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# Thyroid International

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## Thyroid International

Editor-in-Chief: Peter PA Smyth, UCD, Dublin

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# American Thyroid Association Highlights of the 78<sup>th</sup> Annual Meeting

The 78<sup>th</sup> Meeting of the ATA was held in the Sheraton Hotel, New York City, from Oct 5–10, 2007. Both the scientific program and the New York venue (between Times Square and Central Park) were obviously a big draw as the meeting attracted the largest ever number of participants, approximately 1300. As is the rule with ATA Annual Meetings, the program tested the stamina as well as the enthusiasm of participants with early riser CME symposia starting at 6.30 am and their afternoon equivalents continuing into the early evening. Despite the intense program, the sessions were universally well attended reflecting the overall high quality of presentations. The major ATA prize lectures were given by Ken Burman, Washington, DC, Yuri Nikiforov, Pittsburgh, PA and Paul Walfish, Toronto, Canada. An innovative addition was the introduction of a transatlantic symposium on Iodine Deficiency held in conjunction with the ICCIDD, which was honored by a powerful address from Kul Gautam, Assistant Secretary General of the United Nations, setting the question of the continuing problem of IDD at the center of the ATA agenda. The social side of the meet-

ing was well catered for by a Welcoming Reception and Gala Banquet in the Sheraton Hotel. During the course of the latter, the ATA Distinguished Service Award was presented to Robert D. Utiger, Boston and the John B Stanbury Thyroid Pathophysiology Medal to Jerome M. Hershman, Los Angeles. This was undoubtedly one of the most successful meetings for which much credit must go to local chairs Peter Kopp and Michael McDermott, as well as ATA President David Cooper, Secretary Greg Brent and especially to Bobbi Smith and her team.

This Meeting Highlights report represents the personal views of what Stephen Spaulding and I found of greatest interest and is obviously not intended to provide a comprehensive report of the entire meeting. All presented abstracts are published in *Thyroid* (2007) Vol 17 Supplement 1 or from the ATA website <http://www.liebertonline.com/toc/thy/17/s1>. As abstracts of the “Early Riser” symposia are not included in public domain publications, short reports on all of these symposia are included.

Peter Smyth  
Editor-in-Chief

## Early Riser Symposia

The first Early Riser CME Symposium, “*Applying ATA Guidelines to Limited or Localized Thyroid Cancer*” was moderated by ATA President *David Cooper*, Baltimore, MD. The cases against and for the use of radioactive iodine in remnant ablation for low risk papillary thyroid cancer were forcefully and ably argued by *Ian Hay*, Rochester, MN and *Paul Ladenson*, Baltimore, MD. Following their presentations, the moderator presented individual cases and invited the audience to comment and eventually vote on the presenters’ recommendations. Although the debate could be considered to result in a dead heat aided by agreement on some of the cases, the majority of the audience, perhaps not surprisingly, favored continuation of the established practice of remnant ablation advanced by Ladenson.

The second CME Early Riser Symposium, “*Clinical Challenges in Managing Hypothyroidism*” was chaired by *Woody Sistrunk*, Jackson, MO. The subject of screening versus case finding was addressed by *Anne Cappola*, Philadelphia, PA, who explained the difference by providing standard definitions. Screening: ‘applying a test in an unsuspecting population without any clinical indication of disease’: Case Finding or Diagnostic Testing: ‘applying a test to an individual who exhibits signs or symptoms of disease’. She explained how the two can overlap or be confused, perhaps best illustrated by her final comment that “it is hard to walk out of my office without a TSH” but pointing out that she “has a strategy when the abnormal TSH comes back”. *E. Chester Ridgway*, Denver, CO, discussed the question of “*Mild Thyroid Failure: To Treat or Not*”. Having considered the possible causes and clinical manifestations of mild hypothyroidism, he reviewed published recommendations on therapeutic intervention and concluded that while a TSH of > 10 mIU/L warranted therapy, that of 4–10 mIU/L was more problematic. However, the publication of more randomized clinical trials was assisting better evidence-based decision-making in this area. *Mary Samuels*, Portland, OR, in discussing hypothyroidism in the elderly, emphasized the variability of reported prevalences (0.6–3.0% and up to 7% in the

very old). She pointed out the difficulties of making a diagnosis as there is often comorbidity. Despite this, she pointed out that elderly hypothyroid patients complain of the same symptoms as the young. Although there is much accumulated evidence of high rates of progression to overt hypothyroidism in the subclinically hypothyroid, she emphasized the importance of not commencing therapy on the basis of a single elevated TSH, as these frequently normalize over time.

The third CME symposium, “*Pregnancy and Thyroid Disease*” was chaired by *Robert Smallridge*, Jacksonville, FL. *Roberto Negro*, Lecce, Italy, reviewed the effect of either hypothyroidism or the presence of thyroid peroxidase antibodies (TPOAb) on pregnancy outcome. Although there was no significant difference in the pregnancy rate between hypothyroids and controls, the former had a higher risk of miscarriage. The same applied to TPOAb-positive subjects. There was also a greater risk of recurrent spontaneous abortion in TPOAb-positive subjects, although whether this was due to thyroid impairment or autoimmune causes was unclear. While higher TSH undoubtedly increased the risk of miscarriage, even a minor elevation (>2.5 mIU/L) itself increased the risk of preterm delivery. Both miscarriage and preterm delivery risk declined when L-T<sub>4</sub> was administered to TPOAb-positive subjects. However, the timing of such therapy was important. In the event of complications, therapy should be administered as soon as possible (i.e. from 21 weeks), but never after 42 weeks. *Lynn Barbour*, Denver, CO, speaking on hyperthyroidism in pregnancy warned against excess T<sub>4</sub> therapy which can shut down the baby’s thyrotrophs and result in central hypothyroidism. Addressing the problem of subclinical hyperthyroidism, her opinion was that therapeutic intervention was seldom indicated. This was also true for gestational hyperthyroidism or that arising in conjunction with hyperemesis gravidarum. She referred to the need to titrate the dose of propylthiouracil (PTU) used in the treatment of hyperthyroidism in pregnancy. The major indicator should be maternal thyroid status, not the specific dosage. The

objective of the therapy should be to keep maternal T<sub>4</sub> or FT<sub>4</sub> at a high normal level. If overtreated, neonatal hypothyroidism may result. She emphasized the need to maintain a balance between maternal TSAAb-stimulated neonatal hyperthyroidism and possible PTU-induced hypothyroidism. The final speaker was *Alex Stagnaro-Green*, New York, NY, who described how the reported variability in the prevalence of postpartum thyroiditis (PPT) was dependent on time of screening. The PPT stage detected was approximately 45% for hypothyroidism alone, 21% for hyperthyroidism followed by hypothyroidism, and 34% for hyperthyroidism alone. A greater prevalence was observed in women with Type 1 diabetes mellitus. He discussed the role in predicting subsequent PPT of TPOAb positivity during pregnancy and the increased risk of PPT in subsequent pregnancies. This was accompanied by permanent hypothyroidism in a significant number of subjects.

