

Evolutionary Significance of Iodine

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Abstract: The significance of inorganic and organic forms of iodine in the evolution of plants and animals is reviewed. Iodine is one of the most electron-rich atoms in the diet of marine and terrestrial organisms, and it enters cells *via* iodide transporters. Iodide, which acts as a primitive electron donor through peroxidase enzymes, has an ancestral antioxidant function in all iodide-concentrating cells from primitive marine algae to more recent terrestrial vertebrates. Similarly, thyroxine and iodothyronines show antioxidant activities through deiodinase enzymes. About 500-600 million years ago, in parallel with the evolution of the primitive brain in marine animals, thyroid cells originated from the primitive gut in vertebrates, migrated, and specialized in the uptake and storage of iodo-compounds in a novel follicular “thyroidal” structure, an adaptation that enabled the transition from the iodine-rich ocean to the iodine-deficient terrestrial environment.

Keywords: Antioxidants, evolution, iodine, iodide, thyroxine.

INTRODUCTION

The iodine atom (symbol I, atomic mass 126.9, atomic number 53, 53 electrons, 53 protons, and 74 neutrons) is a component of “nuclear ash”. In fact, it derives from a process of nucleosynthesis that occurred more than 10 billion years ago in a star-supernova that exploded and dispersed its dust, which formed our planet Earth about 5 billion years ago. The iodine atom is one of the richest in electrons of our body and is essential in the diet of all living animals. Iodine is scarce in the earth's surface, because, over hundreds of millions of years, it has been washed away by rain and glaciations and transported from the terrestrial crust to the sea, which is enriched in iodine in the form of iodide (I⁻) and iodates [1,2]. Seawater has about 60 micrograms per litre, whereas terrestrial freshwaters (estuaries, rivers, lakes) contain 10- to 200-fold lower quantities. Algal phytoplankton, the basis of the marine food chain, acts as a biological accumulator of iodides, selenium, and also polyunsaturated fatty acids (PUFAs) [2]. Our group has suggested that iodine and selenium played an important role in protecting fragile, polyunsaturated membrane lipids, proteins and DNA from oxidation, and for this reason, these elements are important in animal development and in human brain evolution [3]. In fact, iodide is a mild reducing agent, which is a chemical term for an antioxidant. Its antioxidant properties can be expressed quantitatively as a redox potential:



Because iodide is easily oxidized, some enzymes convert it into electrophilic iodinating agents, as required for the biosynthesis of numerous iodine-containing natural products. In an evolutionary sense, iodides are the most ancient and powerful antioxidant, and as such they are the oldest defence

mechanism against radical oxygen species (ROS). Iodides and peroxidases were present in primitive oxygenic and photosynthetic *Cyanobacteria* about 3½ billion years ago [2,4,5]. Several authors have suggested that the production of volatile iodine (molecular iodine; I₂) and iodo-compounds by marine algae is a result of the development some 3 billion years ago of photosynthesis, oxygen production, and respiration, probably as an adaptation to utilize light in order to reduce the amount of poisonous ROS [6-8]. The importance of antioxidants as protective substances against chronic and degenerative diseases, such as cancer and cardiovascular diseases has been studied for many years. However, the utility of well-known vegetable antioxidant vitamins as protection against or a cure for these diseases has not been demonstrated [9,10]. A recent study tracking the eating habits of 478,000 Europeans suggests also that consuming high amounts of fruits and vegetables has little if any preventative effect against cancer [11]. For this reason, we have hypothesized an “evolutionary hierarchy” for the wide range of antioxidants, where the most ancient might be more essential than the “modern” ones in protecting developing stages of animal and human organisms [2]. Deficiency of iodine, the primitive antioxidant, causes more damage in developing embryos than deficiencies of some other “modern” antioxidants. Iodine-deficiency causes abortions and stillbirths in pregnant women and cretinism and neuropsychological disorders in human infants [12]. The iodine species that exist within a human body at a pH 7.4 are: iodide (I⁻), triiodide (I₃), molecular iodine (I₂), hypoiodous acid (HIO), hypoiodite ion (OI⁻), and the iodine anion (HI₂O⁻) [13].

