

1 | 2008

# Thyroid International

edited by: Peter PA Smyth, UCD, Dublin

published by: Merck KGaA, Darmstadt, Germany



## Report on the 32<sup>nd</sup> Annual Meeting of the European Thyroid Association

George J Kahaly and Peter PA Smyth



# Report on the 32<sup>nd</sup> Annual Meeting of the European Thyroid Association

GJ Kahaly and PPA Smyth

## Correspondence:

**George J Kahaly**  
Department of Medicine I  
Gutenberg University Hospital  
Langenbeckstr. 1  
55131 Mainz  
Germany  
E-Mail: [gkahaly@mail.uni-mainz.de](mailto:gkahaly@mail.uni-mainz.de)

**Peter PA Smyth**  
UCD Conway Institute of Biomolecular & Biomedical Research  
Belfield, Dublin 4  
Ireland  
E-Mail: [ppa.smyth@ucd.ie](mailto:ppa.smyth@ucd.ie)

## Thyroid International

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

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 · 1–2008

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

Cover: City of Leipzig at night

## Hot Thyroidology

ETA's journal on hot and controversial topics

Free access:

[www.hotthyroidology.com](http://www.hotthyroidology.com)

# Report on the 32<sup>nd</sup> Annual Meeting of the European Thyroid Association

The 32<sup>nd</sup> Annual Meeting of the ETA took place in the University of Leipzig which in 2009 will celebrate the 600<sup>th</sup> anniversary of its founding. The city proved to be a highly popular venue attracting 700 attendees from 50 countries who presented 265 oral and poster communications. The Programme Organising Committee under new ETA President Josef Köhrle designed a stimulating scientific programme while Ralf Paschke, his colleagues on the Local Organising Committee and the K.I.T. team of Jörg Herrmann provided a highly efficiently run scientific meeting and together with Andrea Paschke were exemplary hosts for the social events. The latter were highlighted by the opening reception in the modernistic Museum of Fine Arts, a highly informative city tour (as part of the “I love my Leipzig” excursion) and finally the dinner in the historic Auerbach Keller.

Although many delegates would be aware of some of the history of Leipzig, the sheer magnitude of the city’s contribution to European and world history and culture soon became apparent. The meeting paid homage to Leipzig’s most famous son Johann Sebastian Bach as well as the other renowned Leipziger Felix Mendelssohn Bartholdy in the course of a beautiful organ concert in St Thomas’ church in which the former served as cantor. Historical interest was whetted by a visit to the brooding

Völkerschlachtdenkmal commemorating the great Battle of the Nations in 1813 which heralded the end of the Napoleonic era and to the St Nikolai Church, the cradle of the Peaceful Revolution in 1989 which in its way also heralded the end of an era. On a lighter note, delegates enjoyed extracts from Goethe’s Faust in the course of a dinner in the historic Auerbach Keller in the heart of old Leipzig during which LATS President Hans Graf took over the violin.

As with all ETA meetings, their success owes an unaccountable debt of gratitude to the local organizers, in this case Ralf Paschke and his team. Their pride in their city was well founded and I think it could be truthfully stated of the attendees that “We loved their Leipzig”.

This is not intended to be a comprehensive report of all the meeting activities but represents the subjective preferences of George Kahaly and myself on what we found most interesting. The text of all the accepted abstracts for ETA 2007 can be viewed on the ETA website:

<http://www.eurothyroid.com/>

[http://www.hotthyroidology.com/downloads/eta\\_abstractbook\\_2007.pdf](http://www.hotthyroidology.com/downloads/eta_abstractbook_2007.pdf)

ETA 2007 Abstract Book: Hormone Research 68 (Suppl3):1-98 (2007) online [www.karger.com/hre](http://www.karger.com/hre)

*Peter PA Smyth*  
*Editor in Chief*

## Satellite Symposia

As is the custom at ETA congresses, 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.

### ICCIDD

The West Central Europe Regional Meeting of the ICCIDD was named "*François Delange Scientific Symposium*" to honour the memory of our late and much loved colleague Professor François Delange (Brussels) who died on June 15th 2007 and whose death deprived the battle to eliminate IDD of its foremost warrior. The meeting commenced with a tribute from *Aldo Pinchera (Pisa)* whose address recalled the immense contribution made to iodine research by François Delange and outlined the very real advances from his efforts affecting so many and which will continue to benefit future generations.

The next contributor was *Annette Grüters (Berlin)* who described the role of thyroid hormones in fetal and neonatal development. She outlined how the effects of iodine deficiency correlated with the presence of neurological cretinism. Despite the identification of iodine deficiency, methods to prevent its effects were not always available. Even in otherwise well nourished Europeans the incidence of iodine deficiency remained unacceptably high and contributed to a small extent to the prevalence of neonatal hypothyroidism. However she stressed that the major cause of neonatal hypothyroidism remained congenital hypothyroidism arising from thyroid dysgenesis. On the question of screening for neonatal hypothyroidism, Professor Grüters reminded the audience that up to 75% of children at risk were not screened. Universal screening could be achieved by the expenditure of approximately \$150 million with the potential of detecting 30,000 affected children. Despite this evident potential benefit, Grüters explained that screening facilities were not available in underdeveloped countries and other diseases were shown greater priority.