The fourth and final Early Riser CME symposium was entitled “*Imaging Techniques used for the monitoring of thyroid cancer*”. *Bryan McIver*, Rochester, MN, discussed the use of various imaging techniques in addition to ultrasound in the initial staging and follow up of patients with differentiated thyroid cancer. He described the criteria for low, medium, and high risk, and how a variety of imaging techniques could be used in risk assessment in thyroid cancer and the hierarchy of treatment options for metastatic disease. The use of ultrasound coupled with serum Tg measurement was the baseline for low and medium risk while higher risk, more aggressive or Tg positive tumors might require multiple scanning protocols involving CT, PET or MRI scans. *Douglas Van Nostrand*, Washington, DC, reviewed some of the pitfalls in reading thyroid imaging findings in thyroid cancer. It is important to obtain high resolution scans both with and without placing radioactive or anatomic markers on the skin, because the actual location of areas of uptake are frequently distorted and can be particularly misleading in the case of pinhole scanning. He also pointed out that radioiodine uptake in blood pools, the breast, the bladder, the stomach, the nose, and the salivary gland can be misleading. The initial scans should be reviewed before the patient leaves, to determine whether a repeat image should be obtained

to improve resolution or confirm what is presumed to be an artifact. In some cases, simply waiting for such uptake to dissipate or using an oblique scan is sufficient to improve the image. In other cases, swallowing water can wash radioactive saliva from the esophagus, giving lemon juice can eject radioactivity in the salivary gland or a laxative can promote expulsion of radioiodine from the GI tract. Finally *Ravinder Grewal*, New York, NY, described the application of newer imaging techniques such as SPECT-CT (single photon emission computed tomography), which he described as a dedicated gamma scanner coupled to a CT scanner. SPECT-CT can pick up non-iodine avid lesions with precise anatomic localization and is particularly useful in identifying bone metastases. Having identified the precise site of the disease, SPECT-CT has particular utility in carrying out lesional dosimetry.

## Award Lectures

### Paul Starr Award

*Dr Ken Burman*, Washington, DC, in his *Paul Starr Award Lecture*, reviewed recent advances in the investigation of thyroid cancer. Histological variants of papillary thyroid carcinoma differ in prognosis: the tall cell variant has a worse prognosis, while the follicular variant has a better prognosis. Vascular invasion has a markedly worse prognosis for distant metastases. He also reviewed biochemical features of certain cancers. Activated AKT can phosphorylate RAF, inactivating the downstream MEK-ERK pathway. Increased AKT activity has been found in most types of thyroid cancer, but is less common in follicular adenomas. Various different tyrosine kinases have been reported to display increased expression in thyroid cancers: some are overexpressed because they have become fused to other genes, while other cancers display a decrease in the activities of proteins that inhibit tyrosine kinases. Tumors with foci of cells that have lost cell polarity and intracellular adhesion also show a loss of e-cadherin, which permits  $\beta$ -catenin to enter nuclei and activate a variety of gene pathways. These manifestations of epithelial-mesenchymal transition are thought to promote invasiveness and distant metastases.

### Van Meter Award

The *Van Meter Award* was given to *Dr Yuri Nikiforov*, Pittsburg, PA, who was recognized for his contributions to the understanding of radioiodine-induced thyroid cancer. During the Chernobyl nuclear accident, a million children were at risk of exposure to 4 million Curies of  $^{131}\text{I}$  released into the atmosphere. A dramatic increase of carcinoma in the thyroid began 4 years later. The most salient discovery about the cancers in these children was that chromosome rearrangements – rather than single base mutations – were the commonest cause of papillary carcinoma following irradiation. The commonest rearrangement (between the RET and histone H4 genes, both being located on Chromosome 10), was found in over 80% of radiation-induced papillary carcinoma. The second most common finding was a BRAF/AKAP9 in-frame fusion on Chromosome 7.

About 10% of the cancers that developed after radiation have the BRAF/AKAP 9 rearrangement, whereas in sporadic papillary carcinomas, the most common defect is a single base mutation in the BRAF gene (~40%). Although a wide variety of gene mutations have been observed in thyroid cancer, the most commonly encountered appears to involve activation of the MEK-ERK pathway. Nikiforov provided background information showing that DNA exists in very large loops, and each chromosome occupies its own specific region within the nucleus. When a double-strand break occurs in DNA, the complex of proteins that forms to reunite the two strands may also be involved in causing the chromosome rearrangements. Nikiforov performed restriction endonuclease digestions on whole cells after X-radiating them, and deduced that only one double-stranded DNA preceded the chromosome rearrangements that occur either between the RET and H4 gene or between the RET and ELE1 gene.

### Keynote Clinical Address

*Antonio Bianco*, Boston, MA, in discussing “*The Role of Thyroid Hormone in the Regulation of Metabolism*” reviewed the role of deiodinases (DIOs) in fat metabolism, particularly of DIO2 in brown adipose tissue. The subcellular distribution of DIOs affects the cell’s responsiveness to  $T_4$ : DIO1 is located on the plasma membrane, whereas DIO2 is located in the endoplasmic reticulum around the nucleus. Thus,  $T_3$  made by DIO2 is more likely to enter the nucleus and to stay longer than  $T_3$  made at the cell surface by DIO1. Bianco then described the effects of bile acids on the actions of thyroid hormone on metabolism. Bile acids taken up from the gut spill into the systemic circulation and increase thermogenesis. TGR5 is a bile acid-binding protein found in mature brown fat cells. He noted that lithocholic and taurocholic acids are the most potent for activating DIO2 in brown fat. Giving a high-fat diet to TGR5 knock-out mice causes them to gain more weight than do normal mice. In pre-adipocytes, bile acids not only can change metabolism but also can cause their differentiation to mature brown fat.

### Historical Vignette

Arthur Schneider, Chicago, IL, presented the *Clark T. Sawin* Historical Vignette on the subject of “Radiation, Louis Hempelmann and Thyroid Cancer”. In a beautifully delivered talk, he told the story of the development of ionizing radiation leading to the development of the nuclear bomb, as well as early diagnostic and therapeutic uses. Many of these early uses have been implicated as being involved in the genesis of present day thyroid cancers. He described the seminal studies of Duffy and Fitzgerald on the dose–response curve relating radiation to thyroid cancer and in discussing risks from both external and internal radiation stressed the need for long-term studies extending for 30–40 years or longer before such risks can be accurately quantified.

### Sidney H. Ingbar Distinguished Lectureship

This year’s lecture was delivered by *Paul Walfish*, Toronto, ON, and lived up to its title “*Thyroid Hormone Action: A Second Career Odyssey*” by reviewing a remarkable career in many areas of clinical and laboratory thyroidology.

