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Invited Editorial

Thyroid Health and the Environment

Thyroidologists have a long history of identifying, investigating, and addressing environmental influences on thyroid health. A prominent example is the recognition of the importance of iodine nutrition for normal thyroid development and function. Many of our colleagues in the American Thyroid Association (ATA) and sister thyroid societies have contributed extensively to understanding the basic mechanisms of iodine metabolism, determining the most effective methods of iodine repletion, and assessing and monitoring the benefit of iodine repletion programs. These colleagues have been, and continue to be, at the vanguard of efforts to ensure iodine repletion around the world (1,2). More recently, the importance of other trace elements for normal thyroid function, such as selenium, has been recognized (3), as well as the potential interference from nutrients, such as soy (4).

Environmental issues relevant to the thyroid, however, have expanded, with a wider range of toxicants released into the environment and a much greater ability to detect them and determine their effects (5,6). The most logical approach is to categorize agents based on the target(s) of disruption: iodine uptake, thyroid hormone synthesis, thyroid hormone serum protein binding, thyroid hormone metabolism, or thyroid hormone action. It is a challenge, however, to determine from among a very long list of potential thyroid toxicants, primarily tested in rodent and *in vitro* models, which are relevant to human thyroid function (6). The most valuable tool to make this assessment, often not available, is to gather direct data on the extent of exposure to a potential thyroid toxicant in an individual and any adverse effect over time.

In order to assess the impact of any agent on the thyroid, it is necessary to define an adverse thyroid effect. For agents that interfere with thyroid hormone production or metabolism, the earliest effect is often a rise in serum thyrotropin (TSH), usually within the range of normal, with maintenance of normal thyroid hormone levels, as one sees in patients after hemithyroidectomy (7). Many would interpret the mild rise in serum TSH as "compensation" to maintain normal circulating thyroid hormone levels, while some toxicologists define this as an "adverse event." Thyroid hormone production and metabolism are governed by regulatory mechanisms that maintain normal circulating thyroid hormone levels across a fairly wide range of dietary iodine intake. In evaluating the effects of perchlorate contamination on the thyroid, a National Academy of Sciences panel concluded that inhibition of iodine uptake was the earliest effect of perchlorate and the basis for their risk assessment. They stated, however, that hypothyroidism rather than iodine uptake inhibition, was the first adverse effect of perchlorate (8).

Any assessment of environmental agents influencing the thyroid must include an evaluation of the impact on the most susceptible populations, especially pregnant women, developing fetuses, and children. When making this assessment, however, it becomes clear that we have relatively little knowledge of the ability of the fetal or neonatal thyroid gland to compensate for reduced iodine availability or thyroid hormone production, and more research in this area is needed. For example, although the sodium/iodide symporter and deiodinases are expressed in the placenta, we do not know how the iodine supply across the placenta is regulated or whether there are compensatory mechanisms to counteract reduced iodine availability. This is why "uncertainty" factors are included in setting the minimum tolerability limit of any agent, to account for the many unknown effects of toxicants on these susceptible populations.

External radiation is associated with a spectrum of thyroidal effects, including hypothyroidism, stimulation of thyroid autoimmunity, and the induction of thyroid nodules and thyroid cancer. A number of longitudinal cohort studies have provided clear data on the consequences of radiation exposure (9). A few examples include the long-term follow-up of survivors from atomic weapons detonations in Japan (10,11), a large cohort followed after external head and neck radiation (9), the inadvertent consequences of atomic testing in the South Pacific (12), the Windscale nuclear accident in the UK (13), and the Chernobyl nuclear accident (14). The effects of radiation, however, can vary with the nature of the exposure, the duration of follow-up, and in the case of ^{131}I, the ambient iodine intake. For example, careful study of individuals exposed to radiation in Washington State from the Hanford nuclear site, has not demonstrated any adverse effects on the thyroid (15). In the long-term follow-up of survivors in Japan, early studies showed an increase in thyroid autoimmunity (10); these effects were not seen with longer follow-up (11).

What are the barriers to preventing environmental agents from producing adverse effects on thyroid health? Toxicological studies emphasize an unbiased look at the effects of a candidate toxicant on all tissues, as well as on the relationship between dose and effect. Toxicologists, however, use tools very different than most thyroid investigators, and they are generally less oriented to uncovering the underlying mechanisms of action. In some cases, the sites of action of the toxicant are not understood. This is where thyroid investigators from many disciplines can contribute their models and expertise to better elucidate these pathways. Any

evaluation of putative thyroidal toxicants is complicated by the potential for multiple agents to have a cumulative effect at one site, such as multiple inhibitors of iodine uptake, or single agents that affect thyroid hormone synthesis and action at multiple sites.