The ETA Local Meeting Organiser *Ralf Paschke (Leipzig)* described the role of genetics in the pathogenesis of goitre. Mutations of thyroid antigens Tg, NIS, TPO could result from different genes predisposing to disease in different families. In order to investigate these phenomena, Paschke advocated the initiation of population-based studies with appropriate cases and controls. He discussed the pathogenesis of both hot and cold thyroid nodules, in particular the role in hot nodules of genetically mediated activating abnormalities of the TSH receptor. The effect of these mutations could be activated by inappropriate iodine treatment of iodine deficiency goitre provoking Jod Basedow.

*Mariotti (Cagliari)* described the influence of environmental factors in autoimmune thyroid disease. In particular he outlined the problem of the increase in thyroid autoimmunity following the introduction of a programme of iodine prophylaxis. Frequently there was a correlation between thyroid antibody positivity and thyroid volume which might reflect the influence of iodine deficiency. However, he stressed that the presence of a high prevalence of goitre in a population reflects endemic iodine deficiency not autoimmunity.

The second part of the meeting was given over to current iodine prophylaxis issues. *Zimmermann (Zürich)* reported on the WHO 2007 view of the global prevalence of IDD. He reported that 31% of schoolchildren worldwide were not protected against iodine deficiency and this figure rose to 52% in Europe. Median urinary iodine excretion, the major criterion used by the WHO, remained the lowest in Europe. The figures used were from national studies and may have underestimated the problem in sub-national groups. He emphasized the need to concentrate efforts on pregnant women and their offspring who were most at risk. UNICEF has reported an improvement in household access to Universal Salt Iodisation (USI) which in 1990 was < 20%; in 2006 66% and in 2007 70%. Despite this success the problem was far from a solution with slippage being noted particularly in underdeveloped countries.

*Szybinski (Krakow)* reported on the WHO consultations held in Paris and Luxembourg. He stressed that the current campaigns to reduce salt consumption will impact on iodine intake. Possible solutions were to boost iodine supply through a vehicle other than salt or to increase the iodine content of iodised salt.

The interim report on iodized salt and processed food by Justus de Jong was presented by *Vitti (Pisa)*. He repeated the concern about iodine nutrition brought about by the campaigns to reduce total salt intake. Only 4 EU states have a policy of mandatory salt iodisation. Even with USI, sufficient intake of iodine is not guaranteed. The loss of iodine during processing is well established. He stressed the case for the use of iodised salt in processed foods as a means of achieving a satisfactory iodine intake.

The meeting concluded with national reports on iodine status from the region of West Central Europe.

### ETA-CRN

The long-term consequences of L-T4 treatment in thyroid cancer and the possible incidence of differentiated thyroid carcinoma were the main topics of the 7th ETA-CRN meeting on Saturday September 1st, 2007. In an overview of long-term clinical consequences, the President of the ATA, *David Cooper (Baltimore)*, emphasized that TSH suppression is a cornerstone of treatment of differentiated thyroid cancer. Retrospective data suggest that thyroid hormone treatment can prevent recurrences and prolong survival. A recent report from an American thyroid cancer registry (*Jonklaas et al., Thyroid 2006*) analyzed outcomes in 1548 patients followed for a mean of 3.8 years (0–14 years). In multivariate analyses, it was concluded that greater degrees of suppression therapy were associated with improved overall survival in stage two, three, and four disease. The ATA and ETA guidelines for the management of thyroid cancer both suggest a graded degree of thyroid hormone suppression, based on the patients' risk of recurrence or progression. However, neither group's recommendations take into account the patient's risk of adverse events from thyroid hormone therapy. In the future, other strategies for TSH suppression that do

not cause clinical or subclinical thyrotoxicosis may be available. These include retinoic acid derivatives such as bexarotene that suppress TSH centrally, as well as thyroid hormone analogues that differentially suppress pituitary TSH secretion with minimal bone or cardiac effects. These strategies may provide a safer and more effective way of treating patients with thyroid cancer.

*Biondi (Naples)* extensively described the cardiovascular risk in patients with differentiated thyroid carcinoma and TSH-suppressive treatment. This risk is related to short-term effects due to the electrophysiological action of thyroid hormones and to the long-term effects resulting from increased cardiac workload. L-T4 suppressive therapy can induce a higher heart rate and a higher risk of supraventricular arrhythmias, with an increased left ventricular mass. It is often accompanied by an impaired diastolic function and sometimes by a reduced systolic performance on effort and decreased exercise tolerance. Moreover, an increased risk of atrial fibrillation is well documented in elderly patients with subclinical hyperthyroidism. The addition of beta-blocking drugs with LT4 may reduce the increased heart rate and left ventricular mass, improving both diastolic and systolic function during exercise, thus avoiding the long-term adverse effects of TSH-suppression and improving the quality of life of these subjects.

Of additional importance is the controversial question as to whether excessive replacement with exogenous thyroid hormones, or thyroid hormone suppression therapy in patients treated for thyroid cancer, is associated with osteoporosis and an increased fracture risk. For *Williams (London)*, the published data are often conflicting and no clear answer to this question is available despite numerous cross-sectional, retrospective, population and small prospective studies, together with meta-analyses, perhaps because the various studies were conducted in heterogeneous groups of patients in which confounding factors were rarely controlled adequately. A further weakness of many published studies is their small sample size and relatively short duration of follow-up that preclude analysis of the important clinical endpoint of fracture. A recent study performed in a large population of post-menopausal

women, previously shown to have similar bone mineral density to control subjects, demonstrated an increased risk of fracture associated with low levels of TSH. Thus, it is possible that an increase in fracture risk resulting from thyroid hormone excess may be independent of measurable changes in bone mineral density, suggesting that DXA scanning may lack sufficient sensitivity to predict fracture in hyperthyroidism. The inference from this is that high turnover bone loss in hyperthyroidism results in bone micro architectural changes and increased fragility that require more sensitive imaging techniques for accurate quantification.