### Arthur Bauman Clinical Symposium on Thyroid Cancer Management

In this symposium, moderated by *Sebastiano Filetti*, Rome, Italy, *Robert McIntyre*, Denver, CO, spoke on the topic of optimizing initial surgical therapy for thyroid cancer. He contrasted the Japanese practice of prophylactic node dissection with the more conservative approach in the US or Europe. He pointed out the low level of evidence to sustain the approach of central neck dissection with removal of 5–25 nodes. *Richard Kloos*, Columbus, OH, addressed the topic of optimizing radioiodine (RAI) therapy and reviewed the ATA guidelines on choosing the dose used from a range of 100–300 mCi. He stressed that the minimum dose required should be employed: low-risk patients should receive 30–100 mCi; medium risk 100–200 mCi, and those with pulmonary metastases 100–300 mCi. He posed the question “How were these numbers arrived at?” He discussed the questions of quantitative tumor and blood dosimetry, and stressed the possibility of serious complications, particularly at higher RAI doses. He suggested individualized dosimetry based on a diagnostic scan coupled with RAI

retention calculations. *Stevan Sherman*, Houston, TX, described upcoming therapies for thyroid cancer. These would be principally directed at RAI refractory tumors and distant metastases and could also be used in treating medullary thyroid carcinoma. Therapies currently in development are directed at abnormal signaling, cell cycle and apoptosis, and epigenetic modifications, and would include protein kinase inhibitors, VEGF cascade, RET and BRAF, demethylating agents, and histone deacetylase inhibitors. He stressed that we cannot assume that all tumors handle drugs in the same way and therefore there was a need to develop individual personalized combination therapies.

## Clinical Symposia

### Current Thyroid Nodule Evaluation

*Erik Alexander*, Boston, MA, described the apparently increasing prevalence of thyroid nodules, whether it was found in older people or even in postmortem studies. The 'more we look the more we find'. He posed the question "What proportion are cancerous?" While improved detection would account for a major part of the increase, 8–15% had nodules >1.0 cm. He pointed out that persons aged <30 years carried a higher risk of malignancy (15–30%), while those aged 30–60 years had a lower risk (8–15%). The risk in subjects aged >60 years was uncertain. He concurred with the use of a nodule size <1.0 cm being used as a cutoff indicating minimum risk. *Susan Mandel*, Philadelphia, PA, addressed the question "When to biopsy a nodule? When not?" The criteria might be nodule size, sonographic characteristics, and clinical history. She repeated the 1.0 cm nodule size cutoff described by Alexander but noted the interobserver variability of 20% per ultrasound measurement and 50% by volume reported and its implications for reporting a 1 cm nodule versus a true 1 cm nodule. There is frequently a disconnection between pathology and clinical significance. She outlined the sonographic feature of thyroid malignancy but cautioned that ultrasound is not adequately sensitive but can be highly predictive.

*Bryan Haugen*, Aurora, CO, discussed molecular profiling of thyroid carcinomas. He categorized molecular markers as those involved in diagnosis, tumor progression, therapeutic targets and pathogenesis. One of the major diagnostic problems remains the separation of follicular adenoma from follicular carcinoma. This and other important distinctions will require the identification of the differential expression of a protein between tumor and normal tissue. To date, no single marker was adequately sensitive and specific using immunohistochemical techniques. Finally, he outlined various techniques of genomics and proteomics which will assist in identifying suitable tumor markers.

### Abbott State of the Art Lecture

*Craig Thompson*, Philadelphia, PA, talking about "Programmed Cell Death as a Means to Enhance Cancer Treatment" described the regulation of angiogenesis and how the cell has the ability to maintain itself independently of nutrients and growth factors. In a normal cell, significant loss of nutrient transporters results in bioenergetic decline. Oncogenic stress with decreased ATP:ADP ratio is a major factor in apoptosis. Signaling pathways instruct cells to take up glucose, which, in turn, must be converted to lactate and excreted. Both mutations and local environmental conditions promote increased glucose uptake by thyroid cancer cells. Other factors, such as inflammation and loss of P53 suppressor, have been implicated particularly in apoptosis. These features have stimulated efforts to find targeted drugs to replace <sup>131</sup>I in the treatment of thyroid cancer.

### Genetics of Thyroid Cancer

Activation of MAP kinase pathways occurs in many cancers. *Mingzhao Xing*, Baltimore, MD, described how activating BRAF mutations constitutively phosphorylate MEK1 and 2, which, in turn, phosphorylate and activate ERK1 and 2, which then alter the activity of many nuclear proteins involved in proliferation. The T1799A point mutation is by far the most common of the many BRAF mutations found in papillary thyroid cancer, but BRAF mutations are not found in follicular cancer. Although some regional and ethnic differences exist, papillary cancers containing BRAF mutations are generally associated with a higher risk of extrathyroidal spread, metastases, and tumor recurrence. Papillary cancers with BRAF mutations are also associated with overexpression of VEGF, metalloproteases, NF- $\kappa$ B and c-Met.

*Antonio Di Cristofano*, Philadelphia, PA, discussed the role of PTEN, which dephosphorylates phosphatidylinositol-3-phosphates, thus deactivating phosphatidylinositol 3OH-kinase (PI3K) and preventing it from phosphorylating and activating AKT. Loss of PTEN

heterozygosity or mutations in PTEN do occur in some thyroid cancers, but overexpression of PI3K is more common. When PTEN was selectively knocked out in the mouse thyroid, the animals were born with goiters that displayed increased levels of PI3K, p-AKT, and the proliferation marker, Ki67. The TSH level in the mice, however, remained normal. With increasing age, the thyroids of female mice developed adenomas or locally-invasive follicular carcinomas, but the thyroids of males showed no such pathology. If the animals were treated with an mTOR inhibitor starting at four weeks of age, their thyroid weights fell, as did Ki67 and cyclin D1/D3 protein levels, although there were no changes in the mRNA levels. The marked increase in proliferation at 12 weeks in the females could be stopped by removing their ovaries, while, on the other hand, giving estrogen to males increased thyrocyte proliferation. If these PTEN thyroid knock-out mice were crossbred with a K-ras mutant mouse, the animals developed huge thyroids and died of anaplastic thyroid cancer within a few months.

