2 | 2007

Thyroid International

edited by: Peter PA Smyth, UCD, Dublin

published by: Merck KGaA, Darmstadt, Germany

Report of the 31st Annual Meeting of the ETA

September 2–6, 2006, Naples, Italy

PPA Smyth and JH Lazarus

MERCK SERONO

Report of the 31st Annual Meeting of the ETA

September 2–6, 2006, Naples, Italy

PPA Smyth and JH Lazarus

Correspondence:
Peter PA Smyth MSc, PhD
UCD Conway Institute of Biomolecular & Biomedical Research
Belfield, Dublin 4, Ireland
Phone: +353 1 7166736
Fax: +353 1 7166701
E-mail: ppa.smyth@ucd.ie

Thyroid International

This is the title of a publication series by Merck KGaA, Darmstadt, Germany. We are publishing papers from renowned international thyroid experts in order to pass on the extensive experience which the authors possess in their field to a wide range of physicians dealing with the diagnosis and therapy of thyroid diseases.

Responsible at Merck KGaA, Darmstadt, Germany:
Sigrid Butz, M.D.

Thyroid International · 2–2007

Merck KGaA, Darmstadt, Germany, D-64271 Darmstadt
ISSN 0946-5464

Cover: Mount Vesuvius

Report of the 31st Annual Meeting of the ETA

September 2–6, 2006, Naples, Italy

The ancient city of Naples provided a most appropriate venue for the 31st Annual meeting of the ETA. Although the region of Campania is better known to tourists for its archeological sites and the dramatic Amalfi coast, the city of Naples with its elegant Bourbon palaces not to mention its pizzas, also occupies a prime position in the story of modern thyroid research being the home of the late and much lamented Gaetano Salvatore (Nino) and the birthplace of the current father of modern thyroidology Aldo Pinchera. Thus it was no surprise that Gianfranco Fenzi, Giancarlo Vecchio and colleagues provided a template for a most successful ETA. The meeting together with its associated ICCIDD and ETA-CRN satellites provided a stimulating week for all participants. The meeting attracted 753 attendees included 676 active participants, 52 accompanying persons, and 25 company representatives. There were 50 oral presentations presented in 2 topic highlights and 6 oral sessions. A total of 310 posters were displayed and a selection presented in 8 poster discussion sessions.

The quality of the oral presentations, seminars and plenary lectures matched the magnificence of the Monte Sant'Angelo venue. The meeting was characterized by lively well attended poster discussion sessions. This trend towards elevation of the status of poster presentations, first apparent to this observer in the ITC in Buenos Aires, can serve as a means of enhancing the sense of meaningful participation of so many more attendees at our international meetings. Hopefully it will be noted and encouraged by future meeting organizers.

The meeting was not all about work with an opening ceremony in the splendor of the Palazzo Reale where many of us were privileged to learn or top up our learning of the exotic history of the various kingdoms of Naples. Next there was an unforgettable visit and social evening in the incomparable setting of Pompeii. Finally to those fortunate enough to attend there was a delightful banquet at Complesso Monumentale S. Marcellino with its cloisters and wonderfully frescoed church.

Our thanks to Gianfranco Fenzi and Giancarlo Vecchio, their colleagues and FASI for superb organization. Memories of Napoli will long remain.

This is not meant to be a comprehensive report of all the meeting activities but represents the subjective preferences of John Lazarus and myself on what we found most interesting. The text of all the accepted abstracts for ETA 2006 can be viewed on the ETA website *(www.eta2006.com)* linking to Hot Thyroidology *(www.hotthyroidology.com)* ETA Abstract Book (July 28th 2006, 1.5 MB).

Peter PA Smyth, Editor in Chief

Satellite Symposia

The satellite symposium "The cardiovascular risk at the various stages of thyroid failure" sponsored by Merck Darmstadt is separately published as a highlight report.

As is the custom the formal Scientific Meeting was preceded by two satellite symposia, the European Thyroid Association Cancer Research Network ETA-CRN and the ICCIDD West Central Europe Regional Satellite Meeting, both of which took place at the University Congress Centre on the beautiful Naples seafront. The ETA-CRN meeting covered two topics: a Chernobyl Symposium "What have we learned in 20 years?" and a clinical symposium "Tg and thyroid cancer".

ETA-CRN

In the Chernobyl Symposium *Tuttle* (New York) reported that despite the dramatic rise in childhood thyroid cancer directly following the Chernobyl accident, no major rise in either haematological disorders or other solid tumours have been observed. Studies have now commenced looking at possible non-malignant end points in those dwelling in affected areas such as cataracts, cardiovascular disease or emotional sequelae to the disaster. *Kopecky* (Florida) reporting on the findings of an international collaboration demonstrated that uncertainties as to the amount of radiation received, the radiation risk for thyroid cancer was large but not inconsistent with earlier reports. Molecular rearrangements which can distinguish Chernobyl radiation related tumours from their sporadic counterparts were reported by *Lima* (Porto, Portugal) while SNPs occuring in several genes from both radiation induced or sporadic thyroid tumours were reported by *Namba* (Nagasaki). *Bogdanova* (Kiev) outlined pathological findings in children following the Chernobyl accident. Although papillary lesions predominated, a relative increase in the follicular variant with increasing tumour latency was noted. *Zitzelsberger* (Munich) also reported that molecular rearrangements in radiation induced thyroid tumours were polyclonal. Similar gene rearrangements were observed by *Romei* (Pisa) within RET/PTC rearrangements decreasing while BRAF increases with a longer latency period. Finally *Detours* (Brussels) used microarrays to distinguish between mRNA expression profiles in sporadic and Chernobyl radiation induced tumours. The two were indistinguishable in the majority of cases but some subtle mirrored the aetiology of the tumours.

Abstracts available on the ETA website: *http://www.eurothyroid.com/docs_naples/6thETACRNprogramme-Naples-inclLogi280806.doc*

ICCIDD West Central Europe Regional Meeting

The ICCIDD meeting was jointly chaired by *Pinchera,* Chair of the West Central Europe Region and *Burrow* newly appointed ICCIDD Chairman.