INCREASE OF OXYGEN IN EARTH'S ATMOSPHERE AND ITS BIOLOGICAL CONSEQUENCES

The evolution of oxygen-producing cells was probably the most significant event in the history of life after the beginning of life itself. Oxygen is a potent oxidant whose accumulation in the atmosphere forever changed the surface chemistry of the Earth [14]. By the start of the Cambrian

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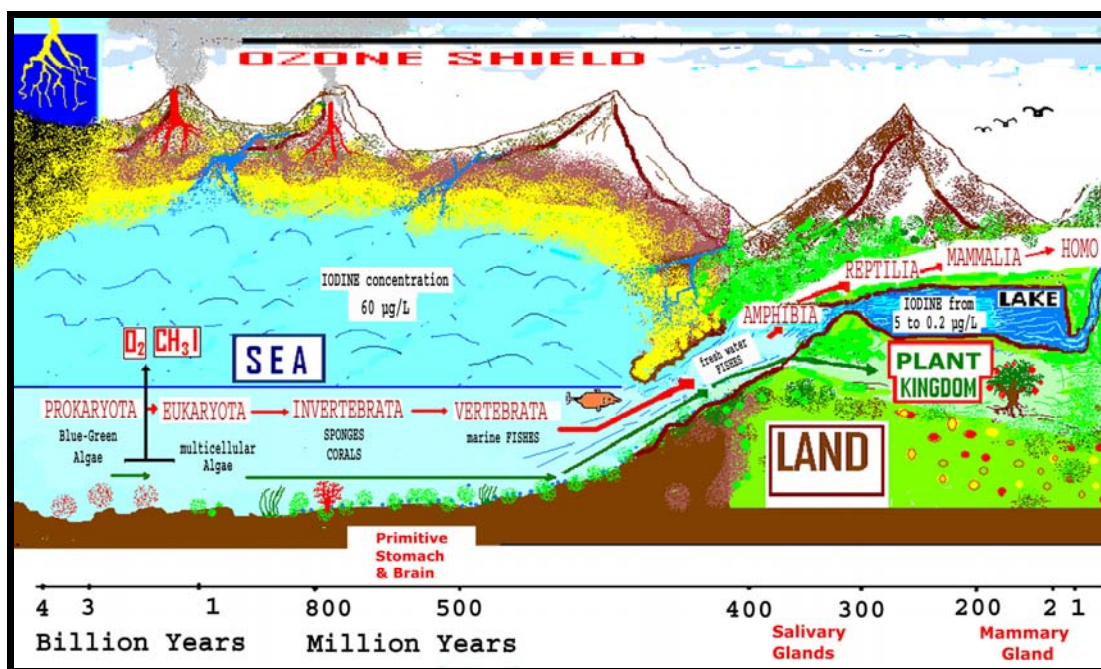


Fig. (1). Iodine in Evolution. Over three billion years ago, blue-green algae were the first living *Prokaryota* to produce oxygen, halocarbons (such as CH_3I) in the atmosphere, and PUFAs in lipid membranes. About 500-600 million years ago (Mya) when the primitive brain evolved in marine animals, thyroid cells originated from the primitive gut in vertebrates, migrated, and specialized in the uptake and storage of iodo-compounds in a novel follicular “thyroidal” structure that served as a reservoir for iodine. Three to four hundred million years ago some vertebrates evolved into amphibians and reptiles and moved to I-deficient land. Thyroid hormones became active agents in the metamorphosis and thermogenesis of vertebrates, facilitating their adaptation to the terrestrial environment. The dry terrestrial diet firstly stimulated in amphibians the formation of I-concentrating salivary glands, and about 200 Mya the formation of I-concentrating mammary gland in mammals (from Venturi *et al.* [27]).