The topic “increased incidence of differentiated thyroid carcinoma – fact or fiction?” was discussed by *Elisei (Pisa)*. According to several cancer registries the incidence of this type of cancer has increased over the last 20-25 years. In the United States, the incidence of thyroid carcinoma in 1982 was 3.1 and 7.1 per 100,000 males and females respectively compared to 5.1 and 14.4 per 100,000 males and females respectively in 2004. Despite this reported increased incidence in thyroid carcinoma the rate of mortality has not changed and is approximately 0.3–0.4 per 100,000 per year. Similar to the US an increased incidence has also been reported in France, Germany, Finland, and Italy. A strong inherited genetic predisposition is suggested by case-control studies showing a 3- to 8-fold risk in first-degree relatives, one of the highest of all cancers. The small papillary thyroid carcinomas are those mostly responsible for this increased incidence, however other contributing factors might include the reclassification of some follicular cancers as papillary cancer, or to the correction of iodine deficiency, or to the widespread use of radiation treatment for benign childhood conditions. But the enhanced incidence also might be attributed to a more efficient and early detection of cancers that may otherwise have remained occult for years, given their indolent course as demonstrated by the high prevalence of small thyroid cancer at autopsy.

*Fugazzola (Milan)* evaluated the possible relationship between radiation and the increased incidence of thyroid cancer. Both external and internal irradiations are involved in thyroid carcinogenesis. Low-dose exter-

nal irradiation to the head and neck is a well established risk factor for the development of both benign and malignant thyroid neoplasms, however the risk of developing a thyroid neoplasm is also increased after high-dose therapeutic radiation during childhood. The latency period for malignancy is higher than five years and continues to increase up to 20–25 years following external irradiation. Thyroid cancer is also associated with radiation deriving from nuclear accidents. With respect to the molecular mechanisms involved in radiation induced carcinogenesis, rearrangements of the Ret oncogene have been identified in 60–70% of radiation induced papillary thyroid cancers, most particularly in children exposed to the Chernobyl accident. The most frequent observed oncogene rearrangements are Ret/Ptc1 and Ret/Ptc3, which occur as the consequence of a paracentric inversion on the long arm of chromosome 10 where ret and the activating genes are located.

*Viola (Pisa)* reported that in a 15-year median follow-up study the BRAF V600E mutation was an independent bad prognostic factor for the outcome of patients with papillary thyroid carcinoma. A somatic BRAF V600E mutation was found in 38 of 102 (37.3%) sporadic papillary cancer cases. The presence of this mutation was linked to a worse outcome, including both a high probability of disease persistence as well as a higher risk of death. Among all prognostic factors found to be correlated with a worse outcome at univariate analysis (age at diagnosis, tumour size, lymph node metastases, extra thyroid extension, distant metastases, and advanced clinical class), only the tumour size and the presence of a BRAF V600E mutation showed an independent correlation ( $p=0.01$ ). The same working group (*Romei, Pisa*) showed that BRAF V600E mutations are related to a lower expression of both NIS and TPO mRNA expression in papillary cancer suggesting that the BRAF mutation might play a role in the dedifferentiation process of this thyroid tumour type.

## Congress Highlights: Thyroid Cancer

### ETA Merck Prize: James Fagin, New York

The title of Professor Fagin's talk was "Thyroid cancer genetics and targeted kinase inhibitors: new opportunities, new challenges". Professor Fagin described mechanism of cancer initiation and its implication in the development of targeted therapies. He outlined how cancer cells become addicted to the signaling process dictated by the oncogenic event critical for their initial development. His hypothesis is based on the finding that transgenic mice with independent oncogene expression develop cancers, which subsequently regress when the oncogene is switched off. He provided many examples of this phenomenon and commented on the finding that widespread endogenous expression of H-Ras G12V in mice reflects the different stages in cancer development. He stressed the need for careful selection both of patients suitable for clinical trials and of experimental design before commencing treatments with tyrosine kinase inhibitors (TKIs).

### Molecular Basis of Thyroid Cancer: Diagnostic and Therapeutic Implications

*Fagin (New York)* presented a review of the MAP kinase signaling cascade in thyroid cancer. He described the mutations assumed to be necessary to initiate tumours and the genotype/phenotype correlations found in papillary thyroid cancer. He reported on studies using various inhibitors of thyroid oncogenes RET, RAS, MAPK and BRAF which may be beneficial in subjects with radioiodine refractive papillary thyroid cancer. MAPK inhibition results in a drop in phosphorylation in various cell lines possibly causing the high degree of sensitivity to growth suppression. Tumours showing RET rearrangements are less sensitive to growth suppression possibly indicating the involvement of other signaling systems. Other inhibitors such as the mammalian target of rapomycin (mTOR) act as a distal effector of TSH and of signaling systems involving the phosphoinositide cascade. To date a range of cell lines have shown varying degrees of resistance to rapomycin.