Timmer, UNICEF, presented data on the current status, challenges and programme perspectives of sustainable IDD elimination in Central and Eastern Europe (CEE) and the Commonwealth of Independent States (CIS).

Delange (Brussels) reported on the recommendations of the 2005 "WHO technical consultation on prevention and control of iodine deficiency in pregnancy, lactation and in children less than two years of age". A daily iodine intake of 250 µg was recommended for pregnant and lactating women. A tolerable upper intake limit was unknown but as the absolute limit depends on previous iodine exposure a limit of 500 µg was suggested on the basis that no obvious advantage was to be gained from greater intake. The aim should be to have iodised salt available to > 90 % of the population. *Delange* stressed the importance of carrying the message of iodine nutrition to a wider audience, particularly to ministers of health. Although it was disappointing that the report on the technical consultation was not available for this meeting, publication was believed to be imminent. *Joost* (ICCIDD Secretary, Capetown) discussed options for improving the accuracy of urinary iodine analyses and highlighted the need to standardize laboratory methods of measuring urinary iodine. He described the

availability of the CDC Equip programme for quality control and the desirability of achieving a certificate of successful participation in the programme. He also described the activities of The International Resource Laboratories for Iodine Network, which has 12 laboratories worldwide.

Santisteban (Madrid) outlined the role of NIS in the pathophysiology of thyroid disease. She described the various factors controlling NIS both in the thyroid and extrathyroidally. The importance for iodide uptake of NIS targeting to the appropriate cell membrane was stressed. Various redifferentiation therapies such as the use of retinoic acid to restore NIS mediated iodide uptake were described. However such therapies need to have the ability to relocalise NIS to the plasma membrane. Finally NIS transfection has the ability to be applied to a wide variety of cancers, from prostate to glioma, which do not express NIS endogenously, providing the basis for a new cytoreductive gene therapy strategy.

The afternoon session consisted of the customary iodine status reports from various countries in the West Central European region. The Chairman *Pinchera* (Pisa) reported that overall the situation has improved. The most recent positive changes to mandatory salt iodisation have been made in Bulgaria (2004), Italy (2005) and Romania (2005) and sufficient iodine status has been achieved in Bulgaria and Croatia. The main themes emerging from this meeting were the importance of iodine intake, particularly for pregnant and lactating women and infants, and the need for government participation in iodine prophylaxis measures.

Meeting Highlights

The ETA meeting proper opened with the customary Topic Highlights session, which included a contribution from *Rohr et al.* (Cologne and Boston) showing the importance of the cardiovascular system in morphogenesis of the thyroid gland in zebrafish. *Di Palma et al.* (Naples) described TAZ a transcriptional co-activator for PAX-8 and TTF1 which promote thyroid specific genes such as thyroglobulin, thyroperoxidase and NIS. *Refetoff* (Chicago) reported how mutations of the thyroid hormone transporter MCT8 in dependent tissues such as brain produced tissue hypothyroidism while tissues expressing transporters other than MCT8, like liver are hypothyroid. The role of the placenta as a transporter of maternal thyroid hormones in early embryonic life was reported by *Nucera* (Pisa). Finally *Gereben et al.* (Budapest and Boston) described the relative instability of deiodinase D2 although fused to NIS at the plasma membrane was independent of its subcellular location but had its half life decided by 6 N terminal AA on the 18 AA loop.

The conference was well served by basic, clinical and educational symposia and the following are summaries of what impressed the authors as highlights. Obviously space considerations prevent more detailed analysis of all presentations.

Basic Symposium: Revision of Thyroid Textbook Chapters

In a masterly discussion as to whether there was diffusion or regulated cellular uptake and efflux of thyroid hormones, *Friesema* (Rotterdam) indicated that in the old days it was thought that thyroid hormones entered a cell by diffusion. More recently, using the T3 binding protein Crym, it has been shown that T3 uptake to the ovary in the laboratory is effected by the MCT8 transporter. In fact, the efflux is also modulated by this transporter. It is known that the Allan-Herndon-Dudley Syndrome (a phenotype characterised by hypotonia, severe mental retardation and other neurological features in young boys) is related to mutations of the MCT8 transporter. There are now at least 15 mutations

described, mostly in the transmembrane domain, ranging from 1 base pair to 300 kilobase deletion. Further work in this area is clearly indicated to unravel the complex biology of the syndrome. In addition, the discovery of the family of transporters of which MCT8 is probably the chief one relating to thyroid hormone transport, raises the interesting question as to whether it is present in the placenta or not.

Larsen (Brookline) discussed the redundancy of deiodinase contribution to T3 production. Both type 1 and type 2 deiodinase convert T4 to T3. He noted that in the rat, 55% of T3 was accounted for by peripheral conversion compared to 80% in the human. Advances in understanding of this problem are coming from studies of knock-out mice. For example, in the D1 knock-out, the peripheral T4 is raised as is the reverse T3 but the TSH is normal.

Bakker (Amsterdam) discussed rapid thyroid hormone signalling and subcellular location of thyroid hormone receptors. He noted that in the liver there was zonal distribution of receptors with differential expression in some cells. This could indicate the presence of non-genomic effects as well as genomic effects. Comment was made of the diurnal variation in TRbeta1 which may affect eating behaviour. TRalpha1 shows a slow increase in concentration going from the portal to the central areas of the lobule, whereas TRbeta concentration is constant until the central area when it is seen to sharply increase. In the heart, TRbeta1was found in the conductive system, but not in the myocardium. Thyroid hormone effect on ion channels in the heart is almost certainly non-genomic. Possible roles of integrin and 3-thyronamine (T1-AM) were briefly discussed. There is a trace amine receptor (TAR-1) mediating the action of thyronamine. The non-genomic actions of T3 on mitochondria were also indicated. It was noted that T2 and T1 AM had actions and that T3 mediated action via the TRalpha P28 moiety which was associated with adenine nucleotide translocator.