Table 1. Biochemical Mechanism of Iodides, the Most Ancient and Powerful Mechanism of Defence Against Poisonous Reactive Oxygen Species

$2 \text{I}^- + \text{Peroxidase} + \text{H}_2\text{O}_2 + 2 \text{Tyrosine, Histidine or lipids} \rightarrow 2 \text{Iodo-components} + \text{H}_2\text{O} + 2 \text{e}^- \text{ (antioxidants)};$

$2 \text{e}^- + \text{H}_2\text{O}_2 + 2 \text{H}^+ \text{ (from aqueous cytoplasm)} \rightarrow 2 \text{H}_2\text{O}$

period 570 million years ago (Mya) oxygen levels had increased enough to permit rapid evolution of large, oxygen-utilizing, multicellular organisms. At the same time, endogenous protection systems need to have been developed to counteract the deleterious effects of oxygen oxidations. Some researchers hypothesized that the relative amounts of many mineral trace elements of the modern animal body are similar to the composition of the primitive sea, where the first forms of life began [2,15,16]. In particular, mineral antioxidants such as some reduced compounds of Rubidium, Vanadium, Zinc, Iron, Copper, Molybdenum, Selenium, and Iodine, seem to play important roles in electron transfer and in redox chemical reactions. Most of these substances are essential trace elements in the cells and occur in redox and antioxidant metallo-enzymes. A few organic antioxidants appeared more recently, in the last 100-200 million years, in fruits and flowers of angiosperm plants [2]. In fact Angiosperms (the dominant type of plants today) and most of their antioxidant pigments evolved during the late Jurassic period. Plants employ many organic antioxidants to defend themselves against ROS produced during photosynthesis. In animals, the primary antioxidant enzymes are superoxide dis-

mutase, glutathione peroxidase, catalase, and peroxiredoxins [15].

IODIDE/IODINE AND IODIDE/THYROXINE: EVOLUTIONARY HISTORY OF A PRIMITIVE ANTI-OXIDANT

Over three billion years ago, blue-green algae were the most primitive oxygenic photosynthetic organisms, ancestors of multicellular eukaryotic algae. Algae that contain the highest amount of iodine (1-3 % of dry weight) and peroxidase enzymes were the first living cells to produce poisonous oxygen in the terrestrial atmosphere [16,17]. Therefore, algal cells needed molecules with protective antioxidant properties, and the iodides seem to have assumed this specific role [2,3]. Küpper *et al.* confirmed this hypothesis showing that iodide scavenges ROS in algae, and that its primary biological role is that of an inorganic antioxidant, the first to be described in a living system and a role that it has kept in blood cells of modern humans [6]. Moreover, recently Soriguer *et al.* also showed a slight anti-inflammatory and antioxidative action of iodide in humans [18].

Brown algae (seaweeds) accumulate iodine to more than 30,000 times its concentration in seawater [6,7]. Primitive marine prokaryotes seem to have an efficient, active “iodide pump”, ancestor of the pump of multicellular eukaryotic algae and of mammalian iodide-transporters (Fig. 1, Table 1). This cellular “iodide-pump” uses a primitive mechanism, and it lacks specificity; in fact it cannot distinguish iodide from other anions of similar atomic or molecular size such as thiocyanate, cyanate, fluoride, nitrate, pertechnetate, and perchlorate, which may act as “pseudo-iodides” [19]. The “iodide-pump” and sodium/iodine symporter (NIS) in the cells are also paradoxically inhibited by an excessive quantity of iodine. This inhibition seems to be an ancient defensive mechanism when, in the primitive sea, excess iodide impaired cellular trophism and functions of I-concentrating organisms. This well-known “Wolff-Chaikoff effect” occurs now in animal and human thyroid with a dosage just in excess of 2 mg iodide [19].

