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Iodine in Evolution of Salivary Glands and in Oral Health

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ABSTRACT

The authors hypothesized that dietary deficiency or excess of iodine (I) has an important role in oral mucosa and in salivary glands physiology. Salivary glands derived from primitive I-concentrating oral cells which, during embryogenesis, migrated and specialized in secretion of saliva and iodine. Gastro-salivary clearance and secretions of iodides are a considerable part of “gastro-intestinal cycle of iodides”, which constitutes about 23% of iodides pool in the human body. Salivary glands, stomach and thyroid share I-concentrating ability by sodium iodide symporter (NIS) and peroxidase activity, which transfers electrons from iodides to the oxygen of hydrogen peroxide and so protects the cells from peroxidation. Iodide seems to have an ancestral antioxidant function in all I-concentrating organisms from primitive marine algae to more recent terrestrial vertebrates. The high I-concentration of thymus supports the important role of iodine in the immune system and in the oral immune defence. In Europe and in the world, I-deficiency is present in a large part of the

population. The authors suggest that the trophic, antioxidant and apoptosis-inductor actions and the presumed antitumour activity of iodides might be important for prevention of oral and salivary glands diseases, as for some other extrathyroidal pathologies.

KEY WORDS: antioxidants; evolution; iodine; oral, dental and salivary pathologies

FOREWORD

In the 1930s a correlation between malnutrition and oral health was reported, and, as cited by Weston A. Price (1939), some researchers have also hypothesized the specific correlation between I-deficient goitre and dental caries (Hardgrove, 1939). Price, in his famous world investigation *“Nutrition and Physical Degeneration: A Comparison of Primitive and Modern Diets and Their Effects”* (1939), mentioned that “in fish and sea food were essential trace-elements such as iodine, copper, manganese and special vitamins, which were very important for the prevention of health problems and tooth decay“ in many coastal populations. The aim of our study is to search for the pathophysiological correlation between these early nutritional studies and more recent (biochemical, autoradiographical and epidemiological) data regarding the correlation between dietary iodine and oral and salivary glands health.

INTRODUCTION

Iodine (I) is the richest in electrons of the required elements in the animal diet, and as iodide (I-) enters the cells. Inorganic iodide is necessary for all living animal cells, but only the vertebrates have the thyroid gland and its iodinated hormones. In humans, the total amount of iodine is about 25-50 mg. About 50-70 % of total iodine is non-hormonal and it is concentrated in extrathyroidal tissues, where its biological role is still unknown. In 1985, Venturi hypothesized that iodide might

have an ancestral antioxidant function in all I-concentrating cells from primitive marine algae to more recent terrestrial vertebrates (Venturi, 1985; Venturi & Venturi, 1999, 2007; Venturi *et al*, 2000-a , 2000-b). In these cells iodide acts as an electron donor in the presence of H₂O₂ and peroxidases. The remaining iodine atom readily iodinate tyrosine, histidine or certain specific lipids, and so, neutralizes its own oxidant power (TABLES. 1, 2). In the wide range of antioxidants, we have recently hypothesised an “evolutionary hierarchy” of these substances, where the most ancient might be more essential than the recent antioxidants in the developing stages of animal and human organisms (Venturi & Venturi, 2007). In fact, deficiency of iodine, as a “primitive” antioxidant, causes more damage in developing embryos than some other phylogenetically more recent antioxidants, as many carotenoids and flavonoids (Venturi & Venturi, 2007). In pregnant women I-deficiency causes abortions and stillborns (Dunn & Delange, 2001). Recently Aceves *et al*. (2005) hypothesized that iodine is a gatekeeper of the integrity of the mammary gland.

IODINE, THYROXINE and EVOLUTION

Report on the evolutionary strategy of vertebrates in I-deficient terrestrial environment .