Educational Symposium: Management of Thyroid Nodules

Hegedüs (Odense) discussed the doubtful benefit of T4 suppression therapy for nodular goiter. He described a metaanalysis which showed no significant reduction in nodular volume. Equally apart from some studies in Germany, iodine was not particularly helpful in the suppression of thyroid nodules. *Jarzab* (Gliwice) describing the management of micronodules stressed that these had a 100-1000 times greater prevalence when investigated by ultrasound compared to clinical examination. Suppression doses of T4 were unwarranted but the major problem was the risk of lymph nodes being undetected following ultrasound identification of tumors. *Wallin* (Stockholm) giving a surgical perspective commented on the success of thyroidectomy in the treatment of thyroid nodules and its high degree of safety in the right hands. He commented on the relatively low cost of the operation. Surgery and radioactive iodine therapy were roughly comparable in cost and effectiveness. Choice of therapy is to be selected on the basis of natural history of the disorder and patient preference. Another therapeutic option was described by *Hay* (Rochester) who reported on his experience in using ethanol to ablate lymph nodes. He described the practice of ethanol injection until the node becomes echogenic. He stressed the importance of an experienced radiologist and reported that of 22 patients so treated, 75% of lymph nodes disappeared with 19 requiring no further therapy. In good hands the procedure could be performed without serious discomfort to the patient.

Clinical Symposium: Appetite Regulation And Thyroid Function

Mantzoros (Boston) discussed hormonal control of appetite and the relative contributions of ghrelin and leptin. He described how, despite conventional wisdom that states that hyperthyroidism is associated with weight loss, some 5–10% of hyperthyroids gain weight. The role of food intake in increasing protein kinase C activity was discussed. ETA Secretary Treasurer *Feldt-Rasmussen* deputising for *Scherer* (New York) described thyroidal regulation of transcription. She demonstrated correlations between leptin/leptin sensitivity and serum

TSH in Graves' disease. The role of leptin in inhibiting TSH stimulated indices such as iodide uptake via cAMP induced NIS was described.

Clinical Symposium: Quality of Life and Cost Effectiveness in Thyroid Disease

The beneficial effects of different therapies for Graves Ophthalmopathy (GO) were discussed by *Kahaly* (Mainz) who invoked Plato to remind us that "behind the eyes lies the brain and the soul". *Torring* (Stockholm) reviewed results of various thyroid disease therapy compliance questionnaires to compare different thyroid treatments. The data showed that social consequences can persist up to 14-21 years after therapeutic intervention. In the case of hyperthyroidism, there were no treatment related differences in quality of life. *Dayan* (London) in reviewing psychological well being in treated hypothyroidism commented that although thyroxine should be the easiest hormone to replace, there were still many dissatisfied patients despite reestablishment of apparently normal thyroid function. Some patients were equally miserable when on T4 or not adequately treated. He asked if this could be attributed to failure to replace T3 or to inadequate intracellular T3 in different tissues. Giving T3 sometimes produced a transient improvement but was not sustained. The problems of co-morbidity were discussed and it was pointed out that general health questionnaires show good correlation with FT4 but not with FT3. Finally *Luster* (Würzburg) looked at quality of life issues and cost effectiveness of thyroid cancer investigations. He compared the use of T4 withdrawal with administration of rhTSH and pointed out the benefits of the latter both in terms of promoting compliance and cost effectiveness. The major benefit of rhTSH continued to be the preservation of quality of life by permitting continuation of T4 therapy.

Basic Symposium: Molecularly Targeted Therapy for Thyroid Cancer

Schlumberger (Villejuif) discussed the need for the development of new therapies for thyroid cancer while *Wells* (Durham) commented on the possible use of prophylactic surgery in hereditary medullary thyroid carcinoma and described a new therapeutic option using the low molecular weight tyrosine kinase inhibitor ZD6474 which was found to block the enzymatic activity of RET-derived oncoproteins in cultured cell lines. Some 27% of patients had objective remissions wile 16.6% progressed. *Marais* (London) discussed targeting RAS and BRAF pathways and described how oncogenic BRAF drives cell proliferation and exerts a significant influence on survival. He emphasised the need for better BRAF directed drugs.

Meet the Expert: UV Screens and Endocrine Disrupters – a Risk for the Thyroid Axis Requiring Regulatory Action?

Schmutzler (Berlin) gave a comprehensive report on the effects of endocrine disrupter chemicals (EDC), in particular those present in UV sunscreen cream, on thyroid function. A major action of such EDCs is in the inhibition of TPO activity and thus thyroid hormonogenesis. Any effect of endocrine disrupters on TPO activity may be aggravated by inadequate dietary iodine supply. The effect of EDC such as 4MBC present in sunscreens can be tested in iodide uptake assays by incubating rat FRTL-5 cells in the presence of the disrupter. The action of the EDCs seems to be mediated by reduction of NIS expression. UV screens and fillers used in their preparation can be absorbed through the skin. The thyroid gland appears to be a major target for EDCs such as PCB (polychlorinated biphenols) and PBDE (polybrominated diphenyl ethers) and also isoflavones present in some UV screens. Possible mechanisms of action include interference with thyroid hormone action, distribution or absorption. Although PCBs have demonstrated adverse effects on psychomotor function, there is no conclusive correlation with thyroid hormone levels or TSH. The question was raised; are PBDE the PCBs of the future? Another potential disrupter was soy protein which is much more abundant in the Asian than in the Western diet. It may exert its effect through promoting malabsorption of medicines. *Schmutzler* concluded by describing various EU and IOECD programmes aimed at the investigation of endocrine disrupters. The European Chemical Agency has a database of some 30000 existing substances, the use of many of which requires no regulation to date. Much emphasis has been placed on

the development of both in vivo and in vitro assays to test and classify substances.