A major challenge in toxicology is understanding the factors that contribute to susceptibility to toxicants. In the case of the thyroid, iodine nutritional status may be the most significant susceptibility factor. Perchlorate, even at relatively high concentrations, seems to have minimal effects in a study of pregnant women from an area in Chile with relatively high iodine intake (16). A recent study in the USA suggested the possibility of altered thyroid function as a consequence of increased perchlorate only in women with low iodine intake ($<100\ \mu g$/day) (17) although this effect was not confirmed in a recent study from Europe where no effect of perchlorate on serum free T4 or TSH was found in iodine deficient pregnant women (18). Ensuring adequate iodine intake may be the most important intervention to limit the effect of toxicants that interfere with iodine transport.

Another area of investigation is the concept that a person's genetic profile might confer susceptibility to environmental agents, similar to pharmacogenomic profiles that can predict those most likely to respond to a given drug. Studies linking specific polymorphisms in genes involved in thyroid hormone synthesis, secretion, metabolism, and action with indices of thyroid function following exposure to putative toxicants would be needed to determine the validity of this concept. Other susceptibility factors certainly include age, gender, and race.

A new class of thyroid toxicants is a growing list of organic pollutants found to affect thyroid hormone action—some by acting directly on the thyroid receptor. Polychlorinated biphenyls and their hydroxylated metabolites (PCBs) interact with thyroid hormone receptors in ways that are incompletely understood (19). The body burden of PCBs is associated with elevated serum thyroxine and an increased thyroid volume on ultrasound (20). The widely used bactericide triclosan has been shown in an amphibian metamorphosis assay to enhance thyroid hormone action (21). Apparent actions of triclosan include increased expression of the thyroid hormone receptors in both the frog tail and brain. Interestingly, triclosan is a diphenylether with three chlorines and a hydroxyl group.

A recent editorial in *Thyroid* called for greater involvement of the sister thyroid associations in environmental issues relevant to the thyroid (22), and we agree with this call. The ATA and sister society members have been involved as individuals in a number of capacities. These include investigating the impact of thyroid toxicants and radiation, recommending potassium iodide (KI) distribution by public health officials to protect the thyroid from radiation accidents (23), and serving on the recent National Academy of Science panels on potassium iodine distribution for thyroid protection in the event of a nuclear accident (24) and the panel on health consequences of perchlorate ingestion (8). The ATA, through its Public Health Committee, has advocated at the state and federal level to promote KI distribution for thyroid protection and has weighed in on regulations for outpatient radioiodine administration. Members have testified before congress on environmental issues relevant to thyroid health. As an association, the ATA has spoken out with public health statements on KI protection, protection of thyroid health in pregnancy, the risk of perchlorate exposure, and most recently the need for iodine supplementation in pregnancy (25) (statements available online at <http://www.thyroid.org/professionals/index.html>). The ATA has also recognized the need to provide greater support to nongovernmental organizations, such as the International Council for Control of Iodine Deficiency Disorders, committed to iodine nutrition worldwide.

A major tool used by the ATA for outreach on public health issues has been a series of annual spring meetings that have highlighted significant areas of thyroid health and public policy. These meetings have drawn an international faculty representing various medical and scientific disciplines to present data, discuss relevant issues, plan outreach for public education, influence public policy, and promote research. Most of the topics have been related in some way to issues of thyroid and the environment, including the first in 2003, entitled "Potassium Iodide in the Event of a Nuclear Accident." Other conference themes have included thyroid disease and pregnancy and thyroid disease in older adults, and the conference in 2006 focused exclusively on the thyroid and the environment. The impact of these conferences has been extended by partnering with other organizations, including the March of Dimes, Centers for Disease Control and Prevention, National Institute of Environmental Health Sciences, National Institute of Child Health and Human Development, and National Institute of Aging.

"Thyroid Health and the Environment: Threats and Effects" was a one-day program sponsored by the ATA and held in Washington, DC, on March 24, 2006. The meeting brought together a diverse group of international speakers representing various disciplines and perspectives. The complete presentations are available in streaming video on the ATA web site at <http://www.thyroid.org/professionals/education/video_broadcasts.html>. Issues, such as the impact of perchlorate exposure on thyroid health, remain highly contentious, but the focus on review of the scientific data informed the discussions. Selected presentations were prepared as manuscripts and are presented in this issue of *Thyroid*.

There continues to be great interest by our patients, the public, and policy makers regarding these issues and thyroidologists need to remain engaged. Our hope is that these presentations will provoke thought and discussion, encouraging those in various areas of thyroid investigation and clinical care to consider how they might use their tools or expertise to make a contribution. The effects of environmental agents on the thyroid are relevant to all of us, and we should all be involved in finding solutions to these difficult, but ultimately solvable problems.

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