*Matthew Ringel*, Columbus, OH, reviewed the role of AKT in thyroid tumorigenesis and progression. The AKT family of protein kinases transmits signals from many pathways to a wide variety of proteins, including many that regulate cell survival and apoptosis. The pleckstrin homology domain of AKT lets it bind to phosphatidyl-myo-inositol-3-phosphates (PIP3s) in the plasma membrane. Thus, when growth factor tyrosine kinase receptors activate PI3K, the PIP3s formed in the membrane bind AKT. Another kinase, PDK1, then activates AKT, allowing it to phosphorylate many target proteins. Normally, the rise in AKT activity is transient: as the signal from a tyrosine kinase receptor decreases, PTEN dephosphorylates PIP3s, thus reducing PI3K activity, while protein phosphatases dephosphorylate AKT, inactivating it. However, AKT1 and 2 protein levels are commonly increased in follicular thyroid cancer, which in some cases could reflect activating mutations and/or increased gene copy number of PI3K. Increased AKT activity is associated with increased tumor size and invasiveness in many papillary and follicular thyroid cancers. Conversely, inhibitors of PI3K and AKT inhibit the growth of many thyroid cancer cell lines. Ringel

also reviewed studies showing that the invasive edge of papillary cancers show higher levels of markers of epithelial–mesenchymal transition than the central area of the tumors.

### Communications: Thyroid Cancer

*Joshua Klopper*, Denver, CO, whose group had previously showed that the RXR-selective ligand, bexarotene, inhibits proliferation in human thyroid cancer cell lines that express the RXR gamma receptor, presented data suggesting that bexarotene acts indirectly by causing the cells to secrete the cytokine LIF (leukemia inhibitory factor). When these cells were grown in nude mice, the plasma contained substantial levels of human LIF protein. Tumors that lacked the RXR gamma receptor produced no human LIF, suggesting that LIF might be a plasma marker for bexarotene-responsive thyroid cancers.

*Jeffrey Knauf*, New York, NY, described how a single base mutation in the BRAF gene produces the V600E mutant found in over 40% of papillary and 20% of anaplastic thyroid cancers, which is associated with a worse prognosis. They bred mice that express the V600E mutation selectively in the thyroid. At 5 weeks, the TSH in these mice rose transiently, and then fell as the mice developed goiters, then cancers. They microdissected poorly- and well-differentiated papillary cancers within the same animal, and compared the patterns of gene expression. Poorly-differentiated cancers had much less e-cadherin and desmocollin 2 but increased expression of procollagen and vimentin – all hallmarks of epithelial–mesenchymal transition. TGFβ was increased in the thyroids of the BRAF mutant mice, and PDGF-B or -D was increased in 8 out of 8 foci of poorly differentiated cancer, suggesting that an autocrine loop between TGFβ and PDGF is involved in the epithelial–mesenchymal transition.

### Targeted Therapies in Thyroid Cancer: Current Updates and Challenges

*Moderators:*

*Martin Schlumberger and Manisha Shah*

*Manisha Shah*, Columbus, OH, reported on current trends of targeted molecular therapies in DTC. She

described findings of Phase 2 studies on the kinase inhibitor Sorafanib which, despite side-effects necessitating a reduction in dosage, was judged successful. However, the true target for this therapy remains unknown. She also described findings targeting angiogenesis using oral multikinase inhibitors and stressed the importance of defining criteria for all targeted therapies of appropriate selection of both patients and endpoints for clinical trials.

*Sam Wells*, St Louis, MO, discussed the role of targeted chemotherapy for the different medullary thyroid carcinomas that result from various activating mutations in the RET gene. The chemotherapeutic oral agent vandetanib is an inhibitor of Ret kinase, although it can affect other tyrosine kinases as well. It inhibits the growth of tumors bearing different Ret gene mutations in nude mice, and reduces blood calcitonin levels by more than 50% in up to half of the patients in whom it was tested. However this may reflect decreased hormone release rather than a decrease in tumor growth. Rash and diarrhea were common side-effects. Interestingly, this agent also caused TSH levels to rise, requiring an increase in thyroid hormone replacement dose.

*Vincent Miller*, New York, NY, in discussing "*Targeted Therapies in Solid Tumors: Challenges and Solutions*" described progress in lung cancer therapy targeting the EGFR, which he described as the hottest current target. Tyrosine kinase inhibitors (TKI) can produce a very rapid response in some patients. However, a major problem is that many tumors develop acquired resistance to the treatment. He described the use of the TKI inhibitor erlotinib in lung cancers. He concluded that targeted therapies based on the molecular phenotype had huge potential for improved survival in solid tumors.

## Translational Symposium

### Thyroid Hormone Synthesis and Thyronamines

The enzyme dehalogenase was cloned and four patients with defects in the gene have been identified by *Jose Moreno*, Rotterdam, NL. Dehalogenase requires NADPH to recapture iodine from the monoiodotyrosine and diiodotyrosine produced in the thyroid when iodinated thyroglobulin is being degraded. All four of the patients studied had goiters, and the mutations identified all occurred near the NADPH binding pocket in the enzyme. Two of these individuals had been screened as neonates and, at that time, the test indicated that they were euthyroid. One of them developed a large goiter at 18 months and became mentally retarded. The other patient developed large goiter at 8 years but was mentally normal.

Dual oxidase 2 (DUOX2) is one of two NADPH oxidases expressed on the apical membrane of the thyrocyte, which generate the H<sub>2</sub>O<sub>2</sub> needed to iodinate thyroglobulin. Attempts to transfect cells with the DUOX genes to express functional enzyme had been unsuccessful until *Helmut Grasberger*, Chicago, IL, found the phylogenetically highly conserved DUOX2A gene located head-to-head with the DUOX2 gene on chromosome 15. DUOX2A encodes a protein that resides in the endoplasmic reticulum, where it functions as a maturation factor that is needed in order for DUOX2 to be expressed on the plasma membrane. In this meeting, Grasberger reported finding a mutant DUOX2A gene in a goitrous patient who has a positive perchlorate discharge test, whereas the DUOX genes were normal.

A new thyroid hormone that has unusual activities in hibernating animals has been described. By improving his assay of 3-iodothyronamine (T1-AM), *Tom Scanlon*, Portland, OR, demonstrated that T1-AM is an endogenous metabolite of thyroid hormone. It is found predominantly in the thyroid, but lower levels are found in fat. T1-AM in the blood is 99% bound to alpha-2 macroglobulin. Furthermore, T1-AM is a ligand for TAAR1, which was previously considered an orphan

nuclear receptor; however, T1-AM also appears to bind to alpha-2 adrenergic receptors. This substance has dramatic effects on body temperature and blood glucose level when administered to hibernating rodents.

### Stem Cells and Thyroid Development

*Reigh-Yi Lin*, New York, NY, briefly reviewed stem cell biology and his 2003 report, which showed that incubating mouse embryonic stem cells with TSH can result in embryoid bodies that express PAX8, NIS, thyroperoxidase and TSH receptor (in normal development, however, the thyroid anlage appears well before the appearance of TSH or its receptor.) A 2007 paper by Mitsutaki et al. used cell sorting to detect a side-population in some thyroid cell lines, and was most abundant in the ARO anaplastic carcinoma cell line. Cells from this side-population formed more clones than those from the main population. The abundance of this side-population increased when ARO cells were grown at low density, but cells from both populations can form tumors in nude mice.