Basic Symposium: Epigenetics and Thyroid Disease

Kelsey (Cambridge, UK) described the concept of gene imprinting as ensuring the expression of a single allele from each parent together with the correct dosage of expression. Normal thyroid function requires the expression of multiple imprinted genes. These are expressed at multiple sites (i.e. mother, conceptus, placenta) and postnatally in the various organs. Mutations can give rise to distinct endocrine symptoms or to opposing changes in BMR and in G protein Gsa mutations. *Sun et al.* (Korea) using methylation specific PCR described hypermethylation of the promoter regions in a variety of genes from thyroid papillary carcinomas. Methylation induced gene silencing appears to increase with cancer progression.

Educational Symposium: The Feminine Side of Autoimmune Disease

Drexhage (Rotterdam) addressed the question as to why women are more susceptible to autoimmunity. Women have higher levels of IgG and IgM and display a more vigorous response to antigenic challenge. A role for sex hormones in mediating female susceptibility has long been postulated. This postulate is partly based on the known protective effect of androgens against the development of autoimmune disease and also their effect on lowering pro inflammatory cytokine production and NK cells. Thus the absence of high androgen levels is thought to render females more prone to autoimmune disease. In contrast estrogens enhance autoimmune responses, particularly the antibody producing Th2 pathway. Despite this received wisdom there have been many reports of paradoxical autoimmune responses to sex hormones. An immune stimulatory effect of androgens is observed in transsexuals while an immune suppressive effect has been attributed to both estrogen containing HRT and OCT. Drexhage postulated an action of androgens during development perhaps acting via prolactin and gonadotrophin networks in the bone marrow and thymus. He concluded that sex hormones were only minor determinants of autoimmune responses in animal models. However they may exert a disproportionate effect in thyroid autoimmune disease. Their mode of action remains to be elucidated but Drexhage suggested incomplete inactivation of XX cells producing higher levels of an X-chromosome gene product or a life event such as pregnancy resulting in microchimerism with fetal cells seeding to the thyroid and there aggravating an autoimmune response to an antigenic challenge. Drexhage has shown, for example, that there is a reduced CD 25 expression level in first and second degree female relatives of autoimmune thyroid disease patients. This implies that these female relatives show signs of a reduced expansion capability of their T cell pool and this may affect T cell tolerance mechanisms more than T effector mechanisms. Interestingly, there are also data to show that female offspring of bipolar parents have a higher prevalence of positive TPO antibodies compared to female high school and young adult comparisons. There is a possibility that bipolar offspring are more vulnerable to develop thyroid autoimmunity independently from the vulnerability to develop psychiatric disorders. These studies are opening new avenues for exploring possible reasons why women are more susceptible to autoimmunity but certainly we do not know the answers yet.

In considering pregnancy and its immunological aftermath, *Lazarus* (Cardiff), commented on the importance of NK cells in pregnancy and noted that recurrent miscarriage is associated with Th1. The importance of TPO antibodies in the pregnant woman both in relation to infertility and miscarriage in addition to the risk of development of postpartum thyroid disease occasioned by the presence of these antibodies was highlighted. Reference was made to exciting new data suggesting that thyroxine treatment of TPO antibody positive euthyroid women in pregnancy could prevent the increase in miscarriage observed in TPO antibody euthyroid women who were not treated with thyroxine. The aetiology of the autoimmune aftermath of pregnancy is not clear, although the switch from TH2 to TH1 is important as also possibly is the phenomenon of fetal microchimerism. It seems also a woman destined to get postpartum thyroid dysfunction who has positive TPO antibodies may have less evidence of immunosuppression during the latter half of pregnancy (lower plasma

cortisol). Further work in these areas is clearly required. *Glinoer* (Brussels) gave an overview of the discussions relating to the recent production of guidelines for the management of autoimmune thyroid disease in pregnancy produced by the American Endocrine Society. There was appropriate representation from different interest groups including the European Thyroid Association and a weighty document has been produced. The difficult problem of screening for thyroid dysfunction in early pregnancy was discussed. It is stated that there is no firm evidence base for this practice at present although some trials are in progress to establish this. Meanwhile a targeted focused approach was recommended. The authors of this document are to be congratulated on bringing to a successful conclusion many hours of debate, some of which was difficult. The chief editor *DeGroot* (Brown University, Providence, Rhode Island) deserves high credit for producing the final draft.

Clinical Symposium: Relationship between Serum TSH and FT4 and Health Outcomes

In his symposium *Peeters* (Rotterdam), *Knudsen* (Smorum) and *Wartofsky* (Washington) (deputizing for Ridgway, Denver) looked at different aspects of this fundamental thyroidal relationship. Examining the role of deiodinases 1 and 2 (D1 and D2) Peeters reported that polymorphisms of the deiodinases and TSHR are associated with thyroid dyshormonogenesis. A slight increase in TSH was associated with obesity and relative insulin resistance. Carriers of D2 polymorphisms are associated with increased insulin insensitivity. This also applies to mutations of the TSHR. Knudsen looked at the effects of iodine, industrial chemicals and smoking on the serum TSH/FT4 relationship. In iodine abundance hypothyroidism is more prevalent while hyperthyroidism is more prevalent in a population with relatively lower iodine intake. He presented evidence for the decline in thyroid function with advancing age. However, despite an increase in TPOAb prevalence in the elderly, there was no association with iodine status. The effects of PCBs on thyroid function as previously reported by Schmutzler were variable. However, cigarette smoking was associated with an increase in serum TSH while mild hypothyroidism was also more prevalent. The mechanisms probably reflected the presence of thiocyanates in tobacco as well as an impaired autoimmune response in smokers. The influence of serum TSH levels on health outcomes was discussed by Wartofsky. A possible beneficial effect of oral contraceptives whose estrogen content promoted a slight increase in TSH secondary to TBG/TT4 alterations was reported in terms of lower occurrences of both goitre and hyperthyroidism.

