

Letter to the editor

Iodine, thymus, and immunity

To the Editor:

The United Nations nutrition policy papers [1,2], Food and Nutrition Board and Institute of Medicine [3], Dunn [4], Dunn and Delange [5] of the International Council for the Control of Iodine Deficiency Disorders reported that extrathyroidal iodine has an important action on the immune system. The high iodide concentration of thymus provides the anatomic rationale for this role of iodine in the immune system [6,7] (Fig. 1).

In 1985, Venturi [8] reported an immune deficiency in the population of Montefeltro (in central Italy) affected by a high incidence of goiter, gastric cancer, and oral and dental pathologies [9].

Marani and Venturi [10] and Marani et al. [11] found significant immune deficiency in iodine-deficient schoolchildren, in the same Italian territory, with a low urinary iodine excretion of 47 $\mu\text{g}/\text{d}$, despite their normal hormonal values of thyroid-stimulating hormone, free triiodothyronine, free thyroxine and absent serum antithyroid antibodies. The oral administration of Lugol's solution (2 mg of iodine/iodide weekly, by drops, for 8 mo) restored in these children a normal immune response evaluated by skin testing. Tay et al. [12] reported that leukocyte myeloperoxidase enzyme uses iodine in cell-mediated immunity, where iodine is used to produce iodine-free radicals. The concentration of myeloperoxidase enzyme is strongest in granulocytes and weakest in lymphocytes, and, as in thyroid cells, this peroxidase oxidizes tyrosine to a tyrosyl radical using hydrogen peroxide, and its inactivity predisposes to immune deficiency [13]. An inhibition of vacuolation toxin activity of *Helicobacter pylori* by iodine has recently been reported [14]. "In vitro" studies have shown that iodine can work with myeloperoxidase from white cells to inactivate bacteria [15]. Weetman et al. [16] reported that iodine could increase immunoglobulin-G synthesis in human lymphocytes in vitro. The immune suppression, which includes impaired cytokine function and a diminished acute-phase response to infections, negatively affects the natural history of inflammatory diseases. Tucker [17] demonstrated that immune defenses play an important role in various types of tumors. Iodine was and is sometimes used therapeutically in various pathologies, where the immune mechanism is known to play a dominant role. It has been administered favorably in patients with tubercular granulomatous, lepromatous, syphilitic, and mycotic lesions. This effect does not depend on iodine's direct action on the micro-organism responsible [11]. Oral iodine is also very effective

therapy in the lymphatic-cutaneous form of sporotrichosis. Zel'tser [18] reported a decreased bactericidal property of the plasma and decreased phagocytic activity of blood neutrophils in rats kept for 4–5 months on an iodine-deficient diet. This was apparently associated with depression of the intracellular metabolism reflected in a decrease of peroxidases in neutrophils. Stone [19] studied the role, in the primitive sea, of iodides as a regulating factor in inflammation. This investigator reported that iodides have many non-endocrine biologic effects, including a role in the physiology of the inflammatory response. In fact, iodides increase the movement of granulocytes into areas of inflammation. Iodides improve the phagocytosis of bacteria by granulocytes and the ability of granulocytes to kill bacteria. The multiple effects of this trace element have suggested that iodide has a physiologic role in inflammation. Extrathyroidal or peripheral thyroid hormone metabolism is mediated by deiodinases (types 1, 2, and 3). Types 1 and 2 catalyze the conversion of thyroxine (T_4) into triiodothyronine (T_3), whereas type 3 catalyzes the inactivation of T_4 into reverse T_3 (rT_3) and of T_3 into 3,3-diiodo-L-tyronine (3,3- T_2) and in this way type 3 deiodinase furnishes into peripheral cells one or two atoms of iodide per molecule of T_4 , which acts without any hormonal action. Boelen et al. [20] showed that part of the type 3 deiodinase protein is expressed by granulocytes and monocarboxylate transporter-8, a novel, very active, and specific thyroid hormone transporter [21], is also present at the site of inflammation. Inflammatory cells surrounding the abscess showed type 3 deiodinase and T_3 -transporter monocarboxylate transporter-8 immunoreactivity and local inflammation strongly induces type 3 deiodinase activity in inflammatory cells, especially in invading polymorphonuclear granulocytes, suggesting enhanced local degradation of T_3 with delivery of iodides [22]. Iodides were once used widely in medicine, especially before a cure for syphilis. Recently, Küpper et al. [22] confirmed the hypothesis of the ancestral antioxidant role of the iodide ion in primitive living cells, algae, and humans, which was first proposed in 1985 by Venturi [8] and by Venturi et al. [9, 23]. Furthermore, some researchers [24, 27] reported that Tasco-Forage, an (iodine-rich) extract from the brown seaweed *Ascophyllum nodosum*, has increased antioxidant activity and immune system in grazing animals and in plants. These results indicate that an adequate iodine intake is necessary for normal immune response in mammals and in some plants, too. In 1939, Hardgrove [28] stated that,

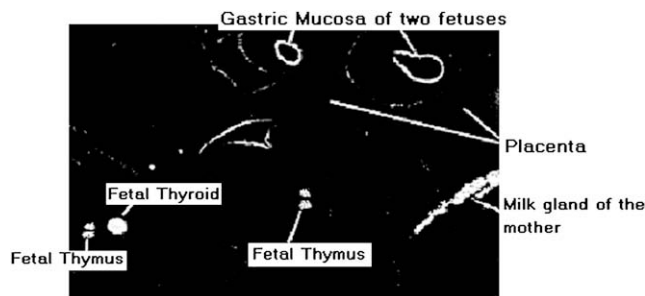


Fig. 1. Distribution of I^{131} (white) in the abdomen of a pregnant mouse 24h after intravenous injection. Two fetuses with a high concentration of I^{131} in the thyroid gland, thymus, placenta, and gastric mucosa [6]. The concentration is also high in the milk gland of the mother. (Reproduced with permission from *Acta Radiologica*.)

“in his community [Fond du Lac, WI, 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.”

The beneficial role of iodine in oral health is supported by studies carried out by Bartelstone et al. [29,30] that showed a direct radioiodine penetration through intact dental enamel, dentin, and pulp and in periodontal tissues. Venturi et al. [31,32], Abnet et al. [33], and Dye et al. [34] showed a correlation between iodine-deficient goiter and gastric cancer and between gastric and esophageal cancer and tooth loss in Chinese populations living in rural areas. Golkowski et al. [35] demonstrated, in Poland, a decrease of the incidence of death from stomach cancer after implementation of the effective iodine prophylaxis. In 2001 Venturi [36] published the first review on the correlation between dietary iodine deficiency and breast cancer, which is currently an interesting and up-to-date field of study. Despite that, Terracciano et al. [37] recently reported that the Italian territory of Campania is still a mildly iodine-deficient area.

The U.S. Food and Nutrition Board and Institute of Medicine [3] recommended a daily allowance of iodine from 150 μg for adult humans to 290 μg for lactating mothers. However, the thyroid gland needs no more than 70 $\mu\text{g/d}$ to synthesize the requisite daily amounts of T_4 and T_3 . These higher recommended daily allowance levels of iodine seem necessary for optimal function of a number of body systems, including the thymus, gastric mucosa, salivary glands, lactating breast, choroid plexus, etc. [7].

In conclusion, we believe that understanding the many effects of iodides requires crossing multiple fields. The diverse biologic effects of extrathyroidal iodides suggest their primitive and important role in immune and antitumor systems.

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