Venturi *et al*. (2000-a, 2000-b) and Venturi & Venturi (2007) reported that when some primitive marine vertebrates emerged from the I-rich sea and transferred to I-deficient fresh-water of estuaries and rivers and finally land, their diet became I-deficient and also harboured vegetable I-competitors such as nitrates, nitrites, thiocyanates, fluorides and some glycosides. About 400-500 million years ago (M/y/a), primitive Chordates started to use a new efficient follicular organ: the thyroid gland, as reservoir of iodine. During progressive slow adaptation to terrestrial life, the ancient chordates began to use thyroxine (T₄) in order to transport antioxidant iodide into the peripheral cells. The remaining triiodothyronine (T₃), the real active hormone, became active in the metamorphosis and thermogenesis for a better adaptation of the organisms to the new terrestrial environment (fresh-water, atmosphere, gravity, temperature and diet). The new hormonal action of T₃ was made

possible by the formation of T3-receptors in the cells of vertebrates. Firstly, about 600-500 M/y/a, T3-receptors with a metamorphosing action appeared in primitive *Chordata* and then, about 250-150 M/y/a, other T3-receptors with metabolic and thermogenetic actions appeared in birds and mammals. In water the iodine concentration decreases step by step from sea-water (60 $\mu\text{g} / \text{L}$) to estuary (about 5 $\mu\text{g} / \text{L}$) and source of rivers (less than 0.2 $\mu\text{g} / \text{L}$ in some Triassic mountain regions of northern Italy), and in parallel, salt-water fishes (herring) contain about 500-800 μg of iodine per kg compared to fresh-water trout about 20 μg per kg (Venturi *et al.*, 2000-a , 2000-b). So, in terrestrial I-deficient fresh waters some trout and other salmonids (anadromous migratory fishes) may suffer thyroid hypertrophy or related metabolic disorders. Youson (1997) and Youson & Sower (2001) showed that 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 Manzon & Youson (1997) in some anadromous migratory fishes (sea lamprey and salmonids), iodine and TH play a role in the initiation of metamorphosis. After metamorphosis, when the adult marine fishes die in fresh-water after reproducing, they release their iodides and selenium (and n-3 fatty acids) in the environment, where they have a beneficial role on the health of native animals and humans, bringing back upstream these essential trace-elements from the sea to I-deficient areas (Venturi *et al.*, 2000-a, 2000-b).

IODINE, REACTIVE OXYGEN SPECIES and SALIVARY GANDS

Summary of the literature on the biochemical, antioxidant, immunological, physiological and protective actions of iodine in saliva.

About 350 M/y/a the dry diet of terrestrial environment, firstly in anuran amphibians and after in reptiles (Shaham & Lewitus, 1971) (FIG. 1), favoured the development of the primitive tongue and of the primitive salivary glands, which embryologically derived from primitive I-concentrating oral cells, and which maintain I-concentrating ability. In amphibian metamorphosis iodides and

thyroxine are the most important factors inducing the spectacular apoptosis of cells of tail, gills and fins. Important functions of saliva are: cleansing of the oral cavity, solubilisation for digestion of food, bolus formation, facilitation of mastication and swallowing, food and bacterial clearance, dilution of detritus, lubrication and protection of oral and esophageal mucosae. Sodium iodide symporter (NIS) is the proteic transmembrane transporter of iodide into the cells (Spitzweg et al., 1998). Oral mucosa and gastric “iodide-pump” and NIS, are more primitive than the thyroidal ones, so have lower affinity for iodide and do not respond to more phylogenetically recent TSH (thyrotropin). Schiff *et al.* (1947) and Hays & Solomom (1965) reported that gastro-salivary clearance and secretions of iodides are a considerable part of “gastro-intestinal cycle of iodides”, which constitutes about 23% of iodides pool in the human body. Mammals, 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 (Miller *et al.*, 1975; Schiff et al., 1947). The entero-thyroidal circulation of iodides seems mediated principally by salivary and gastric NIS (Josefsson et al., 2002) (FIG. 2). In the mammals and humans, dietary iodine is rapidly adsorbed as iodide (I⁻) from the small intestine. Several mammalian and human extra-thyroidal non-follicular organs share the same gene expression of NIS and particularly salivary glands, stomach mucosa and lactating mammary gland (Wapnir *et al.*, 2003; Ullberg & Ewaldsson, 1964; Pellerin, 1961). Thymus, epidermis, choroid plexus and articular, arterial and skeletal systems have I⁻-concentrating ability too (Ullberg & Ewaldsson, 1964; Brown-Grant, 1961; Venturi *et al.*, 2000-b) (FIG. 3; FIG. 4). The fact that radioiodine (131-I) is also detectable in radioautographies of oral mucosa and epidermal fur of rats after 14 days, strongly suggests formation of unknown structural iodo-compounds, probably iodo-lipids and iodo-proteins, in some I⁻-concentrating cells (Pellerin, 1961; Brown-Grant, 1961). Salivary glands and saliva have the most rapid I⁻-concentrating capacity in the body, via an efficient NIS (FIG. 5). According to Banerjee *et al.* (1985, 1986) and De SK *et al.* (1985) the salivary glands and gastric mucosa have high ability to concentrate iodides and to form iodo-compounds by peroxidases. Gelb *et al.* (1962) showed iodine binding by proteins in