Prize Lectures

ETA Merck Prize

This year's ETA Merck Prize Lecture was delivered by *Beck-Peccoz* (Milan). In his elegant talk Paolo discussed his work on the topic of control of thyroid function with particular reference to pituitary organogenesis and to mutations in the TSH receptor leading to partial resistance to TSH action. He commented on his good fortune to work during the three fabulous periods of modern science:

1. discovery of immunometric assay in the '70s. The measurement of free thyroid hormones actually started in our Lab and then went to Pennisi, Romelli from Lepetit Company with the supervision of Roger Ekins
2. the period of the computer, internet and all the electronic facilities in the '80s,
3. the molecular biology era in the '90s. Measurement of TSH, FT4, FT3 and alpha-subunit of glycoprotein hormones were fundamental for my studies on patients with thyroid hormone resistance (RTH) or with TSH-secreting pituitary adenomas.

Measurement of TSH bioactivity was important for studying patients with central hypothyroidism (elevated serum TSH but low B/I molar ratio, evaluation of scarce FT4 and FT3 response to endogenous TRH-stimulated TSH to predict the presence of TSH with reduced bioactivity).

Molecular biology was important for studying RTH, TSH resistance, central hypothyroidism, pituitary transcription factors, PIT1 and PROP1, TSH beta gene muta-

tions and TSH resistance due to G protein alpha-subunit mutation as in pseudohypoparathyroidism type 1a.

Outside the thyroid field Beck-Peccoz told of the first demonstration, with Krish Chatterjee, of mutations of FSH beta leading to primary amenorrhea and muation in BMP15 again as cause of primary amenorrhea and premature ovarian failure. He recounted that most ideas for his work were born during ETA meetings which in his view continue to stand out among all the others as the premier annual meeting.

Harington– De Visscher Prize Lecture

This year's prize lecturer *Zanini* (Naples) discussed the role of thyroid transcription factors with particular reference to the PAX family of proteins (TTF1, FOX E and PAX 8) and their role in cell differentiation. She outlined the interaction between individual transfection factors (TTF1 and PAX 8) and posed the question as to the possible existence of other PAX 8 partners and the remaining unanswered issue of the identification of the target gene in differentiated thyrocytes. She also described domain binding proteins such as WBP-2 and PARP which may make contact with enhancers and directly promote differentiation or do so by promoting transcription factors.

Other Highlights

Thyroid Hormone Agonists as a New Therapeutic Option

Rehnmark from Sweden outlined attempts by the pharmaceutical company Karo Bio to evaluate certain thyromimetics which have been designed to have a variable action on thyroid hormone receptors as well as other nuclear hormone receptors. For example one compound, KA3495 interacted with both the beta and the alpha receptor , it reduced cholesterol and triglyceride but there was no change in heart rate in animal studies. These experiments open up an exciting new development in the generation of thyromimetic compounds for clinical use, although their clinical application is still in the future. A similar approach is being taken by the group of *Scanlan* (San Francisco). The compound GC1 lowers cholesterol with no increase in heart rate in hypercholesterolemic rats given at a dose of 154 nmol/kg per day for 7 days. Compounds based on thyronamine act by a rapid non-transcriptional pathway and may have a neuroprotective effect in an animal model.

Educational Symposium: Quantitation and Normalisation of Molecular Biological Techniques

In this era where more investigators are becoming involved in molecular investigation of thyroid disease, *Forbes Robertson* (Swansea) discussed the importance of quality control in microarray experiments. She emphasized the need to provide high quality RNA samples before embarking on any costly microarray experiment pointing out that many such analyses failed due to poor quality samples.

Graves' Ophthalmopathy

The etiology of Graves' ophthalmopathy is still unclear. *Backdahl et al.* (Stockholm) found no differences in gene expression on microarray analysis of the thyroids of five Graves' patients with orbitopathy, compared to those without. Studies continue on the role of orbital preadipocytes and *Zhang et al.* (Cardiff) using mutant or wild type TSH receptors showed that TSHR activation stimulates early differentiation of preadipocytes

but renders them refractory to PPAR gamma induced adipogenesis. *Ferrari et al.* (Pisa and Florence) showed that PPAR gamma activation can inhibit inflammation produced by the release of chemokines from retrobulbar cell types. The chemokine (CXCL 10) was released from fibroblast and preadipocyte cultures. Aspects of treatment have been approached in many different ways. *Duntas* (Athens) investigated in a randomized placebo controlled study whether selenium administration in conjunction with corticosteroids (CS) is effective in patients with moderate Graves' ophthalmopathy (GO). A higher reduction of clinical activity score (CAS) was detected at 3 and 6 months of treatment in patients receiving selenium (n = 15) as compared to patients treated only with CS (n = 14). Selenium markedly decreased serum TRAB and TPO-AB and the frequency of relapse. The limited number of the patients studied requires that these results urgently need to be confirmed.

The group of *Salvi et al.* (Milan) have shown that Retuximab (RTX) significantly improved active eye disease although it did cause transient subacute thyroiditis like episode, possibly due to RTX induced lymphoid cell lysis. The Danish group *El Fassi et al.* (Odense) concluded that RTX therapy may remain an option in selected patients. In a randomised study *Dalmatova* and *Grineva* (St Petersburg) showed that orbitopathy patients seemed to respond better to oral prednisolone plus cyclosporine compared to pulsed methylprednisolone. Fatal liver failure has been reported with intravenous methylprednisolone, but *Moli* and *Wiersinga* (Amsterdam) showed that the cumulative dose was the strongest determinant of liver abnormalities and positive viral serology increased the risk.

Methotrexate therapy with or without corticosteroids was reported by *Simescu et al.* (Bucharest) and they claimed that the group receiving both drugs performed better than those receiving just corticosteroids. An overall view of management of patients with GO in Europe was presented by *Perros et al.* (Newcastle) on behalf of EUGOGO. Deficiencies such as the lack of multidisciplinary team involvement, poor access to surgery for sight threatening disease, were identified.