*Michel Polak and colleagues*, Paris, France, reviewed how gene expression changes during human thyroid organogenesis. PAX8 is strongly expressed both in the ultimobranchial body and in the thyroid anlage in the floor of the midgut, and it persisted as follicular cells developed. TTF1 was expressed weakly and FOXE1 was even weaker in the thyroid primordium, but both remained expressed as the fetal gland developed. TPO, pendrin, and thyroglobulin expression increased as colloid follicles appeared, while NIS expression increased dramatically, first located around the nuclei but then in the basolateral membrane. In contrast, the levels of TSHR, PAX8, TTF1, and FOXE1 showed no changes over this time.

*Liuska Pesce and Peter Kopp*, Chicago, IL, reported that TSH does not increase pendrin mRNA levels in the thyroid: Pendred syndrome appears to reflect a problem in transporting the iodide/chloride transporter pendrin from the endoplasmic reticulum to the plasma

membrane. They incubated PCCL3 rat thyroid cells with TSH, labeled plasma membrane proteins with biotin, then lysed the cells, pulled the labeled proteins down with streptavidin, and probed western blots with an antibody to the extracellular domain of pendrin. TSH rapidly increased the level of pendrin expressed in the plasma membrane, whereas endosomal levels of pendrin fell. Forskolin had the same effects as TSH, whose action was blocked by the PKA inhibitor H-89. They concluded that the PKA pathway is involved in regulating the level of pendrin that is expressed on the plasma membrane.

*Peter Arvan*, Ann Arbor, MI, reported experiments that indicate that, in addition to the glycosylation and formation of numerous intra-chain disulfide bonds in the nascent thyroglobulin monomer, there are inter-chain disulfide bonds that form between two subunits during processing of the molecule in the endoplasmic reticulum. The homodimer then becomes endoglycosidase insensitive, and is secreted.

### Translational Symposium (ICCIDD)

This innovative symposium on iodine deficiency was dedicated to the memory of *Professor Francois Delange*, Brussels, one of the foremost campaigners for the eradication of iodine deficiency disorders (IDD), who died on June 15th 2007. The symposium was addressed by *Kul Gautam*, Assistant Secretary General of the United Nations and Deputy Director of UNICEF, who in outlining the history of the battle against IDD made a powerful plea and demonstrated an impressive commitment to their eradication. His contribution was followed by a presentation from *Elizabeth Pearce*, Boston, MA, who in outlining the current iodine status of the USA pointed out that a decline in observed urinary iodine excretion may indicate that a significant proportion of American children continue to be born to mothers who are borderline iodine deficient. *Michael Zimmerman*, Zurich, Switzerland, outlined the global situation with regard to IDD and commented that, while there was a definite improvement in dietary iodine intake worldwide, there was some evidence of slippage, particularly in developing countries. He emphasized the importance of continued monitoring of population iodine status.

### Clinical Symposium: Pediatric Thyroidology

*Catherine Dinauer*, New Haven, CT, in discussing thyroid cancer in children, described how the disease can present at <10 years of age. Although it has an excellent outcome, with a 10 years survival of about 99%, the risk of recurrence is high. Thyroid cancer is reasonably common as a second malignancy in childhood leukemia or lymphoma. The prevalence of genetic abnormalities in childhood papillary thyroid cancer is greater than in adults, and the abnormalities usually involve the genes RET and PTC. Diagnosis and surgical management are much the same as in adults. However, treatment with RAI is obviously questionable. She posed the question "Is there a maximum safe cumulative dose for RAI?" Following ablation, a suppressive dose of T<sub>4</sub> should be given with the aim being to maintain TSH in the low normal range. *Scott Rivkees*, New Haven, CT, in discussing pediatric hyperthyroidism, described the absence of a consensus on therapeutic options. Regional preferences were for radioactive iodine (RAI) in much of the NE, surgery in the Midwest and antithyroid drugs in New York. In addition,  $\beta$  blockade readily controlled symptoms. Remission rates (15–30%) on drugs were lower in children than in adults and were better if the gland was not enlarged. However, he cautioned that there were potentially more medical side effects for drug therapies in children and these were not trivial. The same applied to surgical treatment of childhood hyperthyroidism where complication rates were much higher than in adults. In the case of RAI therapy, the rate of hypothyroidism was greater in children than in adults. With radiation exposure, low dose RAI presented a greater risk. The goal should be the induction of hypothyroidism to minimize possible recurrence from the gland remnant. There was no evidence of increased risk of other cancers, although available data was limited.

*Stephen La Franchi*, Portland, OR, described how babies born with congenital hypothyroidism (CHT) may experience a deficit in IQ. He explained how maternal T<sub>4</sub> protects the fetus against severe hypothyroidism: the maternal T<sub>4</sub> has a T<sub>1/2</sub> of 6 days but its effect will disappear by 3–4 weeks. There is, therefore, a window of opportunity to treat CHT. The timing of treatment

is obviously of crucial importance with more severely hypothyroid babies requiring an early and higher T<sub>4</sub> dose. Annually in the USA there are about 4 million births, of which 1635 CHT were detected (~1/2500). Worldwide screening for neonatal hypothyroidism reaches about 20–25% of infants born per annum, in whom hypothyroidism is detected in about 800. The initial T<sub>4</sub> dose is of the order of 10–15 µg/kg/day. The dose can then be increased as maternal T<sub>4</sub> disappears from the neonatal circulation over the first weeks of life. The dose must be tailored to the severity of hypothyroidism as judged by serum T<sub>4</sub> (target range 10–18 µg).

## Thyroid Grand Rounds: Challenges in the Management of Hyperthyroidism

This session was moderated by *Lewis Braverman*, Boston, MA, who presented cases for discussion by a panel consisting of *Jayne Franklyn*, Birmingham, UK, *Martin Surks*, New York, NY, and *Leonard Wartofsky*, Washington, DC. There was much lively discussion on such problems as the treatment of thyroid eye disease and Graves' disease in pregnancy.

### Thyroid Hormone Receptors and Cofactors

*Xia Cao*, Nagoya, Japan, has previously shown that  $T_3$  acts through cytoplasmic TR $\beta$ 1 to rapidly stimulate the phosphorylation of AKT and downstream signaling via an interaction between the thyroid hormone receptor and the p85 $\beta$  regulatory subunit of PI3K. He reported similar findings in neural cells stably expressing TR $\beta$ 1. That receptor interacts with the C-terminal of the 85 kDa regulatory subunit of PI3K, stabilizing pAKT, activating its downstream targets BAD and GSK3 $\beta$ , and inhibiting apoptosis. The effect could be blocked by inhibiting PI3K or by expressing a dominant negative PI3K. Similar findings were obtained in organ cultures of postnatal brain cortex.