gastric mucus. The fact that mucous cells of some metastases from salivary glands (and gastric cancers) show I-concentrating ability might be interesting for a possible radiometabolic therapy (Mandell *et al.*, 1999). The thyroidal and extrathyroidal I-concentration and NIS are inhibited by nitrates, nitrites, fluorides, thiocyanates, some glycosides, salt and also, paradoxically, by an excessive quantity of iodine. Bahar *et al.* (2007) noted that increase in reactive oxygen species (ROS) and reactive nitrogen species (RNS) may have been the event that led to the reduction of salivary antioxidant systems, thus explaining the oxidative damage to the DNA and proteins, and the promotion of oral cancer. The oxidized proteins and DNA found in the saliva of the cancer patients seem to be the first demonstration of a direct link between salivary free radicals, antioxidants and oral cancer. Liskmann *et al.* (2007) and Zilmer *et al.* (2007) indicate that excessive ROS production in peri-implant disease is leading to the situation of excessive oxidative stress, which may be an important factor contributing to the destruction of peri-implant tissues. Maier *et al.* (2007) suggested that iodine restriction causes oxidative stress and DNA modifications in the cells of rats and mice. Furthermore, also an excess of iodides impairs the iodide pump (and NIS) and the cellular trophism of I-concentrating tissues, resulting in functional damage, including the well-known Wolff-Chaikoff effect, which occurs in the thyroid even with a dosage just in excess of 2 mg, as well as degenerative and necrotic lesions in some other I-concentrating tissues (salivary gland and gastric mucosa). Joanta *et al.* (2006) reported that I-excess exerts oxidative stress in some target tissues, in fact I-excess has pro-oxidant effects, leading to an increased lipid-peroxides level and catalase activity in target tissues and in blood. Inorganic iodine regulates the production of epidermal growth factor (EGF) in isolated thyroid cells, and controls DNA synthesis and cell proliferation (Tramontano *et al.*, 1989); this action probably occurs in salivary glands and in gastric mucosa too. EGF is a low-molecular-weight polypeptide first purified from the mouse submandibular gland, but since then found in many human tissues including submandibular gland, parotid gland. Salivary EGF plays an important physiological role in the maintenance of oro-esophageal and gastric tissue integrity. The biological effects of salivary EGF, and also esophageal

derived EGF, include healing of ulcers, inhibition of gastric acid secretion, stimulation of DNA synthesis as well as mucosal protection from intraluminal injurious factors such as gastric acid, bile acids, pepsin, and trypsin and to physical, chemical and bacterial agents. Banerjee demonstrated iodination "in vitro" of salivary (and gastric) proteins by peroxidase enzymes, and reported that the salivary gland is one of the richest sources of peroxidases, which are similar to the lactoperoxidases (Banerjee *et al.*, 1985, 1986). De SK *et al.* (1985) investigated the role of peroxidase-catalyzed formation of iodotyrosines in submaxillary glands and stomach. Abbey *et al.*(1984) noted that women incurred a fourfold-to-fivefold increased risk of a second primary breast cancer subsequent to the first primary salivary gland tumor. In October 7, 1999, the U.S.A. Committee of the House and Senate regarding "Marine Research" stated that "*The Committee notes the unusually low incidence of cancer in marine sharks, skates, and rays and encourages basic researches ...that have the potential to inhibit disease processes in humans.*" The role of iodine in fishes has not been completely understood, but it has been demonstrated that I-deficient fresh-water fishes suffer a higher incidence of infective, parasitic, neoplastic, and atherosclerotic diseases than marine fishes (Venturi & Venturi, 2006, 2007) (FIG. 6).

IODINE, ORAL, DENTAL and UPPER GASTRO-INTESTINAL PATHOLOGIES

Report on the essential literature concerning the role of iodine in oral and gastrointestinal pathologies .

