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Treatment of Hypothyroidism: Possibilities on the Horizon

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for the American Thyroid Association Spring 2013 Program Committee*

We would like to invite you to attend the upcoming spring symposium "Treatment of Hypothyroidism: Exploring the Possibilities." We hope you will share the enthusiasm of the organizing committee regarding our exciting spectrum of topics and speakers.

Although thyroid hormone therapy is by no means in its infancy, many aspects of its use are prescient and remain the subject of debate. We have progressed from the use of dried thyroid glands by ancient Chinese cultures (1), to the pioneering use of thyroid extracts given subcutaneously or orally in the 1890s (2), to the routine use of desiccated porcine or bovine thyroid preparations, and their subsequent replacement by synthetic levothyroxine during the mid-1970s (3). The expectation that use of levothyroxine would provide complete resolution of the constellation of symptoms that characterize hypothyroidism was a reasonable, but nevertheless overly optimistic, hope. Revolutionary though the availability of convenient, effective, and reliable synthetic thyroid hormone preparations has been, the specter of incomplete resolution of all symptoms associated with the hypothyroid condition has not left us.

Individuals with hypothyroidism and normal thyrotropin (TSH) values may have less psychological well-being (4–6) and more fatigue (7) than individuals without thyroid disease. Some (8,9), but not all (10), studies suggest that serum triiodothyronine (T_3) may be lower in levothyroxine-replaced patients than in the euthyroid population. Trials of combined therapy with both thyroxine (T_4) and T_3 in unselected populations have generally been disappointing (11–14). The seeming irreversibility of some ramifications of hypothyroidism may potentially be explained by the existence of genetic variations in deiodinases, TSH receptors, and thyroid hormone transporters (15–17). Our understanding of how such discoveries should influence our approach to the treatment of hypothyroidism will be advanced by adequately powered, prospective trials of the response of individuals harboring these genetic variations to specific therapies. Randomized, blinded, rigorously conducted, within-individual comparisons of therapy that can be subjected to meta-analysis may also advance our understanding (18). Through such means, the options of both synthetic and natural combination therapies will continue to be investigated. The possibility that some thyroid derivatives such as thyronamines have physiologic roles may need to be considered (19). Although there has been a hiatus since such products were reported in the literature (20), preparations of T_3 with a physiologic extended-release profile are also under development and may be one of our options for therapy in the future. Stem cell technology may also be applied in the future to reverse the athyreotic state (21).

As we learn more about the complexities of treating this condition, we are also learning that seemingly simple aspects of therapy such as achieving acceptable adherence to prescribed therapy and maintaining a TSH value within a desired target range cannot always be accomplished (22–24). In addition, different patient groups may require different approaches. Treating hypothyroidism in the elderly (24), for example, may not require the same therapeutic goals and frequency of monitoring as treatment of other populations such as those who are pregnant (25,26).

In conjunction with the work of the American Thyroid Association Task Force on Thyroid Hormone Replacement and Use of Thyroid Hormone Analogues,[†] we have organized a spring meeting that is devoted to these topics. We hope this meeting, scheduled in Washington, DC, on April 25 and 26, will be a forum conducive to exploring new research developments affecting these issues. As a starting point, the symposium will have a half-day of basic science that will review

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key aspects of thyroid hormone homeostasis and action. The topics include our understanding of the sources of T_3 in humans (thyroidal versus extrathyroidal production), the roles of transporters and deiodinases in regulating T_3 in the brain and other tissues, and modulation of thyroid hormone action by co-regulators of thyroid hormone receptors. Many of these elements exhibit multiple layers of regulation and/or variability, such as gene polymorphisms and alternate splicing variants, which could explain different clinical outcomes. Discussion of these possibilities will be addressed. Special emphasis will be given to the advances in measurement, kinetics, and understanding of the biological significance of serum thyroid hormone levels that are seen during therapy; particularly a discussion of how TSH expression is regulated and what significance can be attributed to narrow fluctuations in serum levels of T_3. An emerging subject that will also be covered in the basic science program is the use of thyroid hormone analogues to treat hypothyroid patients. Of course, none of this would be necessary if we could recreate and transfer a normal thyroid gland to our hypothyroid patients. With this in mind, the basic science symposium will be capped with a discussion of the recent seminal publication describing the use of stem cells to re-create functional thyroid follicles (21) [see also the article by Ma *et al.* (27) in this issue of *Thyroid*].

With this underpinning, we will then move onto a selection of clinical topics during the second day of our conference. We are privileged to start this day with some personal insights regarding treatment of hypothyroidism from a thyroidologist who has recently had an award established in his honor. We will discuss both the goals of thyroid hormone therapy and some sources of dissatisfaction with such therapy. We will then review data from studies of both T_3 monotherapy and T_4/T_3 combination therapy. Our lunchtime meet-the-professor sessions will, we hope, be stimulating and provocative, and will include discussion of dietary supplements, use of thyroid hormone for conditions other than hypothyroidism, and ethical issues surrounding thyroid hormone use. Our afternoon session should mitigate any postprandial drowsiness with a discussion of how genetic variations may influence therapy and an update on thyroid hormone analogues. We will be addressing the intricacies of treating hypothyroidism in specific populations such as children, the elderly, and pregnant women. We will also provide perspective from Food and Drug Administration representatives regarding pharmacology and regulatory issues.

The concern that a portion of hypothyroid patients have unmet needs remains with us. The hope exists that better understanding of thyroid hormone physiology and genetics will help us address those needs. We would like this symposium to be one of many meetings that provide an impetus for prospective, controlled trials of alternative therapy for hypothyroidism. Randomized studies designed specifically to determine whether the presence of deiodinase polymorphisms may influence a patient's response to therapy is one example of many such trials that would help guide our choice of therapy.

While we are excited about these innovative opportunities, we do not want to lose sight of the fact that we also need advances in our understanding of issues such as enhancing appropriate monitoring of our patients, ensuring compliance, and protecting our patients from inappropriate therapy or pressures to seek untried therapies. We tread a fine line between remaining open to novel possibilities and not sanctioning approaches to therapy that have not been validated and may not be beneficial when used long term.

We hope that through research in the multiple areas addressed in our symposium we will be in the vanguard of the mission to better tailor therapies for our patients in the era of personalized medicine. The cherry trees may no longer be flowering in Washington, DC, at the end of April, but we hope that nevertheless many ideas will be blossoming.

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