- ³⁹ Wolff J, Chaikoff IL. Plasma inorganic iodide as a homeostatic regulator of thyroid function. *J Biol Chem* 1948;174:555-564.
- ⁴⁰ Abraham GE. The Wolff-Chaikoff effect: crying wolf? *The Original Internist* 2005;12(3):112-118. Available at: www.optimox.com/pics/Iodine/IOD-04/IOD04.html. Accessed Aug 1, 2006.
- ⁴¹ Pearce DN, Gerber AR, Gootnick DB, et al. Effects of chronic iodine excess in a cohort of long-term American workers in West Africa. *J Clin Endocrinol Metab* 2002;87:5499-5502.
- ⁴² Braverman LE, Ingbar SH. Changes in thyroidal function during adaptation to large doses of iodide. *J Clin Invest* 1963;42:1216-1231.
- ⁴³ Kelly FC. Iodine in medicine and pharmacy since its discovery—1811-1961. *Proc R Soc Med* 1961;54:831-836.
- ⁴⁴ Marine D. Prevention and treatment of simple goiter. *Atlantic Med J* 1923;26:437-443.
- ⁴⁵ *The Encyclopaedia Britannica*. Vol 14. 11th ed. New York, N.Y.: Encyclopaedia Britannica Company; 1911:726.
- ⁴⁶ Bernecker C. Intermittent therapy with potassium iodide in chronic obstructive disease of the airways. *Acta Allergol* 1969;24:216-225.
- ⁴⁷ Szent-Györgyi A. *Bioenergetics*. New York, N.Y.: Academic Press; 1957:112.
- ⁴⁸ Sterling JB, Heymann WR. Potassium iodide in dermatology: a 19th-century drug for the 21st century—uses, pharmacology, adverse effects, and contraindications. *J Am Acad Dermatol* 2000;43:691-697.
- ⁴⁹ Tresch DD, Sweet DL, Keelan MH, Ramon LL. Acute iodide intoxication with cardiac irritability. *Arch Intern Med* 1974;134:760-762.
- ⁵⁰ Herxheimer H. Effect of iodide treatment on thyroid function. *N Engl J Med* 1977;297:171.
- ⁵¹ Eskin BA. Mammary gland dysplasia in iodine deficiency. *JAMA* 1967;200:691-695.
- ⁵² Eskin BA, Shuman R, Krouse T, Merion JA. Rat mammary gland atypia produced by iodine blockade with perchlorate. *Cancer Res* 1975;35:2332-2339.
- ⁵³ Eskin BA, Grotkowski CE, Connolly CP, Ghent WR. Different tissue responses for iodine and iodide in rat thyroid and mammary glands. *Biol Trace Elem Res* 1995;49:9-19.
- ⁵⁴ Ghent WR, Eskin BA, Low DA, Hill LP. Iodine replacement in fibrocystic disease of the breast. *Can J Surg* 1993;36:453-460.
- ⁵⁵ Vishniakova YY, Murav'eva NI. [On the treatment of dys-hormonal hyperplasia of mammary glands] *Vestn Akad Med Nauk* (USSR) [Russian] 1966;21(9):19-22.
- ⁵⁶ Low DE, Ghent WR, Hill LD. Diatomic iodine treatment for fibrocystic disease: special report of efficacy and safety results. Submitted to the FDA; 1995:1-38. Available at: http://www.donaldmiller.com/Iodine_For_Fibrocystic_Disease_MX04.pdf. Accessed Jul 30, 2006.
- ⁵⁷ Kessler JH. The effect of supraphysiologic levels of iodine on patients with cyclic mastalgia. *Breast J* 2004;10:328-336.
- ⁵⁸ Symbolon Pharmaceuticals. Study for Treatment of Moderate or Severe, Periodic, "Cyclic," Breast Pain. Clinicaltrials.gov. Available at: <http://clinicaltrials.gov/ct/show/NCT00237523?order=1>. Accessed Jul 26, 2006.
- ⁵⁹ Venturi S. Is there a role for iodine in breast diseases? *Breast* 2001;10:379-382.
- ⁶⁰ Aceves C, Anguiano B, Delgado G. Is iodine a gatekeeper of the integrity of the mammary gland? *J Mammary Gland Biol Neoplasia* 2005;10:189-196.
- ⁶¹ Abraham GE. The safe and effective implementation of orthoiodo-supplementation in medical practice. *The Original Internist* 2004;11:17-36. Available at: www.optimox.com/pics/Iodine/IOD-05/IOD_05.html. Accessed Jul 28, 2006.
- ⁶² Flechas, JD. Orthoiodo-supplementation in a primary care practice. *The Original Internist* 2005;12(2):89-96. Available at: http://www.optimox.com/pics/Iodine/IOD-10/IOD_10.htm. Accessed Jul 28, 2006.
- ⁶³ Brownstein D. Clinical experience with inorganic, non-radioactive iodine/iodide. *The Original Internist* 2005;12(3):105-108. Available at: http://www.optimox.com/pics/Iodine/IOD-09/IOD_09.htm. Accessed Jul 28, 2006.
- ⁶⁴ Brownstein D. *Iodine: Why You Need It, Why You Can't Live Without It*. West Bloomfield, Mich.: Medical Alternatives Press; 2004.
- ⁶⁵ Derry D. *Breast Cancer and Iodine: How to Prevent and How to Survive Breast Cancer*. Victoria, B.C.: Trafford Publishing; 2002.