Tooth loss reduces quality of life and may be related to poorer general health (Burt & Eklund, 2005). Reports from China have suggested that tooth loss may be associated with esophageal and gastric cancers (Abnet *et al.*, 2001, 2005-a, 2005-b; Wei *et al.*, 2005; Dye *et al.*, 2007) and also with oral cancer (Zheng *et al.*, 1990). Although oral cancer and esophageal cancer share common risk factors, such as alcohol and tobacco use, it is unclear whether poor oral health is a risk indicator for esophageal cancer. The high I-concentration of fetal thymus (Ullberg & Ewaldsson, 1964) (FIG. 7) suggests an important role of iodine in immune system. In 1985, we reported a significant immune-

deficiency in our population of Montefeltro (Italy) affected by high incidence of goitre, gastric cancer and oral pathologies (Venturi, 1985). In our I-deficient district of Montefeltro, before I-prophylaxis, comparison of decayed missing and filled teeth (DMFT index) in 12-year old children in 1980-1985, was 5.2, with a caries component of 89 %. In Italy, the mean value was 3.0 (in 1985), and 1.2 (in 1991) in I-sufficient Finland. Littleton & Frohlich (1993) showed that twelve skeletal samples, from the Arabian Gulf have been used to trace differences in diet and subsistence patterns through an analysis of dental pathology. The skeletons date from 3,000 BC to AD 1,500 and cover a variety of geographical locations: off-shore islands, Eastern Arabia, and Oman. The dental conditions analyzed are attrition, caries, and ante-mortem tooth loss (AMTL). Results indicate four basic patterns of dental disease which, while not mutually exclusive, correspond to four basic subsistence patterns. Marine dependency (rich in iodine) in population, is indicated by severe attrition, low caries rates, and a lack of AMTL. The second group of dental diseases- moderate attrition, low rates of caries, and low-moderate rates of AMTL affects populations subsisting on a mixture of pastoralism or fishing and agriculture. Mixed farming populations experienced low-moderate attrition, high rates of caries and abscessing due to caries, and severe AMTL. The final group of dental diseases affects inland populations practicing intensive gardening. These groups experienced slight attrition, high rates of caries, and severe AMTL. Sealy *et al.*(1992) reported that incidences of dental caries are presented for three groups of prehistoric human skeletons from different regions of the Cape Province, South Africa. The isotopic analyses of bone collagen demonstrate the importance of (I-rich) marine foods in the diet. The incidence of dental caries ranges from 0% among heavily marine-dependent individuals from the south-western Cape coastal area, to 17.7% among skeletons from an archaeological site on the south coast. The authors hypothesized that the extremely high incidence of caries in population might be related to lack of fluoride in the water. Elvery *et al.*(1998) in an anthropological investigation of the Ngarangbal Aboriginal Tribe's, a hunter-gatherer population, at Broadbeach, Australia, the caries prevalence (0.8%) was very low. These results support the proposal that the Ngarangbal tribe with

a diet that included marine foods. In fact, it is rare to find oral diseases, as well as malignant tumours, in I-rich marine fishes. Recently, Oxenham and Matsumara (2007) showed in two bio-archaeological studies of human skeletons (in Alaska and in Japan) the cariostatic effects of marine fish and sea-food diet in contrast with cariogenetic agricultural and animal food.

Many researchers (Weetman *et al.*, 1983; Parisi & Glick, 2003; Enwonwu & Sanders, 2001; Schneider, 1975; Marshall *et al.*, 2002; Wharton, 1987) showed that immune-deficiency and malnutrition in adolescence and I-deficiency and dental caries are associated. Cordain *et al.* (2005) hypothesized that the profound 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. Cordain suggests that I-deficiency was probably one, among other dietary variations, introduced during the Neolithic and Industrial Periods, which have altered crucial nutritional characteristics of ancestral human diets (simultaneously fibre and polyunsaturated fatty acid contents). For this reason, we believe that the I-deficient modern diet might also have damaged human oral health. In our I-deficient district of Montefeltro, Marani & Venturi (1985, 1986) reported a significant immune-deficiency in a group of 215 I-deficient schoolchildren, showing, however, normal values of thyroid hormones (T4, T3 and TSH). The authors improved the immune response of these schoolchildren, giving them an oral administration of Lugol's solution (2 mg of iodine weekly, by drops, for 8 months). In 1939, Hardgrove (1939) stated that "*in his community (Fond du Lac, Wis, USA), since the beginning of administration of iodine to prevent goitre, children have less caries. Iodine seems to increase resistance to caries, retarding the process and reducing its incidence.*" Researchers hypothesized also a general anti-tumour activity of I-rich edible marine algae and a favourable activity in human chemoprevention of oral cancer (Mathew *et al.*, 1995). The hypothesis of nutritional and indirect beneficial role of iodine in oral health is supported by studies carried out by Bartelstone (1949, 1950, 1951) and Bartelstone *et al.*, (1947) that showed an important direct radio-iodine penetration through intact