Clinical pointers in the diagnosis and course of orbitopathy included computerized perimetry for identification of subclinical visual field alterations *(Labonia et al.,* Catanzaro), the relationship of the TSH concentration *(Fattakhova* and *Radionova,* Saratov) and the prognostic capability of glycosaminoglycans while treatment is being received with corticosteroids (*Daroszewski et al.,* Wroclaw) in relation to prognosis were also reported.

Thyroid and Pregnancy

In relation to placental physiology *Smyth et al.* (Dublin) suggested that the placenta may act as a store in the supply of iodine to the fetus and therefore it might maintain the iodine supply in mothers with an inadequate dietary iodine intake. Using a transgenic mouse expressing a reporter gene tracing thyroid hormone action during embryo fetal development, *Nucera et al.* (Messina and Rome) showed that maternal thyroid hormones cross the placenta and are transcriptionally functional through the synergic action of embryonic thyroid receptors before the onset of fetal thyroid function.

There is a requirement for trimester specific reference ranges of thyroid hormones in pregnancy. *Stricker et al.* (Switzerland) examined 1262 women and calculated reference values for each 4-week interval of pregnancy. They found an elevated TSH in 5.96 %, 3.54 % and 3.27 % in the first, second and third trimester respectively. These data underpin the strategy for screening of pregnant women. *Kaklamanou et al.* (Cardiff) noted that while gestational transient thyrotoxicosis occurred in 1.3 % of nearly 15,000 sera from the first trimester, TSH was suppressed in 1.47 %. It was suggested that TSH receptor antibodies should be measured in the case of women who are found to have positive TPO antibodies in association with a suppressed TSH. They have a 60–70 % chance of being positive. Transient gestational hypothyroxinaemia (TGH) is predictive the occurrence of fetal neurological damage and was studied by *Moleti et al.* (Messina) in women starting iodised salt at the beginning of gestation and women regularly supplemented by iodised salt for at least 24 months prior to pregnancy. The risk of TGH was much higher (five to

seven fold) in the first group, suggesting that an early gestational systematic screening of maternal thyroid function should be carried out in order to prevent or correct TGH. The prevalence of hypothyroidism in a pregnant population in Moscow *(Burumkulova et al.,* Moscow) was recorded at 5% in a moderately iodine deficient area; it was emphasized that TSH should be measured in early pregnancy. In a study of thyroxine requirements during pregnancy *(Rousseau et al.,* Italy) it was found that a rise in dose is required only in a minority of pregnant women with nodular goitre taking suppressive therapy, but in the majority of hypothyroid women, especially in those without residual tissue. The same group *(Gianetti et al.,* Italy) reviewed 262 pregnancies in relation to the safety of the treatment of their thyroid diseases during pregnancy. This retrospective review showed that neonatal TSH values, weight and length were not different between the different groups of patients and the prevalence of miscarriage and fetal malformations was no higher than that reported in the literature. A comprehensive study of neonatal TSH in Ireland *(Burns et al.,* Dublin) demonstrated the importance of utilising readily available neonatal TSH data to detect altered trends in maternal iodine nutrition. The authors showed over time that there was a consistent shift to the right towards higher TSH values with an accompanying decline in median urinary iodine over a 16 year period.

Young Investigators

In the young investigators session *Llorente* (Madrid) reporting on genotyping for medullary thyroid carcinoma (MTC) found 7 loci for low penetrance genes conferring increased risk for MTC mainly belonging to the RET proto-oncogene pathway. These loci could be potential therapeutic targets. *Oczko-Wojciechowska* (Gliwice) posed the question "which ontology classes are characteristic of thyroid cancer?" They conducted a metaanalysis from 35 papers of data obtained by microarray and found 1161 unique gene Ids which could be correctly mapped to their own dataset obtained from microarray of papillary thyroid cancers and controls. They also found that cell adherence was the most over represented ontology class in thyroid cancer. The Leipzig group of Paschke *(Eszlinger et al.)* looked at gene expression in normal thyroid tissue obtained from the surrounding tissue of both autonomously functioning and cold thyroid nodules. Examining thyroid related genes such as NIS, D1, TSHR, TPO, SIAT1 showed that surrounding tissue of the hot nodule more closely approached the normal. The authors stressed that care must be taken when selecting reference normal tissue for comparisons as gene expression reflects the exposure of tissues to TSH stimulation. *Bodo et al.* (Lübeck, Warsaw and Munich) in a fascinating study on human hair found TSH and TRH, NIS, Pendrin but not TPO expression. TSH was increased after TRH stimulation as was cAMP. They suggested an autofunctioning or paracrine signally loop through which locally (hair follicle) produced TRH stimulates TSH production.

The use of NIS gene transfer to promote iodide uptake by hepatocellular tumours was reported by *Spitzweg et al.* (Munich and Rochester). Using an AFP promoter construct to target NIS to hepatocellular cells, an increase of radioiodide uptake of up to ten fold was reported. An improved method of detecting inborn errors of metabolism in the form of iodine dehalogenase defects was reported by *Affink et al.* (Amsterdam). The technique was that of HPLC tandem mass spectrometry (HPLC-tMS) allowed direct measurement of MIT and DIT in urine as well as being applicable to their detection and conversion in small quantities of cells.

Pedersen and Danish colleagues reported on the difference in the prevalence of hypothyroidism following the introduction of a programme of salt iodisation in Denmark. The incidence rate of hypothyroidism increased in an area with previous moderate iodine deficiency (Aalborg) but not in Copenhagen where iodine deficiency was mild. The increase occurred in young and middle aged adults only.

Thyroid Cancer

A special lecture on the European consensus on thyroid cancer was given by *Pacini* (Siena).

The consensus document is available in the Eur J Endocrinol 2006 Jun;154(6):787-803.