### Thyroid Autoimmunity

*Yaron Tomer*, Cincinnati, OH, reviewed some of the difficulties in determining whether finding genetic variation associations really does influence the risk of developing autoimmune diseases. Some associations appear to be important only in certain populations. Others are not disease-specific: for example, a single nucleotide polymorphism (SNP) at residue 274 in thyroglobulin increases the risk of Graves' and Hashimoto's disease five-fold. Similarly, a SNP in exon 33 doubles the risk for these two autoimmune thyroid diseases. However, if both polymorphisms are present, the risk for having at least one disease is increased more than 16-fold. The environment also influences the development of autoimmunity: 30% of patients receiving interferon alpha therapy for hepatitis C develop anti-thyroid antibodies and 10% develop frank thyroiditis. This could be related

to the in vitro observation that treating thyrocytes with interferon causes them to increase their expression of the TSH receptor and various stress proteins, while inhibiting cell growth and increasing cell death via necrosis.

*Sergio Lira*, New York, NY, discussed mechanisms involved in the recruitment, entry, and organization of lymphocytes in the thyroid. Most cells in the body, if appropriately stimulated, secrete various chemokines. There are some 40 chemokines, which are the ligands for different receptors expressed on the surface of leukocytes. Upon their release, the gradient in chemokine levels attracts leukocytes by chemotaxis. As a model of lymphocytic infiltration of the thyroid, the chemokine CCL21 was selectively expressed in the transgenic mouse thyroid, which attracted T and B cells to the thyroid in separate locations. The recruitment of T-cells caused 'high endothelium venules' to appear, which further increased the uptake of lymphocytes into the thyroid. Genetic deletion of the lymphotoxin-beta receptor abrogated development of lymphatic vessels in the inflamed areas, indicating it is involved in this process.

*Patrizio Caturegli*, Baltimore, MD, used serum from 28 patients with autoimmune hypophysitis to probe Western blots of human pituitary cytosol that had been depleted of immunoglobulins. Increased immunoreactivity in the 25 kDa region was found in serum of 50% of these patients, in 20% of patients with autoimmune thyroiditis and in fewer than 10% of normal sera. Neither the sensitivity nor specificity was adequate to be clinically useful, but the observation may be useful in identifying more potential candidates for the antigen(s) involved in the autoimmune hypophysitis.

*Raymond Douglas*, Los Angeles, CA, reviewed data that indicate more fibroblasts from Graves' patient express IGF1 receptor than do fibroblasts from normal subjects.

They also found more T-cells that are CD3 and IGF-1 receptor positive in patients with Graves' disease than in controls, and IGF-1 in vitro appeared to increase memory T-cells.

### The Thyroid and Lipid Metabolism

*Eduardo Nillni*, Providence, RI, reviewed the important role of prohormone convertases (PC) in regulating leptin and thyroid hormone feedback in the brain. PC1 and PC2 cleave preproTRH, proopiomelanocortin (POMC), and proneuropeptide Y (pro-NPY) in the secretory granules of neurons, thus releasing the mature peptides. If the circulating level of thyroid hormone falls, the expression of PC1, PC2, and proTRH genes increase, and more TRH is released from the paraventricular nucleus into the portal system. Conversely, if the level of T<sub>3</sub> rises, it reduces the expression of PC1 and PC2, and thus reduces TRH secretion. Exposure to cold decreases the suppressive response to T<sub>3</sub> by norepinephrine acting to increase PC1 and PC2 expression, whereas fasting increases the sensitivity to T<sub>3</sub>. Fasting decreases the expression of the proTRH, PC1, and PC2 genes and reduces the level of mature TRH in the PVN, whereas leptin reverses these responses to fasting. One way that leptin acts is by increasing PC1 and PC2 levels in the arcuate nucleus, increasing the production of NPY and  $\alpha$ MSH. They in turn act on the PVN to inhibit TRH release. The circulating level of leptin, which is directly related to fat stores, therefore provides feedback on the sensitivity of TRH to thyroid hormone.

*Sheue-yann Cheng* and *Osamu Araki*, Bethesda, MD, both gave talks on the effects of PV mutant thyroid receptors on fat metabolism. The PV mutation (a dominant negative frame-shift in the C-terminal 14 amino acids of TRs) destroys the ability of T<sub>3</sub> to bind to receptors and activate transcription. In vitro studies have shown that PV mutant receptors can still bind to peroxisome proliferator response elements in DNA, both as homodimers and as heterodimers with retinoid X receptors, and competition by these defective receptors appears to alter thyroid hormone actions on adipogenesis (when wild type mice are given PTU, the level of PPAR $\gamma$  mRNA in white fat decreases, but if the mice are also given T<sub>3</sub>, the PPAR $\gamma$  levels are restored

to normal). TR $\alpha$ <sup>PV/PV</sup> homozygote knock-in mice are not viable, but some TR $\alpha$ <sup>PV/+</sup> heterozygotes do survive, although they are small and have decreased white fat. The remaining white fat has only 20% of the normal level of PPAR $\gamma$ , and the downstream responses to this 'master regulator' of adipogenesis are repressed. TR $\beta$ <sup>PV/+</sup> heterozygote mice are slightly lighter and have ~1/3 less white fat than wild type mice. The expression of PPAR $\gamma$  in the white fat of TR $\beta$ <sup>PV/+</sup> heterozygote mice is reduced by 50%, and the downstream responses to this 'master regulator' of adipogenesis are repressed, but not as much as in TR $\alpha$ <sup>PV/+</sup> heterozygote mice. The PV mutation in TR $\alpha$  caused a greater decrease in the mRNAs that are downstream in the PPAR $\gamma$  signaling pathway, but both  $\alpha$  and  $\beta$  PV-mutants caused about the same decrease in mRNAs encoding lipogenic enzymes.

*E. Chester Ridgway*, Denver, CO, a consultant for Karo Bio on the study drug KB 2115, reviewed some clinical information behind the June release concerning this Phase II study. KB2115 has a 2-hour half-life in blood, displays seven-fold greater affinity for TR-beta compared to T<sub>3</sub>, and produces a 10-fold greater response in some genes. When either 100 or 200  $\mu$ g were given daily for 12 weeks to 99 hypercholesterolemic patients T<sub>4</sub> levels dropped to low-normal levels, circulating T<sub>3</sub> levels fell slightly, but circulating TSH levels were not affected. LDL, cholesterol, and APO-B levels fell, while HDL and ApoA1 did not change. There were no changes in cardiac or bone parameters, but liver function showed a slight increase in ALT and sex hormone-binding globulin levels.