dental enamel, dentin and into the pulp, and an important uptake by the periodontal tissues. The authors also showed radioautographic evidence of indirect penetration of ^{131}I into enamel in cats and humans being following systemic administration of radioiodide. Ren *et al.* (2007) reported that selenium and iodine have beneficial effects on bone, cartilage growth plate and chondrocyte differentiation in rats. Recently Abnet *et al.* (2006) and Dye *et al.* (2007) showed a correlation between I-deficient goitre and gastric cancer and between gastric and esophageal cancer and tooth loss in Chinese population living in rural areas. Golkowski *et al.* (2007) reported, in Poland, a close association between improved iodine supply and decrease of incidence rate and death rate from stomach cancer after implementation of the effective I-prophylaxis. These researches support the study of Altorjay *et al.* (2003) showing that the expression of NIS is markedly decreased or absent in gastric cancer and in intestinal metaplastic mucosa of Barrett's oesophagus. According to current W.H.O. statistics more than 3 billion people in the world live nowadays in I-deficient countries. In Europe and throughout the world, I-deficiency is present in a large part of the population.

Recently, Dasgupta *et al.* (2008) described an alarming low iodine content of iodized salt in the United States. In the analysis of "National Health and Nutrition Examination Surveys" data of moderate to severe iodine deficiency is present now in a significant proportion (11.7%) of the U.S.A. population, with a clear increasing trend over the past 20 years, caused by reduced iodized table salt usage (Hollowell *et al.*, 1998).

In conclusion, many researches have hypothesized the important role of the diet in aetiology of oral and dental diseases, and have pointed out the importance of fluorine, magnesium, iron, immunity and ROS damage. In this study we wish to outline that iodine deficiency might have an essential role, and we also wish to highlight the role of iodine in the evolution of terrestrial life. The U.S. Food and Nutrition Board (2001) recommended daily allowance (RDA) of iodine ranges from $150\ \mu\text{g I/day}$ for adult humans to $290\ \mu\text{g I/day}$ for a lactating mother, while the thyroid gland needs no more than $70\ \mu\text{g I/day}$ to synthesize the requisite daily amounts of T4 and T3 used to

regulate metabolism and ensure normal growth and development (Miller, 2006). These higher levels of iodine-RDA seem necessary for proper functioning of a number of body systems, including the salivary glands, mammary glands and gastric mucosa (Miller, 2006).

The antioxidant, apoptosis-inductor and presumed anti-tumour activities of iodide might be useful in oral and salivary gland health, as reported in the prevention of some extrathyroidal pathologies.

We should also point out that I-deficient disorders are one of the more easily preventable conditions, at low cost, through dietary consumption of iodized table salt, and that extrathyroidal actions of iodide might be an important new area for investigation.

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TABLES 1, 2

Table. 1. Proposed antioxidant biochemical mechanism of iodides (From Venturi, 1985).

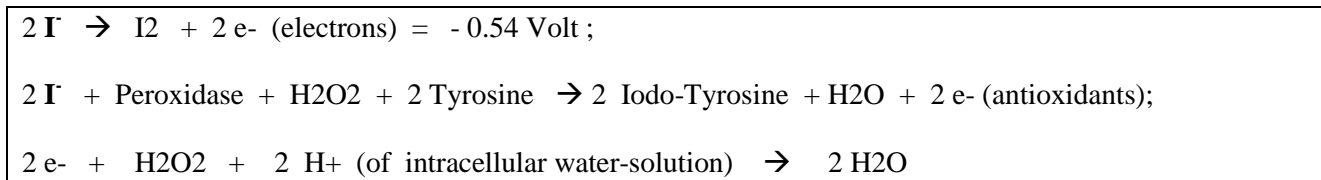
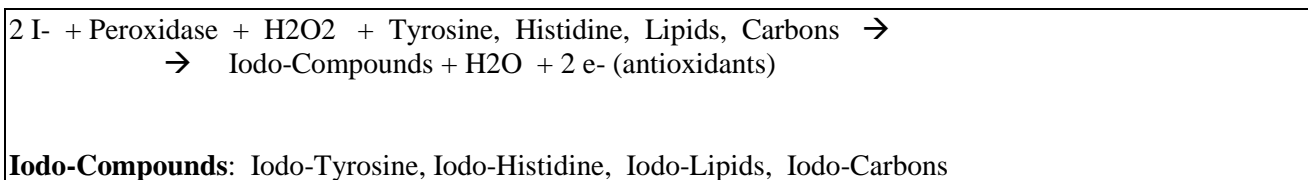