### Symposium: Thyroid Cancer Management

During this symposium chaired by *Schlumberger (Paris)*, *Elisei (Pisa)* told of current practices in adjunctive thyroid ablation. In particular she stressed that the purpose of ablation was not only to remove tumour remnant but to increase the specificity for any future investigations. She outlined the varying practices in different centers and commented on the prospective randomized studies in Euro Consensus 2006. Among the three classifications of thyroid cancer very low, low and high risk categories, only the latter two required ablation and advocated using a radioiodine dose of 30 mCi without a prior diagnostic dose, this dose recommended to be increased to 100 mCi in high risk tumours. The rate of ablation was defined as no visible uptake on whole body scan (WBS). There was a lower rate of ablation with lower <sup>131</sup>I doses with better results produced by the higher doses. Commenting on the use of rhTSH, *Elisei* reported on its benefits as an adjunct to ablation compared to T4 withdrawal. This particularly applied to patient quality of life and indeed conferred societal benefits with regard to a smaller number of missed work days. This factor more than offset the cost of rhTSH administration. The use of ultrasound and serum Tg estimation in the follow up of patients following ablative therapy for thyroid cancer was discussed by *Alevizaki (Athens)*. She advocated the use of serum Tg rather than WBS in follow up. While the more sensitive Tg assays obviously increased the sensitivity for detection of recurrence, she warned against the loss of specificity and commented on the importance of following a trend in serum Tg rather than relying on single determinations. Finally she emphasized the merits for accurate follow up of sticking to the same assay performed in the same laboratory.

*Williams (Cambridge)* reported on the genetics of thyroid tumours in the context of the occurrence of multiple tumours. He reminded the audience that in 1965 about 10% of medullary thyroid cancers were thought to be genetically mediated while today this figure has

increased to about 25–30%. Up to 70% of non-medullary thyroid cancer is thought to be genetically mediated. He discussed the coexistence of thyroid carcinomas with tumours of other organs, which included multiple oxyphilic (Hurtle Cell) tumours and multiple benign nodules. He emphasized the importance of studying gene involvement in tumours such as Cowden's or familial adenomatous polyposis (FAP) and emphasized the difficulty of determining the multiplicity of papillary thyroid cancers. Finally he commented on the possible interaction between germline mutations and environmental factors such as radiation or iodine deficiency with consequent TSH hyperstimulation which may eventually result in thyroid carcinoma.

*Dumont (Brussels)* reported on the application of microarray technology to the study of gene expression in various thyroid regulatory pathways. He demonstrated both regulatory pathways common to all tumours and others specifically regulating different tumour types. (Note: Professor Jacques Dumont of Brussels was the recipient of the 2007 Lissitzky award for outstanding contributions to thyroid research. Dumont together with colleagues in Brussels and beyond has been involved in many areas of thyroidology including both basic and clinical studies. In a previous issue of *Thyroid International* the Editor failed to attribute to Dumont's team the first description of the myxedematous form of cretinism. It had been discovered in India in the early 1900s and was explained as myxoedematous by PA Bastenie and the group of Dumont. The mechanism underlying this form of thyroid disorder was explained by B Contempré and colleagues in Dumont's group. We apologise for this omission.)

*Fusco (Naples)* described altered expression of micro RNA (miRNA) in differentiated and undifferentiated thyroid cancer. He described how upregulation of miRNA is involved in PTC pathogenesis by latching onto a strand of mRNA can scramble its ability to carry out its original coding instructions. Although little is known about the regulation of miRNAs, he outlined the hypothesis how the less mature forms of miRNA (pri-miRNA) can diminish production of thyroid associated tumour suppressor genes. miRNA upregulation, particularly miR221, 222 and 146 are upregulated by factors of up to 19.3 (miR146)

in PTC tumours compared to unaffected tissue. In addition, the target for miRNA in the thyroid (KIT) showed dramatic falls in both transcript and protein.

*Haugen (Aurora)* described the possible thyroidal side effects of new therapeutic agents such as tyrosine kinase inhibitor (TKI). These included an elevated level of TSH in patients with thyroid cancer despite their being on T4 suppression therapy. These and other similar therapeutic agents may affect T4 absorption or may inhibit deiodinase activity. In many of these cases a low TSH preceded hypothyroidism while <sup>123</sup>I uptake was reduced. As TKIs did not appear to be associated with destructive thyroiditis, he postulated that the antithyroid mechanism may involve inhibition of NIS or TPO. Other substances such as retinoids or rexinoids (nuclear receptor analogues) may affect both the HPT axis and peripheral T4 to T3 conversion. The therapeutic implication of these findings was a possible requirement to increase the T4 dosage in order to maintain TSH suppression in thyroid cancer.

*Nikiforov (Pittsburgh)* discussed the use of FNA in testing for oncogene mutations in thyroid cancer. The specificity of RET rearrangements, Ras, PAX 8 and PPAR  $\gamma$  mutations for PTC was examined. FNA from thyroid served as an excellent source of cells for molecular testing with DNA being particularly well preserved. Mutation testing in thyroid FNA as well as providing information on tumour biology increased the accuracy of FNA cytology while also serving to identify targets for molecular therapies.

*Hay (Rochester)* reported on long term outcome in a unique cohort of PTC in younger patients studied over the period 1940–2005. In discussing changes in therapeutic regimes over the period, he outlined how the use of radioactive iodine remnant ablation (RRA) had declined to < 40% in the most recent study period. RRA did not improve recurrence rate at any site. He posed the question as to what role RRA might have played in the excessive cause specific mortality seen in the ablated group after 30–50 years and observed that 79% of patients in the group who died of non thyroid cancer causes had received previous RRA.

