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Iodine in the Therapy of Graves' Disease: A Century After Henry S. Plummer

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In this issue of *Thyroid*, Uchida et al. present a mouse model of Graves' hyperthyroidism generated by immunization of BALB/c mice with the human thyrotropin receptor A-subunit.[1] The investigators then compared the serum thyroxine (T4) and triiodothyronine (T3) levels, the intrathyroidal content of iodothyronines, as well as expression profiles of genes involved in thyroid hormonogenesis and secretion in untreated mice (GD-C) and mice treated with inorganic iodide (GD-NaI). Unimmunized BALB/c mice were used as controls. The results document a normalization of the serum T4 and T3 levels in the GD-NaI mice, whereas GD-C mice continued to have elevated serum concentrations relative to unimmunized mice.

Compared with unimmunized mice, GD-C mice had higher *intrathyroidal* concentrations of T3, reverse T3 (rT3), and T4. In the GD-NaI mice, the mean intrathyroidal T4 and rT3 concentrations were roughly twofold higher in comparison with the GD-C mice. Transcriptome analyses showed an upregulation of genes coding for proteins involved in thyroid hormone synthesis, transport processes, and redox balance in the GD-C mice. In contrast, treatment with iodine inhibited the upregulation of these genes in the GD-NaI mice. More specifically, GD-C mice showed an upregulation of key genes such as *Tshr*, *Tpo*, *Dio1*, and the thyroid hormone transporter *Slco4a1* compared with controls. In GD-NaI mice, genes such as *Slc5a5 (Nis)*, *Slc26a4 (pendrin)*, *Tpo*, *Duox2* and *Duoxa2*, *Dio1*, and *Slco4a1* were downregulated, whereas *Dio3* was upregulated.

The data document that treatment with inorganic iodide results (1) in a decrease in thyroid hormone synthesis, (2) a decrease in thyroid hormone secretion, (3) an intrathyroidal increase of T4 and rT3, and (4) a normalization of serum T3 and T4. In aggregate, these studies add additional mechanistic details on the effects of inorganic iodide in Graves' disease,[1] a treatment that has been introduced a century ago by Henry S. Plummer (1874–1936; see Fig. 1, also cover figure of this issue).[2–5] This latter aspect is not mentioned by Uchida et al., and it is relevant to briefly summarize the history of the use of iodine in the treatment of goiter and hyperthyroidism.

After its discovery in 1811 by Chatin, iodine was used in the therapy of numerous diseases. Coindet, practicing in Geneva, Switzerland, used potassium iodide for the therapy of goiter.[6] In 1821, he reported that this often led to remarkable volume reductions but that some patients developed major toxic side effects, including severe tachycardia.[7] Without understanding the underlying mechanism, Coindet was confronted with iodine-induced thyrotoxicosis. Switzerland was severely iodine deficient at that time and, hence, many of these patients had goiters with autonomously functioning thyroid nodules. In 1910, Kocher coined the term *Jod-Basedow* (Jod = iodine in German) to describe this form of hyperthyroidism.[8] Because of the risk of inducing thyrotoxicosis in goitrous patients, the use of iodine then fell into disrepute.

But with time it also became apparent that there are two distinct etiologies of the syndrome that we now call hyperthyroidism. Some patients present with *simple or adenomatous goiter*, others with *exophthalmic goiter*.[5,9] *Exophthalmic goiter* had been recognized independently by several individuals, including Caleb Parry (1786), Giuseppe Flajani (1833), Robert Graves (1840), and Carl Adolph von Basedow (1840).[10,11] In 1909, William Osler formulated the hypothesis that *exophthalmic goiter* (now Graves' disease in the English literature) is ''due to disturbed function of the thyroid gland, probably a hypersecretion of certain materials which induce a sort of chronic toxaemia.''[10] The treatment consisted in thyroidectomy, which was generally associated with a high mortality in the hands of most surgeons.

It was also believed that Graves' disease was a form of ''dysthyroidism'' in which the gland secretes an abnormal thyroid hormone or toxin. Plummer, practicing at the Mayo clinic, reasoned that the secreted product could perhaps be

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FIG. 1. Dr. Henry Stanley Plummer (1874–1936), past president of the American Thyroid Association in 1933.

iodine deficient. Henry Plummer joined the Mayo clinic in 1901, became the fourth Mayo partner, had a major impact on the development and structure of the burgeoning firm, and made numerous contributions to medicine.[12,13] In 1922, Plummer administered iodine in the form of Lugol's solution (an aqueous solution containing potassium iodide and iodine) to patients with exophthalmic goiter scheduled for thyroidectomy. Surprisingly, the signs and symptoms of hyperthyroidism often disappeared within a few days.[2–5]

Equally important, the surgical mortality dropped from about 4–5% at the Mayo Clinic, an expert center, to <1%. In addition to the impact on thyroidal blood flow, it is likely that the decrease or normalization of the peripheral thyroid hormone levels contributed to the improvements in outcomes. This so-called *Plummer effect* describes the fact that large intrathyroidal concentrations of iodide inhibit hormone secretion in patients with Graves' disease.[14] Remarkably, Armand Trousseau documented the following observation already in 1862: ''However, …, it happens, …, that iodine preparations can be tolerated without damage and even with a semblance of improvement by certain persons suffering from Graves' disease.''*,[15] Starr et al. at the Massachusetts General Hospital confirmed the findings of the Mayo group,[16] and many subsequent clinical studies further corroborated the validity of administering iodine to patients with Graves' disease.[17–20]

*Original text in French: ''Cependant, …, il arrive, …, que les préparations iodées, peuvent être supportées sans dommage et même avec un semblant d'amélioration par certaines personnes atteintes de la maladie de Graves.''

Plummer's name lives on in the Plummer–Vinson syndrome (sideropenic dysphagia) and, relevant to thyroidologists, in Plummer's disease, which designates hyperthyroidism due to one or several autonomous thyroid adenomas. Of note, Plummer was the 9th president of the American Association for the Study of Goiter, now the American Thyroid Association, in 1933.[21]

The chronic inhibitory effect of inorganic iodide in patients with Graves' disease needs to be distinguished from the well-known autoregulatory *Wolff-Chaikoff effect*, which describes the transient inhibitory effect of high concentrations of iodide on *iodine organification* in the thyroid *in vivo*.[22,23] The seminal study by Wolff and Chaikoff was published in 1948 and had been preceded by the demonstration of an acute inhibitory effect of iodide *in vitro* in 1944.[24]

To this date, the administration of iodine is one of the cornerstones in the treatment of thyroid storm,[25,26] and it can also be used as an alternative to thionamides in selected instances.[27–29]

While certain details may be different in the human thyroid (e.g., the type of involved thyroid hormone transporter(s)), the study by Uchida et al. discussed earlier adds further detail on the role of inorganic iodide in regulating thyroid cell function—a century after the observations of Plummer, and two centuries after the reports of Coindet.

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