*Mark Erion*, Metabasis Therapeutics, La Jolla, CA, described their approach for developing lipid-lowering anti-obesity agents based on selective activation of thyroid hormone receptor beta (TR $\beta$ ). They previously had identified a compound that showed some specificity for the liver, but the amount needed to be given in order to reduce lipid levels in rats with diet-induced obesity was large enough to increase the heart rate as well. They therefore added an aryl group, which gets oxidized by Cyp 3A4 in the liver, to form the active drug. The new agent (MB07811) was able to reduce circulating cholesterol, triglyceride, and hepatic triglyceride levels

at a dose one-third that needed to affect the heart, body weight, fasting blood glucose, insulin, free fatty acid levels or the thyroid-pituitary axis.

*Jinzhao Hou*, La Jolla, CA, reported preliminary results with MB07811, the liver-targeted thyroid hormone receptor agonist, indicating that it is safe and well-tolerated at the doses studied, and has minimal effects on genes in extrahepatic tissues.

### Thyroid Hormone Receptors and Cofactors

*Samuel Refetoff*, Chicago, IL, reviewed how he discovered the original patient with resistance to thyroid hormone, who had deaf-mutism, a small goiter, a high PBI, and stippled epiphyses on X-ray. Forty years later, 2000 patients in 400 families have been identified, with a wide variety of mutations in the three functional thyroid hormone receptor genes that have been characterized. In some patients, there are signs of hypothyroidism in one tissue but hyperthyroidism in another, the signs and symptoms being related to differences in relative receptor expression in different tissues.

*Herbert Samuels*, New York, NY, reviewed the distribution of thyroid hormone receptors and how additional factors are involved in thyroid hormone action. TR $\alpha$ -1 is expressed predominantly in skeleton and brown fat, TR $\beta$ -1 is expressed widely but at low levels in the heart, and TR $\beta$ -2 is present in the pituitary, retina, hypothalamus, hippocampus, and inner ear. In the absence of T<sub>3</sub>, various co-repressors interact with unliganded receptors on DNA. However, in the presence of T<sub>3</sub>, the co-repressors are replaced with co-activators. Some of the co-activators and co-repressors produce opposing covalent modifications on chromatin proteins, changing the structure of chromatin around particular genes. One interesting finding is that when some thyroid hormone receptors have been totally knocked out, the phenotype produced is not as dramatic as the change the phenotype produced by hormone deficiency.

*Thomas Zoeller*, Amherst, MA, described the role of thyroid hormone analogs, such as Bisphenol-A, which antagonize TR- $\beta$  mediated negative feedback in the brain. He also described the action of other endocrine

disrupters such as PCBs, which may be selective for particular types of receptors or tissues.

*Anthony Hollenberg*, Boston, MA, described the selective expression of a mutant of the co-repressor NCoR in the livers of transgenic mice, which prevents its interaction with thyroid hormone receptors. When these animals were made hypothyroid, thyroid hormone-responsive hepatic mRNAs did not fall as much as in hypothyroid animals bearing the normal NCoR gene. Furthermore, in euthyroid animals expressing the mutant NCoR, several hormone-regulated mRNAs (Cyp7A, spot 14, and DIO1) were expressed at much higher levels than in normal animals. These *in vivo* data indicate that NCoR affects the thyroid hormone receptor function both in the presence and absence of thyroid hormone.

Several patients have been described who have relative central resistance to thyroid hormone but display some peripheral responses to their elevated circulating thyroid hormones. *Machado, DS*, New York, NY, studied mice engineered to express a thyroid hormone receptor, TR $\beta$  bearing a mutation commonly found in clinical cases of central resistance, R429Q. Mice heterozygous for the mutant TR $\beta$  gene had free T<sub>3</sub> and T<sub>4</sub> levels twice normal, while the levels were four times normal in TR $\beta$ -homozygous mice. Confirming the fact that there was central resistance, pituitary levels of TSH were 2.6- and 4.5-fold higher than normal, respectively. The heterozygotes weighed 15% less and the homozygotes 20% less than the normal mice, and the levels of two T<sub>3</sub>-responsive genes in the liver, spot 14 and 5'-deiodinase, were increased. When propylthiouracil and a low iodine diet were given to the mutants, the level of TSH beta subunit mRNA increased more than in wild type mice. Some of the observations made in this mouse model of central resistance have not been noted in humans bearing this mutation, suggesting that modifiers of TR $\beta$  may act differently between species.

*Vijay Panicker and colleagues*, Bristol, UK and Oslo and Trondheim, Norway, described the role of TSH in predicting depression. They found that while a lower TSH does appear to predict anxiety in a population, subjects on T<sub>4</sub> therapy had a positive association between serum

TSH and both anxiety and depression. This may have implications for treatment targets in thyroid disease and may explain dissatisfaction with therapy in a subgroup of patients on thyroxine.

### Translational Symposium: Deiodinases/Selenoproteins

*P. Reed Larsen*, Boston, MA, discussed the role of selenoproteins in biology. He described how selenoproteins incorporated in enzymes such as glutathione peroxidase protect DNA, RNA and proteins from oxidative damage. In addition to their involvement inactivating thyroid hormones through deiodinase enzymes, he described their role in spermatogenesis. The importance of selenium in deiodinases was emphasized by the fact that replacement of S by SE in Type 1 deiodinase increased the speed of deiodination by 100 times. The topic of deiodination was continued by *Ronald Lechan*, Boston, MA, who discussed central mechanisms for thyroid hormone regulation by deiodinases. He described how D2 mRNA was expressed by tancytes in the third ventricle. These tancytes touched neurons and blood vessels. Interestingly, tancytes also expressed the thyroid hormone transporter MCT8. Tancyte D2 is upregulated by endotoxins, unlike in the pituitary where the effect is mediated by thyroid hormone. Finally *Jack Leonard*, Worcester, MA, discussed deiodinase dimerization and pointed out that full catalytic activity of D1 required both appropriately fused deiodinase units.

### Reports from ATA Research Grant Holders

*Douglas*, Los Angeles, CA, discussed “*The Phenotype of Mononuclear Cells in Graves Ophthalmopathy*”. He described the aberrant immune response in orbital fibroblasts which uniquely produce cytokines leading to orbital tissue remodeling. *Sara Danzi*, New York, NY, described her work on the project “*Is there a role for thyroid hormone in congestive heart failure?*” and outlined how a low T<sub>3</sub> is an indicator of heart failure. The working hypothesis she outlined involved the progression to congestive cardiac failure following an acute MI with decreased T<sub>4</sub> to T<sub>3</sub> conversion. She pointed out that replacement with T<sub>3</sub> will improve cardiac function in congestive cardiac failure. *Orsolya Dohán*, New York, NY, speaking on “*the Na<sup>+</sup>/I<sup>-</sup> symporter (NIS) transports*

*two of its substrates, I<sup>-</sup> and ClO<sub>4</sub><sup>-</sup>, with different stoichiometries*” explained the basis underlying the use of perchlorate (ClO<sub>4</sub><sup>-</sup>) as a thyroid function blocker. She explained how ClO<sub>4</sub><sup>-</sup> is translocated first, and only when all is translocated is I<sup>-</sup> transported by NIS. The NIS has a higher affinity for ClO<sub>4</sub><sup>-</sup> than for I<sup>-</sup>, with a lower V<sub>max</sub> due to 1:1 Na ion stoichiometry. She explained how ClO<sub>4</sub><sup>-</sup> transport into milk inhibits I<sup>-</sup> transport to the suckling newborn suggesting that ClO<sub>4</sub><sup>-</sup> contamination may be more harmful in the nursing mother. Finally, *Honey Reddi*, Rochester, MN, reported on “*the oncogenic potential of PAX8=PPARγ fusion proteins*” (PFRP) in thyroid follicular carcinoma. She reported on possible modes of action and on the therapeutic potential of the PFRP fusion proteins.