It is hypothesized that 80% of the Earth's oxygen is produced by planktonic algae, prochlorophytes, *Cyanobacteria*, and by free-floating unicellular microbes inhabiting the sea close to the surface. Thus far, only one aspect of halogen metabolism, the production of volatile halocarbons, seems to have attracted attention from researchers, because these compounds and particularly their iodinated forms have a significant impact on the chemistry of the atmosphere and depletion of its ozone shield. Halogen metabolism in marine algae involves haloperoxidase enzymes [16,17,20]. Since the iodo-peroxidase of *Laminaria* seaweeds is more efficient than their bromo-peroxidase in the oxidation of iodide, this former activity may be largely responsible for the uptake of iodide from seawater. There is an increased emission of iodinated halocarbons and I_2 both from kelp beds at low tide during daytime and from kelp plants incubated under high solar irradiation causing photo-oxidative stress [6,16,17]. The family of peroxidase enzymes includes vertebrate, plant, algal, fungal, and microorganism peroxidases. Some of these, known as halo-peroxidases, use halide ions (iodide, bromide, and chloride) as natural electron donors, and have an antioxidant function in *Cyanobacteria* [2,7]. Taurog [21] hypothesized that animal and non-animal peroxidases are

probably an example of convergent evolution to a common enzymatic mechanism.

“EVOLUTION” OF IODINE FROM NON-HORMONAL TO HORMONAL FUNCTIONS

Since 700-800 Mya, thyroxine has been present in fibrous exoskeletal scleroproteins of the lowest marine invertebrates (sponges and corals) [22]. More recent studies found that the thyroid hormones (THs) thyroxine (T4) and triiodothyronine (T3) are also present in unicellular planktonic algae (*Dunaliella tertiolecta*) and in echinoid larvae (sea-urchin) [23,24]. The original sources of animal hormones might have been plants/algae in many cases, and could well have been independently derived from plants/algae in distinct lineages. The ancestral function of THs in algae and/or plants could also have been as feeding deterrents with the signalling functions in animals acquired secondarily, perhaps even through horizontal transfer from their hosts or other co-associated microbes that had more ancient relationships with the host [24-26].

The iodine concentration decreases stepwise from seawater (60 $\mu\text{g/L}$) to estuary (about 5 $\mu\text{g/L}$) to source of rivers (less than 0.2 $\mu\text{g/L}$ in some Triassic mountain regions of northern Italy), and in parallel, saltwater fishes (herring) contain 500-800 μg of iodine per kg compared to freshwater trout with about 20 μg per kg [27]. Thus, in terrestrial I-deficient freshwaters, some trout and other salmonids (anadromous migratory fishes) may suffer thyroid hypertrophy or related metabolic disorders, as do some sharks in captivity [2,27,28]. Youson and Sower [29] reported that the I-concentrating ability of the endostyle of sea lamprey was a critical factor in the evolution of metamorphosis and that the endostyle was replaced by a follicular thyroid, since post-metamorphic animals needed to store iodine following their invasion of freshwater. According to Youson's group in some anadromous migratory fishes (sea lamprey and salmonids), declining serum concentrations of T4 induce metamorphosis [29,30]. After metamorphosis, when these adult marine fishes die in freshwaters after reproducing, they release their iodide, selenium, and PUFAs to the environment, where they are beneficial for the life and health of na-