### Free Communications on Thyroid Cancer

Initial reports from a multicenter Phase 2 trial of the angiogenic inhibitor AMG 706 was presented by *Sherman (Houston)*. The differentiated thyroid cancer arm of the study showed encouraging evidence of anti-tumour activity with tolerable toxicities. *Vivaldi (Pisa)* described resistance of medullary thyroid carcinoma (MTC) to chemotherapy as a result of over expression of MDR-1 which encodes for a transporter that actively pumps drugs out of the cell. MDR-1 is upregulated by COX-1 and COX-2. In this study the authors reported on the effect of the COX-2 inhibitor Celecoxib on an MTC derived TT cell line. Celecoxib inhibited both growth

of TT cells and expression of MDR-1 suggesting its potential for use in combination with chemotherapy in the treatment of MTC.

*Prante (Erlangen and Rockville, MD)* reported on the development of a superactive rhTSH analogue TR-1401 which greatly enhances the effect of both radioiodide and <sup>18</sup>F-fluorodeoxyglucose (FDG) in rat FRTL-5 thyroid cells. TR-1401 was 40–50 times more potent than Thyrogen in terms of cAMP accumulation and also displayed a 33% increase in potency and a 34% increase in  $V_{max}$  in terms of <sup>18</sup>F-FDG in FRTL-5 cells suggesting its possible use in the diagnosis and treatment of thyroid cancers as a second generation recombinant TSH.

## Clinical Highlights

In a special ETA clinical symposium entitled “guidelines for the diagnosis and treatment of benign thyroid nodules”, *Gharib (Rochester, NY)* gave an informative review of current guidelines, practices and prospects. The excellent presentation included case reports, followed by an interactive question and answer session and a brief discussion. With respect to the alternative answers, the current recommendations of the ETA, ATA, and those of the American Association of Clinical Endocrinologists (AACE) were compared. Clear differences were noted between the ETA and the ATA (80% vs. 34%) on the desirability of performing an ultrasound (US) examination in a 42 year old patient with a solitary 2 x 3 cm thyroid nodule and a TSH of 0.6 mU/L. Also, markedly more ETA than ATA members would obtain an imaging test in this patient (thyroid scan 66% vs. 23%; scan plus US 58% vs. 13%, only!). All sister societies would perform FNA in this case. According to *Gharib and Papini (Endocrinol Metabol Clin N Am 2007)*, usual FNA results are the following: benign or negative 65% with a probability of malignancy of <1%; malignant or positive in 5% with a probability of malignancy >99%; nondiagnostic or unsatisfactory 20%, >3% probability of malignancy; finally suspi-

icious or indeterminate 10% with a 20% probability of malignancy. The question of calcitonin measurement in patients with nodular thyroidal disease is also answered differently: ETA 32% vs. 3.6% for the ATA, only. For comparison, the Latin American Thyroid Society, LATS, and the AOTA measure calcitonin in 5.4% and 1% of the cases, respectively. The ETA consensus statement (EJE 2006) recommends calcitonin measurement in the initial diagnostic evaluation of thyroid nodules. In contrast, in the ATA guidelines (Thyroid 2006), there is no recommendation either for or against routine CT measurement. The AACE recommends it only if FNA or familial history suggests medullary thyroid cancer. All in all, the risk of cancer is 14.8% and 8.1% in solitary and multiple nodules, respectively. The patient age does not correlate with malignancy whereas gender does. The more cystic a nodule, the less likely it is malignant, and completely cystic nodules are never malignant. Finally, there is concordance between the sister thyroid societies regarding which nodule to biopsy when multiple nodules are present. Cytological sampling should be focused on lesions suspicious by US characteristics rather than on nodule size.

*Papini (Rome)* presented the recommendations based on evidence and lack of evidence according to the recently issued thyroid nodules & differentiated cancer guidelines of the ETA, ATA, AACE, British Thyroid Association (BTA), and the National Comprehensive Cancer Network (NCCN). He compared the methodology and the quality of these guidelines, as well as the strength of evidence upon which guideline recommendations were based. For example, the grade of evidence of the following statement “ultrasound evaluation of the thyroid is indicated if a nodule or goitre are palpable and fine needle aspiration (FNA) is the procedure of choice” is only fair. The rating of the recommendation should be fair to high as there is a concordance between the guidelines. The grade of evidence that “the initial thyroid laboratory evaluation requires TSH only” is low! However, the rating of this recommendation is low, too. The evidence for “the indication of a radioisotope scan in nodules with a follicular neoplasm cytological report or when TSH is suppressed” is low to medium and the rating is fair as there is concordance between the guidelines. In contrast, the grade of evidence is high (!) that “T4 treatment for thyroid nodule is not indicated or should be restricted to a minority of selected patients”. Although the rating of the recommendation is also high, there is discordance between the guidelines. Furthermore, the evidence that “the best follow-up for a benign thyroid nodule is palpation and ultrasound every 1–2 years plus FNA in selected cases only” is low with a concordance between the guidelines. Finally, evidence is also low for the statement “lobectomy and total thyroidectomy are indicated if nodules are monolateral or bilateral, respectively”. The rating of this recommendation is fair and the guidelines are concordant. Thus, although overall quality of clinical practice guidelines is good, the score of consensus statement is obviously lower. The strength of evidence in endocrinology is frequently weak and some recommendations are based mostly on expert opinions. The same recommendation is based on different sets of evidence and the same evidence sometimes induces a different recommendation. Therefore, to improve their clinical implementation, renewed efforts are needed to both produce clinical evidence of greater strength, as well as using a similar grading and rating scale for the guidelines.