Table. 2. Proposed antioxidant biochemical mechanism of iodides, probably one of the most ancient mechanisms of defence from poisonous reactive oxygen species (Modified from Venturi, 2007).



7 FIGURES

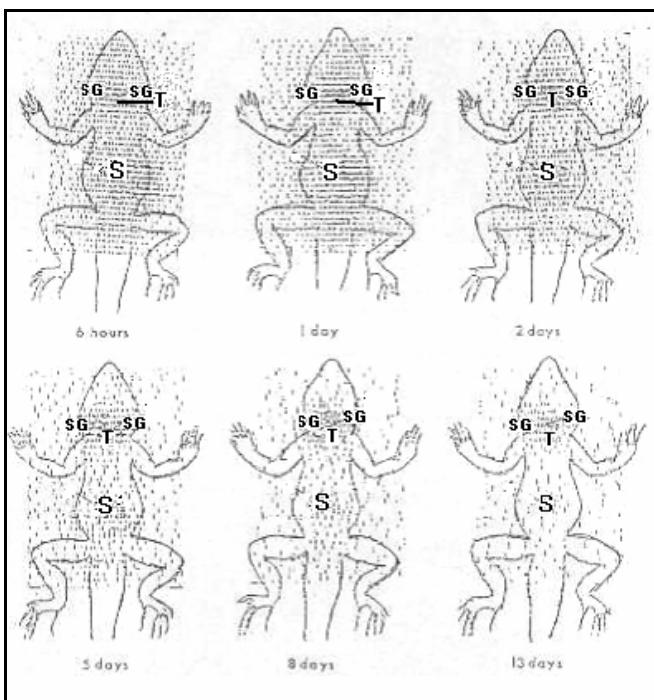


Fig. 1. Whole-body radioiodine (¹³¹I) scintiscans of reptile (lizard) showing high I-concentration in stomach (S) and in thyroid (T) and in near salivary glands (SG) (Modified from Levitus, 1971).

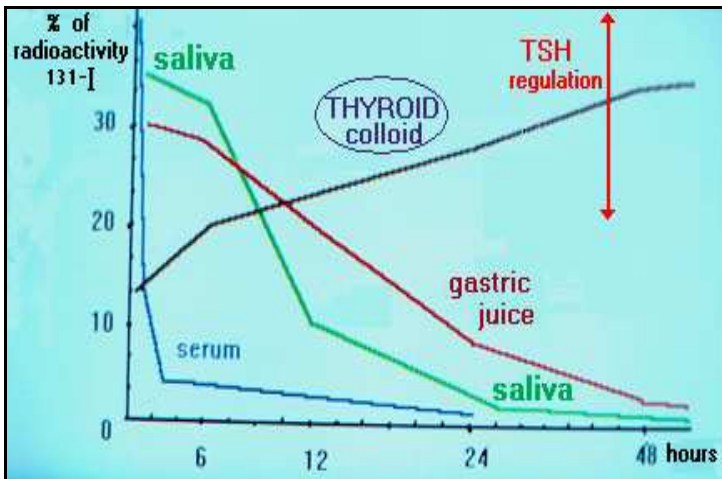


Fig. 2. Percentage of radioactivity in serum, in salivary and gastric secretions and in thyroidal colloid, after intravenous injection of ^{131}I , in man with normal I-uptake (Modified from Schiff, 1947).