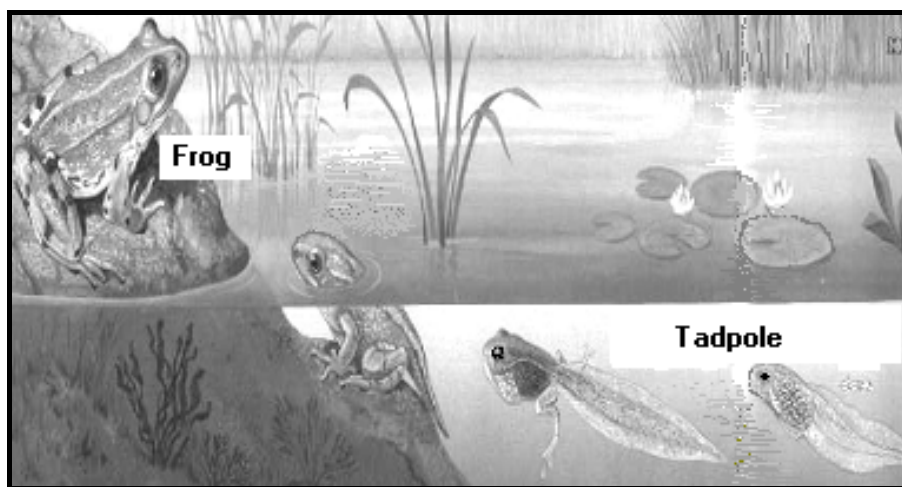


Fig. (2). In amphibian metamorphosis, iodides and thyroxine exert a spectacular apoptotic action on the cells of gills, tail, and fins, initiating the transformation of an aquatic tadpole into a “more developed” terrestrial adult frog.

tive animals, bringing essential trace elements back upstream from the sea to I-deficient inland regions [2,26]. The new hormonal action was made possible by the formation of nuclear thyroid-hormone receptors (THRs) in the cells of vertebrates. About 500 Mya, the primitive THRs with a metamorphosing action appeared first in marine chordates, and then about 250-200 Mya more recent THRs with metabolic and thermogenic actions evolved in birds and mammals. THR genes are c-erbA oncogenes, which have been implicated as tumor suppressor genes in non-thyroidal cancers and are altered in some human gastric and mammary cancers [31,32]. The role of iodine in marine and freshwater fishes is not yet completely understood, but it has been reported that I-deficient freshwater fishes suffer higher incidences of infective, parasitic, atherosclerotic, and neoplastic diseases than marine fishes. On October 7, 1999, the U.S.A. Committee of the House and Senate regarding "Marine Research" reported that "The Committee notes the unusually low incidence of cancer in marine sharks, skates, and rays and encourages basic research through the study of the immune system of these marine animals and the examination of bioactive molecules from shark, skate, and ray cells and tissues that have the potential to inhibit disease processes in humans". In amphibians, environmental iodine is the essential metamorphic factor, and it stimulates the spectacular apoptosis of the cells of larval gills, tail, fins, and some gastrointestinal cells, adapting and transforming the aquatic vegetarian tadpole into a "more developed" terrestrial carnivorous frog (Fig. 2). In fact, programmed cell death, with nuclear changes and removal by phagocytic macrophages, occurs in a variety of organs during amphibian metamorphosis, which is under the control of T4. Indeed, because of the massive cell death that occurs during a short period, amphibian organs serve as an ideal model system for the study of mechanisms underlying programmed cell death. T4 induces apoptosis of larval cells and differentiation of pepsinogen-producing cells in the stomach of the adult carnivorous form of the frog *Xenopus laevis* [33].

IODINE IN TERRESTRIAL ORGANISMS

Around 300-400 Mya when some living plants and animals began to transfer from the sea to rivers and land, environmental I-deficiency was a challenge for the evolution of terrestrial life. The terrestrial diet of freshwater fishes, plants and other animals was deficient in many marine inorganic antioxidants, including iodine and selenium [27]. Terrestrial plants slowly optimized the production of novel endogenous organic antioxidants such as ascorbic acid, polyphenols, carotenoids, flavonoids, and tocopherols, some of which became essential "vitamins" in the diet of terrestrial animals (vitamins A, E, and in humans vitamin C) [2]. According to Coic and Coppenet [34] and Lamand [35], iodine and selenium became no longer necessary for many plants. In a different way, about 500 Mya, some chordates also began to use the novel "thyroidal" follicles as reservoir for iodine and T4 in order to transport antioxidant iodide and triiodothyronine (T3) into the peripheral cells. T3, the biologically active form of T4 in vertebrates, acquired activity in the metamorphosis and thermogenesis processes that facilitated adaptation to terrestrial freshwaters, atmosphere, gravity, temperature, and diet. Moreover T4, reverse-T3, and other

iodothyronines are important as antioxidants and inhibitors of lipid peroxidation: they were shown to be more effective than vitamin E, glutathione, and ascorbic acid [27,36].