In the symposium on thyroid hormone catalysed energy metabolism entitled “Live Fast Die Young”, *Grandy (Portland, OR)* discussed the involvement of brown adipose tissue in energy metabolism and how it is stimulated by prostaglandin PGE<sub>2</sub>. He also explained how endogenous or exogenous thyronamines T1AM produce hypothermia. *Diano (Yale)* described obesity trends in the USA graphically illustrated by the presence of an escalator to facilitate entry to a fitness gym! She explained how energy balance is controlled by the hypothalamus and how the enzyme deiodinase 2 (D2) is upregulated during fasting by facilitating increases in serum T<sub>3</sub>. The UCP 2 proton pump which regulates ATP production may be under T<sub>3</sub> control. Although the mechanism for such control is unknown, it may involve T<sub>3</sub> induced AMPk phosphorylation. *Lanni (Caserta)* described thyroid hormone control of ATP synthesis and utilization and uncoupling. He explained that the uncoupling protein UCP 3 is not exclusively present in brown adipose but in all tissues and is associated with the stimulatory effect of T<sub>3</sub> on resting metabolic rate (BMR). Other iodothyronines such as T<sub>2</sub> have been shown to rapidly increase BMR in hypothyroid rats. *Fliers (Amsterdam)* described innervation of the hypothalamic-pituitary-thyroid axis. Following injection of a neuronal tracer into the thyroid, he identified the CNS neurons that were found to dip into the thyroid. The autonomic input into the thyroid gland produced the neurological changes observed in hyperthyroidism such as tachycardia, lipolysis, and insulin resistance, the sites of action of these stimuli being the heart, thyroid and liver.

*Faggiano (Naples)* discussed thyroid dysfunction in inherited thyroid diseases such as cystic fibrosis, lysosomal storage diseases and Fabry’s disease. He detailed changes in thyroid function induced by enzyme replacement therapy (ERT) which resulted in removal of harmful lysosomal storage with improvement in endocrine function including a decrease in serum TSH and thyroid antibody levels.

In a session on Graves’ orbitopathy (GO) chaired by *Wiersinga (Amsterdam)*, interesting cases with this complex disease were reported by research groups from

Leipzig, Pisa, and Copenhagen. In particular, the three cases from Denmark caught the attention of the audience and were intensively discussed. All three patients developed severe cardiovascular and cerebrovascular events during high dose intravenous methylprednisolone (one gram daily in five ongoing days). A 71-year-old woman with atrial fibrillation died at day three of the pulse therapy after three g of steroid. The cause of death was a coronary and a pulmonary thrombosis. A 76-year-old woman with no prior history of heart disease developed a coronary thrombosis after a second pulse therapy with 2.5 g of steroids. Finally, a 24-year-old woman received a 5 g pulse therapy and developed a fatal cerebral thrombosis two days after completion. The reported serious side-effects were seen after cumulative doses of iv methylprednisolone of between 5 and 8 g. Discussion mainly focused on the optimal way to deliver high doses of steroids (with intervals?) and on the optimal iv steroid pulse therapy in terms of both efficacy and safety. Actually and to answer this question in a proper way, the European group on Graves' orbitopathy (EUGOGO) is conducting a randomized prospective trial comparing three different cumulative doses of iv glucocorticoids in patients with moderately severe GO.

### Meet the Expert

*Bartalena (Varese)* introduced the EUGOGO consensus statement on management of thyroid eye disease. The reached consensus recommends that all patients with GO should a) be referred to specialist centres, b) encouraged to quit smoking, and c) receive prompt treatment in order to restore euthyroidism. Patients with sight-threatening GO should be treated with intravenous glucocorticoids as the first-line treatment; if response is poor after 1–2 weeks, they should be considered for urgent surgical decompression. The treatment of choice for moderate to severe GO is intravenous steroids if GO is active, and surgery if the disease is inactive. In patients with mild GO, local measures are sufficient in most cases.

*Georg Brabant (Manchester)* conducted a well-attended "Meet the Expert" session on the vexed topic of serum TSH reference ranges. In presenting specimen clinical cases, he discussed the potential impact of factors

affecting the reference range such as diurnal variation, acute illness, dietary iodine supply and smoking habits. He posed the question "Do we have to change the reference range currently in use?". There was much debate on the consequences of any change in reference ranges without any firm consensus being reached.

In another session, *Kahaly (Mainz)* elaborated on epidemiology, aetiology, differential diagnosis, organ involvement (e.g. heart, bone), possible cardio- and cerebrovascular complications, as well as management of subclinical endogenous and exogenous hyperthyroidism (defined by normal circulating levels of free T4 and T3 and low levels of TSH). Subclinical hyperthyroidism has been associated with an increased risk of atrial fibrillation and mortality, decreased bone mineral density in postmenopausal women, and mild hyperthyroid symptoms. Treatment of this thyroid dysfunction remains controversial, given the lack of prospective randomized controlled trials showing clinical benefit with restoration of the euthyroid state. Nevertheless, treatment of older individuals whose serum TSH levels are less than 0.1 mU/L, and of high-risk patients (history of heart disease, osteoporosis, or symptoms), even when the serum TSH is between 0.1 and the lower limit of the normal range, is recommended.