In an extensive study on 4310 cancer patients *Miyaki et al.* (Kurumi) reported on the use of 18F- fluorodeoxyglucose PET scanning for diagnostic localization of cancers. This methodology could detect thyroid carcinomas on the basis of focal uptakes. Results of studies on the continuing prognostically dismal problem of anaplastic thyroid carcinoma were explored in numerous presentations. The role of interstitial fluid pressure presenting a barrier to tumour uptake of anticancer drugs was discussed by *Heldin et al.* (Uppsala). These workers used an inhibitor of TGF B1 and B3 to lower IFP in anaplastic tumours grown in athymic mice. Reduction in IFP correlated with reduced tumour inflammatory characteristics. *Massart et al.* (Rennes) reported on the effect of the histone deacetylase inhibitor sodium butyrate on VEGF expression and cell differentiation in both anaplastic and poorly differentiated thyroid follicular thyroid carcinoma cell lines. They postulated that the upregulation of VEGF and angiogenic activity was a consequence of dedifferentiation and not anti angiogenicity. The effects of redifferentiation therapy such as retinoic acid *(Breitenbach et al.,* Rio de Janero) or the reverse transcriptase inhibitor neviripene, used in human therapy, was reported by *Maasaki et al.* (Pisa) and *Fabiano et al.* (Foggia). Inhibition of mRNA shown by *Takakura et al.* (Nagasaki) to be highly expressed in anaplastic (ARO) thyroid cancer cell lines might provide a novel therapeutic target in anaplastic thyroid cancer therapy. Studies on other thyroid cancers included the report of *Thomas et al.* (Swansea and Kiev), who looked at RET rearrangement and BRAF mutation in post Chernobyl radiation induced papillary thyroid cancers found that in young patients, age at diagnosis was more important than any other aetiological factor. *Pussuda et al.* (Perugia) reported that proteomic analysis showed papillary cancer to be characterized by disruption of signal transduction and resistance to oxidative stress, which may provide a basis for new disease markers.

Selected Topics

In a special lecture *Croce* (Columbus) described the role in the development of thyroid cancer of micro RNA produced by degradation of mRNA. *Sanders* (Cardiff) described interactions of TSH and TSH receptor antibodies. Understanding such stimulating and blocking structural interactions may have a therapeutic potential. *Benvenga et al.* (Messina), reported on an increase in the yearly prevalence of thyroid hormone antibodies in both Graves' disease and Hashimoto's thyroiditis. The reason is unknown but a hypothesis was advanced that that increased prevalence may reflect environmental influences enhancing the antigenicity of hormonal epitopes of thyroglobulin. *Giustarini et al.* (Pisa) suggested that the increased prevalence of TPO Ab in treated breast cancer patients reflected the stress of surgery and is independent of independent stresses linking breast cancer with thyroid autoimmunity. On a similar subject *Giani et al.* (Pisa) did not demonstrate a predictive value for TPOAb in breast cancer survival. *Krassas et al.* (Thessaloniki) in a fascinating study showed that being born in winter carried an increased risk of developing autoimmune thyroid disease later in life. This risk was greatest in females perhaps due to the female predominance of Hashimoto's diseases. An interesting report from the group of *Tutuncu et al.* (Ankara) showed a significant relationship between different personality traits and the presence of thyroid antibodies.

All in all this was a highly successful ETA meeting. Well done to the organisers. Roll on Leipzig.

Former Editions of Thyroid International

No 1-2007 The story of the ThyroMobil (F Delange, CJ Eastman, U Hostalek, S Butz, PPA Smyth)

No 3-2006 Thyroid Peroxidase – Enzyme and Antigen (Barbara Czarnocka)

No 2-2006 Genetics of benign and malignant thyroid tumours (Dagmar Führer)

No 1-2006 Highlights of the 13th ITC (Sheue-yann Cheng, Peter PA Smyth)

No 4-2005 Thyroid Eye Disease: Current Concepts and the EUGOGO Perspective (Gerasimos E Krassas, Wilmar M Wiersinga)

No 3-2005 Clinical Expression of Mutations in the TSH Receptor: TSH-R Disorders (Davide Calebiro, Luca Persani, Paolo Beck-Peccoz)

No 2-2005 Transient Hypothyroxinaemia and Preterm Infant Brain Development (Robert Hume, Fiona LR Williams, Theo J Visser)

No 1-2005 The Spectrum of Autoimmunity in Thyroid Disease (Anthony P. Weetman)

No 5-2004 Postpartum Thyroiditis: An Update (Kuvera E. Premawardhana, John H. Lazarus)

No 4-2004 Report of the 29th Annual Meeting of the European Thyroid Association (G. Hennemann)

No 3-2004 Autoimmune Thyroiditis And Pregnancy (Alex F. Muller, Arie Berghout)

No 2-2004 Report of the 75th Annual Meeting of the American Thyroid Association (G. Hennemann)

No 1-2004 Thyroid and Lipids: a Reappraisal (Leonidas H. Duntas)

No 5-2003 Use of Recombinant TSH in Thyroid Disease: An Evidence-Based Review (Sara Tolaney M.D., Paul W. Ladenson M.D.)

No 4-2003 New Insights for Using Serum Thyroglobulin (Tg) Measurement for Managing Patients with Differentiated Thyroid Carcinomas (C.A. Spencer)

No 3-2003 The Significance of Thyroid Antibody Measurement in Clinical Practice (A. Pinchera, M. Marinò, E. Fiore)

No 2-2003 Etiology, diagnosis and treatment of Graves' disease (A.P. Weetman)

No 1-2003 Report of the 74th Annual Meeting of the American Thyroid Association (G. Hennemann)

No 6-2002 Report of the 28th Annual Meeting of the European Thyroid Association (G. Hennemann)

No 5-2002 Iodine Deficiency in Europe anno 2002 (François M. Delange, MD, PhD)

No 4-2002 Thyroid Imaging in Nuclear Medicine (Dik J. Kwekkeboom, Eric P. Krenning)

No 3-2002 Congenital Hypothyroidism (Delbert A. Fisher)

No 2-2002 The Use of Fine Needle Aspiration Biopsy (FNAB) in Thyroid Disease (Antonino Belfiore)

No 1-2002 Report of the 73rd Annual Meeting of the American Thyroid Association (G. Hennemann)

No 6-2001 Report of the 27th Annual Meeting of the European Thyroid Association (G. Hennemann)