On the other hand, the new terrestrial diet harboured plant iodide-transport inhibitors such as thiocyanates, cyanates, nitrates, and some glycosides. Many plant substances that inhibit iodide transport seem to have antiparasitic activity. In a previous work, Venturi *et al.* [2,27] hypothesized that, contrary to amphibian metamorphosis, thyroidectomy and hypothyroidism in mammals might be considered a sort of phylogenetic and metabolic regression to a former stage of reptilian life. In fact, many disorders that seem to afflict hypothyroid humans have reptilian-like features such as a dry, hairless, scaly, cold skin and a general slowdown of metabolism, digestion, heart rate, nervous reflexes with lethargic cerebration, hyperuricemia, and hypothermia.

ROLE OF IODIDE IN ANIMAL CELLS AND TISSUES

Heyland and Moroz suggested that dietary sources of THs may have been ancestral, while the ability to synthesize these hormones endogenously may have evolved independently in a variety of metazoans, resulting in a diversity of signalling pathways and, possibly, of morphological structures involved in TH-signalling [25]. In fact, increasing evidence suggesting that THs also function in a variety of invertebrate species are reviewed by Heyland *et al.* and Eales [24,25]. These researchers propose that the oxidation of iodide to iodine in some marine invertebrates is a critical step for scavenging ROS, and that the reaction of iodine with tyrosine residues removes potentially poisonous iodine from the cells. Berking *et al.* [37] demonstrated the antioxidant action of iodide and T4 in some marine invertebrates (polyps of the jellyfish *Aurelia aurita*). In vertebrates, isolated cells of non-thyroidal I-concentrating tissues, such as gastric mucosa, salivary and mammary glands, can produce protein-bound mono- and diiodotyrosine as well as some iodolipids [38]. This pathway for iodine organification involves iodine incorporation into specific lipid molecules such as PUFAs. Iodolipids have been shown to regulate mammalian cellular metabolism [39]. Recently, several authors reported the effects of different iodo-components on growth inhibition and apoptosis in different tumoral cell lines [40,41]. In thyroid cells active iodide transport is facilitated by three transporters: NIS, pendrin, and apical iodide transporter. All three transporters are also expressed in I-concentrating extrathyroidal tissues [42,43]. Gastric "iodide-pumps" are phylogenetically more primitive than the thyroidal ones: they have lower affinity for iodide and do not respond to the more recent thyroid stimulating hormone (thyrotropin). Hays and Solomon found that gastro-salivary clearance and secretions of iodides are a considerable part of the "gastro-intestinal cycle of iodides", which constitutes about 23% of the iodide pool in the human body [44]. Mammals, such as cows in their abomasum, have an efficient iodine recycling system via the oral-salivary and gastro-intestinal tract, which conserves iodine and can protect them against low dietary iodine [45]. The entero-thyroidal circulation of iodides seems to be mediated principally by salivary and gastric NIS [46]. In mammals, dietary iodine is rapidly adsorbed as I⁻ from the small intestine. The fact that radioiodine ¹³¹I is also detectable in radioautographies of oral mucosa, elastic arterial

walls (aorta), and epidermal fur of rats after 14 days strongly suggests the formation of as yet unknown structural iodo-compounds, probably iodolipids and iodoproteins [47]. Human salivary glands rapidly take up iodine and secrete it in saliva [48]. According to De *et al.* [49], the salivary glands and gastric mucosa have high activity for both iodide uptake and for peroxidase-catalyzed synthesis of iodo-compounds. On the other hand, the chronically high quantities of iodine-intake can cause degenerative, necrotic, and neoplastic lesions in thyroid gland, and also in stomach and salivary glands [50]. Our group studied the toxic effect of excess iodide in stomach, and Joanta *et al.* described the daily intake of up to 200 mg iodine per person exert high oxidative stress in I⁻concentrating tissues [51]. Indeed, Contempre *et al.* [52], Yang *et al.* [53], and Chen *et al.* [54] found that an appropriate dose of the antioxidant selenium is a beneficial intervention in cases of damage to the thyroid and immune system induced by excess of iodide.