*Zimmermann (Zürich)* presented a talk with the intriguing title "Ironing the thyroid (the rusty organ)" in which he considered the interrelationship of iron, selenium and I (Se-Fe-I) deficiency. He suggested that Fe deficiency may itself be a determinant of thyroid function in late (3rd trimester) pregnancy. This hypothesis is based on the requirement for Fe of the heme group in the enzyme TPO which is necessary to utilize dietary iodine for thyroid hormone formation. In addition, Fe deficiency predicts higher maternal TSH and lower FT4. Other nutrients such as Vitamin A (Vit A) can influence the TSH  $\beta$  subunit, which is suppressed with high doses of Vit A. He hypothesized that high doses of Vit A could be detrimental to children living in an area of iodine deficiency.

## Free Communications

*Dardano (Pisa)* reported that the follicular variant of PTC had a higher prevalence of 1513A/C polymorphism in the gene coding for P2X7 receptor than did the classical variant with loss of function variant being associated with advanced disease stage.

*Jansen (Rotterdam and Greenwood, SC)* examined the correlation with loss of function by various mutants of the thyroid hormone transporter MCT8. They reported that those mutants associated with loss of function were generally located in the cytoplasm while those with residual function were found at the cell membrane. This finding demonstrated that loss of function occasioned by MCT8 mutations involves reduced protein expression, impaired trafficking to the plasma membrane and reduced substrate affinity. The advanced psychomotor development observed despite mutations may be attributed to the nature of the mutation.

*Cecchi (Siena)* reported that the presence of antiparietal cell antibodies (PCA) in patients with autoimmune thyroiditis resulted in impaired T4 absorption and an increased requirement for T4 replacement. They suggested that screening for PCA should be considered when an unexplained increased requirement for T4 was observed.

*Kleinau (Leipzig)* reported that the high basal activity of the TSH receptor contribute to the high susceptibility to constitutively active mutations (CAMs). Increased cAMP accumulation as a result of CAM can modulate both basal TSHR activity and that of CAMs demonstrating inverse agonism of a TSHR mutation.

*Van Zeigl et al. (Amsterdam)* studied the differentiation of orbital fibroblasts (OF) into adipocytes under the influence of the TSH receptor. Hyaluronan synthetase producing hyaluronan, a precursor of glycosaminoglycan could be stimulated by Graves IgG but not by control IgG in differentiated OF. In contrast, neither IgG produced this effect in undifferentiated OF.

*Gursoy (Ankara)* reported on the use of needle free injection of the local anaesthetic lidocaine before conducting thyroid FNAB. The procedure, four aspirations per nodule, was well tolerated by patients demonstrating satisfactory pain control in 90% of patients tested compared to 44% in a control group.

*Jensen (Odense)* examined the consequences to TSH reference intervals of applying the NACB guidelines. They examined the impact of time of specimen collection and noted a decrease of approximately 30% in TSH values from morning to noon and suggested reference ranges based on sampling time (08:00–09:00: 0.58–4.1 mIU/L; 15:00: 0.41–2.8 mIU/L). Using the NACB recommended cut off of 2.5 mIU/L, 16% of healthy Danish subjects would fall above the reference range and 1.2% below, thus resulting in an increased number of unnecessary investigations in otherwise healthy individuals.

The group of *Laurberg (Aalborg)* examined the number of urine samples required to estimate the iodine status of a population. They examined sequential sample taken from 16 healthy male volunteers over a 13 month period and concluded that a sample size of 500 subjects is required to achieve 95% accuracy within  $\pm 5\%$  while an accuracy of  $\pm 10\%$  could be achieved with 125 subjects. They suggested that misleading results might result if less than 10 samples are taken from any individual.

*Burns (Dublin)* examined the range of neonatal TSH values in an Irish national neonatal screening programme and found a trend towards higher values which mirrored a fall in UI values in Irish adults. They concluded that readily available findings from neonatal TSH screening programmes could be used to detect trends in population dietary iodine intake.

*Watt and colleagues (Copenhagen, Lincoln RI and Odense)* reported on differences in the assessment of quality of life in thyroid patients when the assessment was made by clinicians or by the patients themselves.

These differences referred to the importance attached by either group to the relevance of thyroid related issues. The authors concluded that the different priorities cited by each group were complementary and their combined use may increase the specificity of quality of life questionnaires. The same group *Feldt-Rasmussen et al. (Copenhagen)* reported on findings of magnetic resonance spectroscopy (MRS) in 27 patients with newly diagnosed Graves' disease assessed before and after antithyroid medical treatment. They found that glutamate in occipital grey matter decreased with therapy while glutamine was and remained significantly reduced in parieto-occipital white matter. They concluded that there is a persistent loss and progressive disturbance of glutamate-glutamine cycling in Graves' disease.

*Duntas (Athens)* reported on the use of selenomethionine together with ASS in diminishing inflammation in De Quervain's thyroiditis. This therapy reduced indices of inflammation such as CRP and ESR as well as increasing sonographic echogenicity in thyroiditis. Selenium therapy in De Quervain's may act via inhibition of the transcription factor NF kb and its use may result in diminished requirement for salicylates or even steroids in autoimmune thyroid disease.

*Campi et al. (Milan)* reported on the effects of rituximab (RTX), a MAPK inhibitor, on lymphocyte populations in patients with Graves' disease, some of whom had associated TAO. A reduction in DR+CD20+ and DR+CD3+ cells was observed following RTX but CD19+5+ elevations persisted even after retreatment with RTX. The authors concluded that RTX promoted reduced DR+CD3+ cells at a time of  $\beta$  cell depletion which may involve reduced antigen cell presentation in treated TAO and consequently T cell activation in the orbit.