## Selected Communications

*Lewis Braverman and his colleagues*, Boston MA, Albuquerque, NM, and Cary, NY, studied plasma, cord blood, and amniotic fluid iodide, and concluded that the human placenta, unlike that of the rabbit, was unable to concentrate iodide for the fetus.

*Angela Leung and colleagues*, Boston, MA, reported that colostrum contained iodine in the range 27–385 µg/L (median 65 µg/L) but was not significantly associated with maternal UI. They postulated that dietary iodine was available to nursing infants immediately at birth.

*Aranda N and colleagues*, Queretaro, Mexico, applied to prostate cells lessons learned from treatment of breast cancer cell lines with molecular I<sub>2</sub>. They observed that I<sub>2</sub> inhibited proliferation on prostate cell lines, which was reversible when I<sub>2</sub> was removed.

*Tran NQ and colleagues*, Los Angeles, CA and Suwanee, GA, reported that TSH actively promoted perchlorate transport into thyroid cells in a dose dependent manner and was nontoxic to cells as determined in an MTS cell proliferation assay.

*Marie Hansson and colleagues*, Goteborg, Sweden, described sample variation for in vitro studies of iodine in thyroid tissues using X-ray fluorescence analysis. They found that tissues frozen at –20 °C gave results comparable with those obtained from fresh tissue, allowing the possibility of measuring iodine in small samples of benign or malignant tissues collected at surgery and then stored.

*Steven Lamm and colleagues*, Washington DC and Kansas City, KS, described how the negative association of serum thyroxine and urine perchlorate found for women of child bearing age with low iodine defined by UI was not found for those with low iodine defined by the Urinary Iodine:Creatinine ratio (UICr).

*Takahiko Kogai and colleagues*, Los Angeles, CA, reported that phosphoinositide-3-kinase (P13K) inhibitors

enhanced both iodide uptake and NIS mRNA expression in FRTL5 cells treated with TSH. Radioiodide uptake but not NIS mRNA expression was enhanced in papillary cancer BHP2-7 cells. The inhibitors alone, even in the absence of TSH, promoted increased radioiodide uptake. They concluded that the inhibition of PI3K signaling has a potential to increase the radioiodide accumulation in some differentiated thyroid cancer tissue.

*Okrojek R*, Mainz, Germany, described proteome analysis of tear fluid in Graves' orbitopathy (GO). Tear proteins were analyzed by mass spectrometry (MS) using SELDI-TOF MS arrays. The authors were able to identify proteins which could serve as biomarkers for the diagnosis and follow-up parameters during treatment for GO

*Joanne Rovet and colleagues*, Toronto, ON, studied subjects with defined hypothyroidism in early pregnancy including contrast sensitivity (CS) conditions that tap regions of the visual neuroanatomic pathway. They found that children with high TSH and low FT<sub>4</sub> had lower CS compared to normal controls, whereas the groups did not differ in visual acuity.

*Sanziana Roman*, New Haven, CT, reported on calcitonin screening in the US. The cost per test was \$40 compared to \$23 for TSH. The prevalence of medullary thyroid carcinoma (MTC) was 0.78% of thyroid nodules. Thus it cost approximately \$5000 to detect one case of MTC. They concluded that calcitonin screening is feasible, with reduced mortality and a 13% increase in cost, but that cost-effectiveness decision analysis studies of routine calcitonin screening in patients with thyroid nodules are needed.

*Cristina Romei and colleagues*, Pisa and Siena, Italy, demonstrated in a 10 year follow-up study that somatic RET mutation in MTC correlates with the presence of lymph node metastases at diagnosis, with a worse outcome in terms of persistence of disease and a significantly lower survival rate.

*Valter Boldarine and colleagues*, Sao Paulo, Brazil, reported on an enhanced quantitative RT-PCR assay for blood thyroglobulin (Tg mRNA) using modified primers prepared from a region covering exons 40–41. This new method for Tg mRNA quantification was reliable, allowed separation of patients free of disease from those with metastases, and could be an appropriate molecular marker in the follow up of patients with DTC, especially those with positive TgAb.

On the same subject, *Claudia Nakabashi*, Sao Paulo, Brazil, reported that using a sensitive immunoassay for Tg had comparable sensitivity in follow-up of patients with DTC on T<sub>4</sub> suppression to measuring serum Tg levels after stimulation by inducing hypothyroidism.

*Raffaele Napoli*, Naples, Italy, postulated that TSH itself may have an effect on vascular function independent from its role in stimulating thyroid hormone production and release. They found that infusing high levels of TSH into the brachial artery for 4 hours acutely and directly affects forearm blood flow and potentiates the vasodilatory response to acetylcholine and the vasoconstrictory response to norepinephrine.

*Stephen James and colleagues*, Birmingham, UK, proposed a role for the monocarboxylate transporter MCT8 independent of its T<sub>3</sub> transporting function. They found that repression of MCT8 by siRNA resulted in a significant increase in proliferation in fetal embryonal NT2 and placental JEG-3 cells in vitro, similar to that seen with mutations of MCT8 reported in males with severe psychomotor defects. These results further extend the evidence of a potential role for MCT8 in the modulation of cell proliferation, independent of T<sub>3</sub> transport.

The possibility that some of the effects of hypothyroidism on bone could be due to the high levels of TSH, rather than the low level of thyroid hormone, was addressed by *Wendy Van der Deure and colleagues*, Rotterdam, NL. They studied mice with total knockout of the TR $\alpha$  gene, the TR $\beta$  gene or TSH receptor gene. Homozygous TR $\alpha$ 1 knockout mice appear euthyroid, but have delayed ossification. In contrast, homozygous TR $\beta$  knockout mice have advanced ossification,

decreased growth plates, and elevated T<sub>4</sub> and TSH. Finally, the TSH receptor knockout animals have very high levels of TSH with very low levels of T<sub>4</sub>. These animals later develop severe osteoporosis that is not reversed with treatment with T<sub>4</sub>.

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