Cunnane suggested that “iodine is the primary brain-selective nutrient in human brain evolution” [55]. Dobson suggested that Neanderthal man suffered I-deficiency disorders caused by their inland environment or by a genetic difference of his thyroid compared to that of modern *Homo Sapiens* [56]. I-deficient humans like endemic cretins suffer physical, neurological, mental, immune, reproductive, and skeletal diseases. Ongoing proximity to riverine, lacustrine, and maritime diets is crucial for optimal brain development and function [57-59].

Obendorf *et al.* [60] and Oxnard *et al.* [61] hypothesized that *Homo floresiensis*, a pygmy-sized, microcephalic hominin who lived from 95,000 to 13,000 years ago on the Indonesian island of Flores, were myxoedematous endemic cretins. Their congenital hypothyroidism led to severe dwarfism, mental retardation, and reduction of brain size. Indeed iodine has favored animal development and evolution of the nervous system for a better adaptation to the terrestrial environment [2,27,55]. Ullberg and Ewaldsson [62] found high concentrations of radioiodine in skeletal and articular systems, indicating the likely anatomical basis of I-deficient skeletal and articular deformities and dwarfism. Our group studied cases of cretinism which afflicted about 0.3 % of the total population of I-deficient Montefeltro (in the central Apennines of Italy) in the 1980's. In these cretins, our group reported a high prevalence of microcephaly, hip dysplasia, immune deficiencies, gonarthrosis, and oral and dental pathologies. Furthermore, a few years after implementation of I-prophylaxis, goiter, immune deficiency, hip dysplasia, and dental caries in children had disappeared or was greatly decreased [48,63-65]. Price, in his famous world investigation, mentioned that fish and seafood contain essential trace elements such as iodine which are very important for the prevention of health problems, physical degeneration, and tooth decay in many coastal populations [66]. Hardgrove [67] stated that in his community (Fond du Lac, Wis. USA), “since the beginning of administration of iodine to prevent goitre, iodine seems to increase resistance to caries, retarding the process and reducing its incidence”. Bartelstone's group [68,69] showed in cats and humans high direct and indirect penetration of radioiodine in intact dental enamel, dentin, and pulp and in periodontal tissues.

