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EDITORIAL

Thyroid hormone therapy: past, present, and future

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"Unfortunately, no satisfactory treatment is known."
Sir William Osler, Principles and Practice of Medicine, 1892

"…that we can restore to life the hopeless victims of myxoedema is a triumph of experimental medicine… the results, as a rule, are most astounding—unparalleled by anything in the whole range of curative measures."
"Sir William Osler, Principles and Practice of Medicine, 1898"

Thyroid hormone therapy was truly one of the landmark achievements of medicine in the last century. Thyroid hormone deficiency is common, and failure to diagnose and treat it appropriately can lead to significant morbidity, and in extreme cases, even death. The purpose of this special issue of *Endocrine* is to celebrate thyroid therapeutics, and, more specifically, the use of synthetic levothyroxine (T4) and triiodothyronine (T3). While these compounds were isolated in 1914 and 1952, respectively, their use in the management of thyroid hormone deficiency did not occur until decades later. Desiccated thyroid was the major form of therapy in the USA until the mid-1970s, and, since then, levothyroxine has been favored above all other forms of replacement therapy in the USA [1] and the UK [2]. Currently, levothyroxine accounts for over 90% of all prescriptions for thyroid hormone in the USA [3] and the UK [2]. Indeed, levothyroxine has been one of the top one or two drugs prescribed in the USA for over a decade [4], with over 110,000,000 prescriptions in 2016.

In this special issue, we have endeavored to present information about levothyroxine therapy in the most comprehensive way possible, starting from the very beginning with the use of thyroid extracts, followed by the isolation of the two thyroid hormones, to their current therapeutic uses, and looking toward the future, with potentially novel uses of these molecules and the exciting therapeutic horizon of thyroid hormone analogs.

This special issue begins with an overview by Dr James Hennessey of thyroid hormone usage by the ancient Chinese and, centuries later, by 19th century Europeans, to the modern-day use of the synthetic sodium salt of levothyroxine. This is followed by a paper by Drs John Morris and Valerie Anne Galton charting the history of the isolation of thyroxine (T4) by Kendall in 1914, the clarification of its structure by Harrington in 1924, and the isolation of triiodothyronine (T3) in 1952 by Jack Gross and Rosalind Pitt-Rivers in England and Roche, Lissitsky, and Michel in Paris. Drs Morris and Galton also review the discovery of T4 to T3 conversion by Ingbar, Braverman, and Sterling, and the isolation of the iodothyronine deiodinases and the clarification of their crucial role.

Biondi and Cooper review the contemporary use of thyroxine to treat hypothyroidism, and emphasize not only the benefits, but also the potential risks. They additionally discuss approaches to managing patients with persistent hypothyroid symptoms despite normal thyroid function tests. Magri and colleagues review the common and controversial topic of subclinical hypothyroidism and provide guidelines for therapy based on patient age and serum TSH levels. The important issue of hypothyroidism in pregnancy, including the contentious topic of subclinical hypothyroidism, is reviewed by Shan and Teng, two authors who have conducted important research in this area. The differences in the management of hypothyroidism in children and adolescents, as compared with adults, is reviewed by Bauer and Wassner. They stress the importance of appropriate long-term treatment of hypothyroidism in childhood due to its

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multiple deleterious effects in this age group. Duntas and Yen provide an update on the use of thyroid hormone in elderly patients, including considerations related to cardiovascular risk. Inadvertent thyroid hormone abuse is probably a more common problem than is realized, and this topic is thoroughly discussed by Bernet, who has been at the forefront of this issue. Wiersinga reviews the recent developments in treatment of hypothyroid patients with persistent symptoms using combination T4 + T3 therapy. He highlights the considerable number of these patients and the multifactorial etiology of this condition, among which there is the recently described single nucleotide polymorphism (Thr92Ala) in DIO2 which may derange T4 to T3 conversion. Virili and Centanni review thyroxine in both softgel and liquid form, and the advantages that these new formulations may offer to certain categories of patients. Durante et al. have reviewed levothyroxine therapy in patients with differentiated thyroid cancer. While TSH suppressive therapy is justified in those with intermediate to high risk disease, it is of no benefit in the majority of patients.

An overview on thyroid hormone derivatives, called novel thyroid hormones, is presented by Zucchi et al., who discuss the biosynthetic pathways of these molecules, such as 3,5-diiodothyronine (T2), 3-iodothyronamine (T1AM), and 3,5,3′-thyroacetic acid (TA3). TA3 has been used as a therapeutic modality for TH resistance syndromes and is currently under assessment in patients with Allen Herndon Dudley syndrome. Senese and colleagues update us on the exciting area of thyroid hormone analogs and metabolites and their potential uses in the treatment of lipid disorders and obesity. Finally, Razvi reviews experimental studies showing a positive effect of thyroid hormone administration in patients with acute myocardial infarction and undergoing surgery. He briefly presents the pathophysiology of thyroid hormones in cardiac disease, while he also stresses the need for large randomized trials to clarify whether T4 or T3 might be beneficial.

We wish to thank *Endocrine* Editor-in-Chief, Dr Sebastiano Filetti for the opportunity to serve as coeditors of this special edition of the journal that is dedicated to thyroid hormone therapy. We hope that our readers will enjoy reviewing what they may have already learned, and acquiring new knowledge about these fascinating and deceptively simple molecules.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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