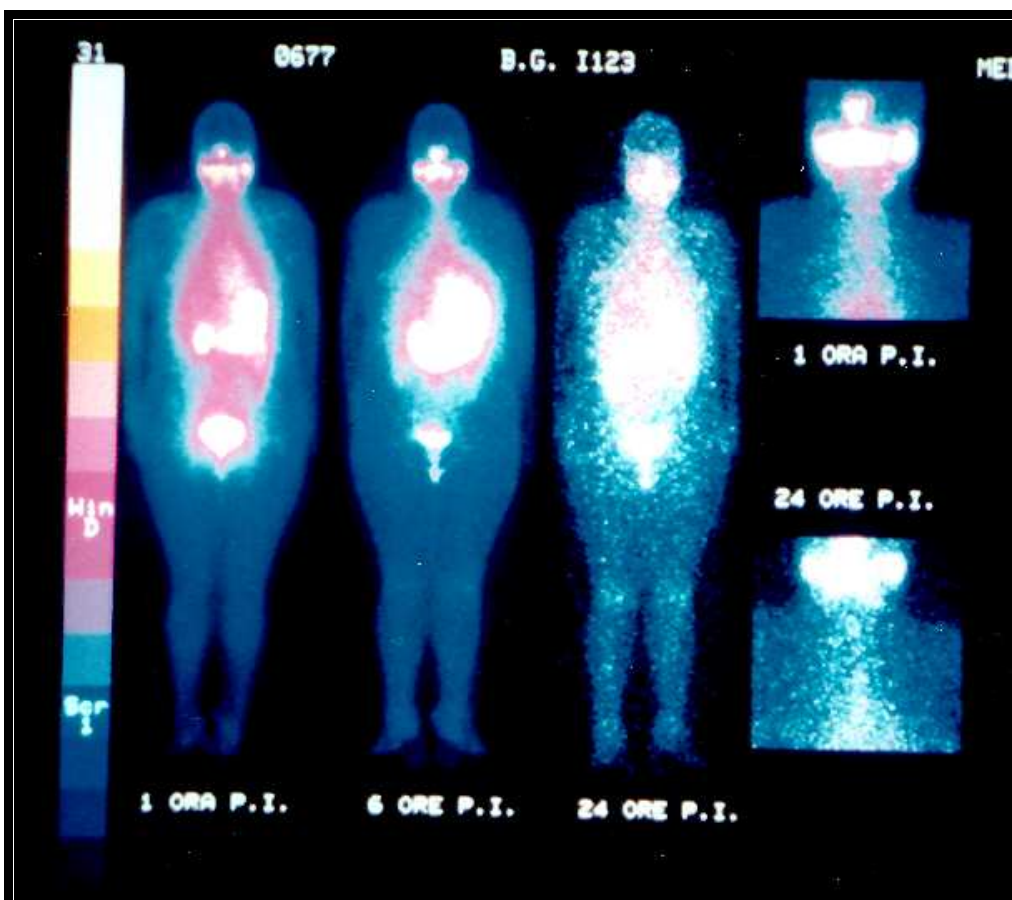


Fig. 3. Sequence of ^{123}I -I total-body scintiscans of a thyroidectomized

woman (for thyroid cancer) after intravenous injection of ^{123}I ; (from left) respectively at 1, 6 and 24 hours. The highest and rapid concentration of radio-iodide in oral mucosa and salivary glands and in gastric mucosa of the stomach and urinary I-excretion is evident.

Upper right: I-concentration in salivary glands and oral mucosa after 1 hour.

Bottom right: I-concentration in salivary glands and oral mucosa after 24 hours.

(From Venturi, 2000).