Cordain *et al.* indicated that the significant changes in diet that began with the introduction of agriculture and animal husbandry approximately 10,000 years ago occurred too recently on an evolutionary time scale for the human genome to adjust [70]. In conjunction with this discordance between our ancient, genetically determined biology of hunter-gatherer and fish-gatherer human societies and the nutritional patterns of contemporary Western populations, many of the so-called diseases of civilization have emerged. These authors suggested that I-deficiency was probably one of several dietary variations introduced during the Neolithic and Industrial Periods which have altered crucial nutritional characteristics of the ancestral human diet. Thus, the evolutionary collision of our ancient genome with the nutritional qualities of recently introduced foods may underlie many of the chronic diseases of Western civilization [71]. In 1883, Kocher observed that atherosclerosis, thought to be caused by ROS, frequently appeared following thyroidectomies, suggesting that hypothyroidism is causally associated with atherosclerosis [72]. Between 1930 and 1960, potassium iodide was used empirically in patients with arteriosclerosis and cardiovascular diseases by European physicians [73]. Turner's group reported efficacy of iodine and desiccated thyroid in prevention of atherosclerosis in rabbits [74]. The antioxidant action of dietary iodides has also been described in brain cells of rats as well as in therapy of some human chronic diseases of the cardiovascular, articular, and ocular systems [2,75,76]. In addition, iodine also plays an important role in antitumor defence of the organism. Antineoplastic and apoptotic effects have been observed in both *in vivo* and *in vitro* conditions when the cells capable of iodine-uptake become cancerous [50,77,78]. In the mammary gland I₂, but not iodide, supplementation alleviates human mastalgia and exerts potent antineoplastic and apoptotic effects on cancerous cells [79-84]. In thyroid gland, I⁻ has an apoptotic effect that is mediated by arachidonic acid or eicosapentaenoic acid derivatives such as 6-iodo-5-hydroxy-8,11,14-eicosatrienoic acid (also called 6-iodolactone; 6-IL) or alpha-iodohexadecanal, respectively [84-86]. The formation of these iodolipids requires, in addition to iodide uptake by NIS, its oxidation by thyroperoxidase. The oxidized iodine intermediate has not been identified, but one of the candidates is I₂ [87]. Aceves *et al.* have shown that mammary glands of virgin rats and MNU-induced tumors take up ¹²⁵I₂ by mechanisms independent of NIS or pendrin and that in the human tumoral cell line MCF-7, ¹²⁵I₂ is taken up by a facilitated-diffusion system and covalently bound to lipids similar to 6-IL in both the presence and absence of peroxidase inhibitors, indicating that the oxidized iodine form I₂ is organified in the absence of peroxidases [88]. Moreover, data of several groups showed that cancerous and normal cells exhibit differential I₂ sensitivity, and on basis of these data, two hypotheses have been proposed to explain the I₂ effects: a direct action, where the oxidized iodine dissipates the mitochondrial membrane potential, thereby triggering mitochondrion-mediated apoptosis, or an indirect effect through iodolipid formation [82,84,88,89]. These effects are discussed in detail in the following chapters.

The US Food and Nutrition Board and the Institute of Medicine recommended daily allowance of iodine ranges from 150 µg /day for adult humans to 290 µg /day for lactat-

ing mothers [90]. However, the thyroid gland needs no more than 70 µg /day to synthesize the requisite daily amounts of T4 and T3. These higher recommended daily allowance levels of iodine seem to be necessary for optimal function of a number of body systems, including all non-thyroidal I-concentrating organs [2,3]. Based on phylogenesis and embryogenesis, our group [50] hypothesized in previous reports about the importance of non-hormonal iodine and of iodine per se, considering three mechanisms for its action, which are all present in the cells of modern vertebrates:

1. An ancient and direct action on endodermal fore-gut and stomach and on ectodermal epidermis, where inorganic iodides act as antioxidants.
2. A recent and direct antioxidant/ apoptotic action on normal and neoplastic cells of different tissues that take up iodine like thyroid, mammary glands, salivary glands, ovary, and the nervous, arterial, and skeletal systems.
3. A more recent indirect action of the thyroid *via* its iodinated hormones on all vertebrate cells, where they act in very small quantities and utilize T3-receptors. Indeed thyroid hormones contain less than 1/30th of total body iodine.

CONCLUSION

Research on the evolutionary significance of iodine has stimulated our need for knowledge beyond its role in thyroid hormones. The actions of iodine seem much more complex, and we hope to have enlightened a few of these: its role as antioxidant and apoptosis-inductor and its possible anti-tumoral and anti-atherosclerotic activities. We should point out that extrathyroidal actions of iodide might be an important new area for investigation. Studies of molecular evolution of this trace element provide the basis for further studies about many pathologies.

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ABBREVIATIONS

(I ⁻)	=	Iodide
(HIO)	=	Hypoiodous acid
(HI ₂ O ⁻)	=	Iodine anion
(6-IL)	=	6-iodo-5-hydroxy-8,11,14-eicosatrienoic Acid or 6-iodolactone
(I ₂)	=	Molecular iodine
(I ₃)	=	Triiodide
(Mya)	=	Million years ago
(OI ⁻)	=	Hypoiodite ion
(PUFAs)	=	Polyunsaturated fatty acids
(ROS)	=	Radical oxygen species

(T3)	=	Triiodothyronine
(T4)	=	Thyroxine
(THs)	=	Thyroid hormones
(THR _s)	=	Thyroid-hormone receptors

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