No 5-2001 Subclinical Hyperthyroidism (E.N. Pearce, L.E. Braverman)

No 4-2001 Thyroid hormone treatment – how and when? (A.D. Toft)

No 3-2001 Resistance to thyroid hormone (O. Bakker, W.M. Wiersinga)

No 1/2-2001 Report of the 12th International Thyroid Congress (G. Hennemann)

No 5-2000 Percutaneous ethanol injection therapy for thyroid diseases (Enio Martino)

No 4-2000 Inheritable forms of thyroid carcinoma (Martin Schlumberger)

No 3-2000 Multinodular goitre (Peter Laurberg)

No 2-2000 Drug effects on thyroid function (Jan R. Stockigt)

No 1-2000 Thyroid disease, menstrual function and fertility (Gerasimos E. Krassas)

No 6-1999 Report of the 27th Annual Meeting of the American Thyroid Association (G. Hennemann)

No 5-1999 Report of the 26th Annual Meeting of the European Thyroid Association (G. Hennemann)

No 4-1999 Report of the 8th Biannual Meeting of the Latin American Thyroid Society (LATS) (Geraldo Medeiros-Neto)

No 3-1999 Subclinical Hypothyroidism (Demetrios A. Koutras)

No 2-1999 Radioactive iodine treatment for benign thyroid disease (L. Hegedüs)

No 1-1999 Report of the 26th Annual Meeting of the European Thyroid Association (G. Hennemann)

No 6-1998 Thyroid and Bone (P. L. A. van Daele, H. A. P. Pols)

Supplement 1-1998 Skin disorders associated with and dependent on thyroid abnormalities (H. Niepomniszcze, H. Amed)

No 5-1998 Report of the 25th Annual Meeting of the European Thyroid Association (G. Hennemann)

No 4-1998 The Thyroid and the Heart (George J. Kahaly)

No 3-1998 Nonthyroidal illness (Elaine M. Kaptein, M.D.)

No 2-1998 Report of the 70th Annual Meeting of the American Thyroid Association (G. Hennemann)

No 1-1998 Hazards of Diagnostic and Therapeutic Use of Radioactive Iodines in Thyroid Disorders (Per Hall, MD, PhD)

No 6-1997 Report of the 24th Annual Meeting of the European Thyroid Association (G. Hennemann)

No 5-1997 Report of the 7th International Meeting of the Latin American Thyroid Society (LATS) (Geraldo Medeiros-Neto)

No 4-1997 Symposium Metabolism and action of thyroid hormone Special Issue Dedicated to G. Hennemann (Edited by: T. J. Visser, P. Krenning)

Full text copies of these editions can be found in the Internet under **http://www.thyrolink.com**

When the thyroid secretly steals life.

Taking the offensive against hypothyroidism. With Euthyrox.

- multiple dosage strengths for precise dose titration
- galenic formulation with reliable unit conformity
- first levothyroxine preparation with a European and FDA approval

Other registered tradenames: Eutirox, Supratirox

Euthyrox®
Lévothyrox®

Offensive against hypothyroidism.

Active substance: Levothyroxine sodium. Prescription only medicine. Composition: Each tablet (round with cross score) of Euthyrox 25/50/75/100/125/150/175/200 µg contains 25/50/75/100/125/150/175/200 µg of levothyroxine sodium. Other ingredients: Corn starch, croscarmellose sodium, gelatin, lactose monohydrate, magnesium stearate. **Indications:** Euthyrox 25 - 200 µg: Euthyroid goitre, prophylaxis of relapse goitre after goitre resection, hypothyroidism, suppression therapy in thyroid cancer. Additional indication for Euthyrox 25 - 100 µg: Concomitant therapy in antithyroid drug therapy of hyperthyroidism after having achieved a euthyroid function. Additional indication for Euthyrox 100/150/200 µg: Thyroid suppression test. **Contraindications:** Intolerance to the active substance or any of the excipients. Untreated adrenocortical insufficiency, untreated pituitary insufficiency, untreated hyperthyroidism. Do not initiate therapy in acute myocardial infarction, acute myocarditis, acute pancarditis. **Adverse reactions:** Adverse reactions are not to be expected under adequate therapy. In (individual) intolerance of the chosen dosage or overdosage (particularly if the dose is increased too quickly at the start of treatment): tachycardia, palpitations, cardiac arrhythmias, angina pectoris, headache, muscle weakness and cramps, sensation of heat, fever, vomiting, menstrual disorders, pseudotumor cerebri, tremor, restlessness, insomnia, hyperhidrosis, weight loss, and diarrhoea. In such cases reduce the daily dosage or interrupt treatment for several days. Allergic reactions may occur in the case of hypersensitivity. **Other notes:** Treatment with thyroid hormones should be continued consistently during pregnancy in particular. The thyroid hormone quantity secreted into breast milk during lactation is not sufficient to cause development of hyperthyroidism or suppression of TSH secretion in the infant. During pregnancy contraindicated as concomitant treatment to antithyroid drug therapy. Exclude or treat coronary insufficiency, angina pectoris, arteriosclerosis, hypertension, pituitary or adrenocortical insufficiency, and thyroid autonomy before initiating therapy with thyroid hormones. Prevent drug-induced hyperthyroidism in coronary insufficiency, heart failure, and achycardiac arrhythmias. Clarify cause of secondary hypothyroidism before initiating replacement therapy. In compensated adrenocortical insufficiency start adequate replacement therapy where necessary. When hypothyroid, postmenopausal women at increased risk of developing osteoporosis are treated, their thyroid function should be checked more frequently in order to prevent supraphysiologic levothyroxine blood levels. Do not use in: patients with galactose intolerance, lactase deficiency or glucose-galactose-malabsorption. **Presentation and pack sizes:** depending on the local registration state. For more detailed information please refer to the data sheet or package leaflet. **Issued:** October 2001. **Merck KGaA, D–64271 Darmstadt, Germany.**

MERCK