*Nakamura (Hamamatsu)* described the critical role of the Pit 1 in activating the TSH  $\beta$  gene and reported on its suppression in CV 1 cells. Both PIT 1 and GATA2 can activate the TSH  $\beta$  gene. He described the presence of GATA2 within the TSH  $\beta$  gene which he termed the suppressor region (SR). PIT 1 may protect GATA2 from the inhibitory effects of the SR. Finally he described

how DNA binding of both PIT 1 and GATA2 in the TSH  $\beta$  promoter is mutually independent.

Papers from *Furmaniak and Saunders (Cardiff)* looked at the binding properties of the TSH receptor. Furmaniak showed that the thyroid stimulating human monoclonal antibody M22 bound to the TSH receptor to form a stable complex TSHR 260. Both heavy and light chains were involved in the binding. The structure of this complex formed the foundations for new strategies allowing understanding and possible control of both glycoprotein receptor activity and the autoimmune response to the TSH receptor. Saunders reported on a cell culture prepared from lymphocytes expressing a TSH receptor binding 5CP antibody which inhibits binding of both M22 and TSH. She demonstrated inhibition of cAMP production for the constitutive activity of 3 activating mutations and wild type TSHR expressed in CHO cells. The blocking antibody presented exciting prospects for use in the treatment of Graves' disease, GO and TSHR activating mutations.

An immunotherapeutic concept was proposed by *Schott (Düsseldorf)* who demonstrated that polypeptide hormones may serve as tumour antigens. In this case, dendrite cells were immunized with calcitonin and were shown to possess an antigen specific immunity resulting in significantly reduced tumour growth. This regime forms the basis of a new immunotherapy clinical trial in patients with medullary thyroid cancer.

*Friesema (Rotterdam)* examined competition between the MCT8 thyroid hormone transporter and a closely related (49% identity) MCT10. Although both transporters facilitated T3 uptake into COS-1 cells, MCT8 was also a good T3 exporter from cells. A major difference between the two transporters was that while T3 uptake by MCT10 was predominantly inhibited by iodothyronines, that by MCT8 was inhibited by iodothyromamines, which interaction was postulated to be important for the pathogenesis of psychomotor retardation in patients with MCT8 mutations.

*Müller (Leipzig)* presented studies on the hinge region of the TSH-R which links the extracellular hormone bind-

ing domain to the transmembrane domain and found that several charged amino acids are important for intracellular signaling transmission. Mutations resulting from single alanine substitutions variably affected cell surface TSHR expression, TSH binding and cAMP accumulation.

*Persani (Milan)* discussed the consequences in terms of recognizing congenital hypothyroidism (CHT) of lowering the cutoff point for blood TSH values used in neonatal recall. Reducing the cutoff point from 12 mIU/L to 10 mIU/L increased recall rates from 0.57–1.06%. Examining representative groups of recall patients suggested a higher rate of CHT, mainly of a transient variant associated with gland in situ, than had been previously identified.

*Vila (Barcelona)* reporting on a Spanish multicenter study on autoimmunity and iodouria in pregnancy found no correlation between iodine supplementation and TPO AB prevalence. *Dohan (New York)* reported on NIS transport of both iodide ( $I^-$ ) and perchlorate ( $ClO_4^-$ ). Using a polarized MDCK epithelial monolayer in which NIS was only expressed only on one side the authors showed that simultaneous addition of  $I^-$  and  $ClO_4^-$  markedly slowed NIS translocation of  $I^-$  to the opposite side because  $ClO_4^-$  was translocated first and only when transport of  $ClO_4^-$  has been achieved is  $I^-$ -transferred. This finding suggests that recently reported perchlorate contamination of water may have relevance for the iodine supply to pregnant, lactating mothers or their neonates.

## Former Editions of Thyroid International

- No 4–2007** The thyroid and twins (Pia Skov Hansen, Thomas Heiberg Brix and Laszlo Hegedüs)
- No 3–2007** Clinical Aspects of Thyroid Disorders in the Elderly (Valentin Fadeyev)
- No 2–2007** Report of the 31th Annual Meeting of the European Thyroid Association (John H Lazarus, Peter PA Smyth)
- No 1–2007** The story of the ThyroMobil (F. Delange, C.J. Eastman, U. Hostalek, S. Butz, P.P.A. 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. Niepomniszczce, 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.)





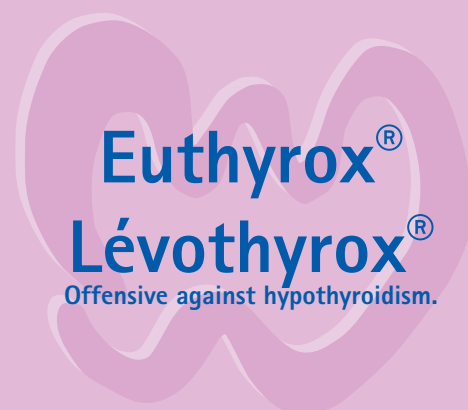


# When the thyroid secretly steals life.

*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



**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 pericarditis. **Adverse reactions:** Adverse reactions are not to be expected under adequate therapy. In (individual) intolerance of the chosen dosage or overdose (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 suprathysiologic 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.