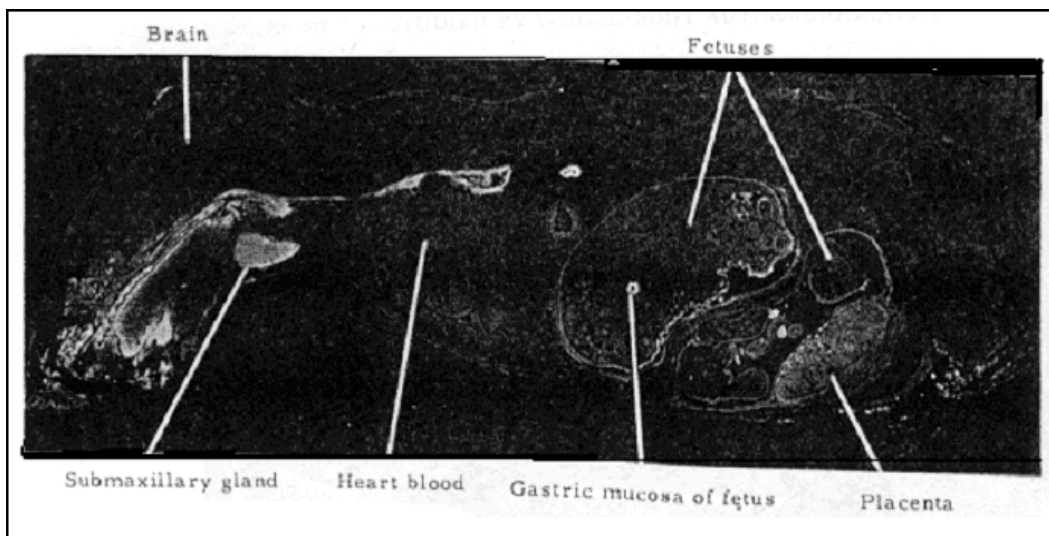


Fig. 4 . Distribution of ^{125}I (white) in radioautography of the body of a pregnant mouse 1 hour after intravenous injection. It is evident the high concentration in submaxillary gland and oral mucosa, and in gastric mucosa and placenta of the fetuses. (Reproduced with permission, from Ullberg and Ewaldsson, 1964. Courtesy of Acta Radiologica).



Fig. 5. NIS expression in iodide-transporting probed with anti-NIS Ab in salivary gland showing basolateral plasma membrane immunoreactivity in ductal cells, that exhibit active I- transport (Modified from Wapnir, 2003).



Fig. 6. Oral papilloma on the lips of terrestrial fresh-water salmon brown bullhead. Large papilloma on the right side and a smaller one on the left side of the lower jaw.

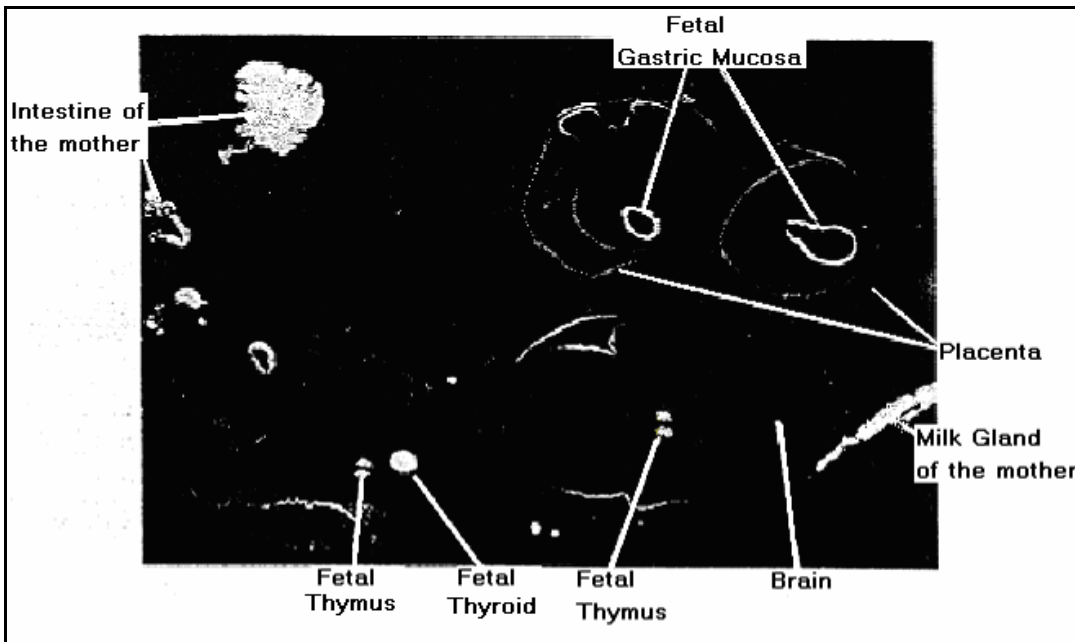


Fig. 7. Distribution of ¹³¹I in the abdomen of a pregnant mouse 24 hours after intravenous injection. It is evident high concentration of ¹³¹I in the fetal thymus, gastric mucosa and thyroid of two fetuses. The concentration is also high in the milk gland of the mother (on the right). (Modified, reproduced with permission from Ullberg & Ewaldsson, 1964. Courtesy of Acta Radiologica).