THYROWORLD

Volume 12, No. 1 Summer 2009

Working for the benefit of those affected by thyroid disorders throughout the world

# Thyroid Federation International

## Thyroid Patients Worldwide

## In this Issue

**ThyroWorld** is the official newsletter of the Thyroid Federation International.
ISSN 1488-223X
Email: **tfi@thyroid-fed.org**
Internet: www.thyroid-fed.org
Website Coordinator: info@thyroid-fed.org

*Layout & design by Fresh Image (Canada)—www.freshimage.ca*


# From the Editor's Notebook

*JRB, Retiring Editor*

It's Hail and Farewell time or perhaps more logically the other way around – farewell first to the old and then hail to the new. With this issue of ThyroWorld, I am stepping down after a decade of putting TFI's newsletter to bed and handing over the editorial responsibilities to others. With new ideas, projects and faces at TFI, it seems an appropriate time to do so.

Beate Bartès and Ulla Slama have offered to take on the job although they both have other duties within TFI. Producing ThyroWorld is no small task, but it has its rewards as well. I wish them all the best in this new experience. For myself, I always looked forward to learning what other TFI groups were doing on the international thyroid scene. In these days of electronic innovation, that's relatively easy to do.

So I'll pack away my red pen and be on my way. All the best to all the readers. Keep on reading and supporting ThyroWorld. That's the farewell part and now it's time to hail the new team and learn about their plans. Over and out!

*June Rose-Beaty, Retiring Editor*

# From the New Editors'

*BB, Co-Editor*

It is a big challenge to take over the editorial responsibilities from June Rose-Beaty, who has done a tremendous job over so many years. We are now two co-editors instead of just one and we'll do our utmost, but June is "irreplaceable"!

*US, Co-Editor*

Luckily, as has she shared her experience with us over the last couple of years, the change has been progressive. We've learnt a lot from her and should now be "fully-fledged"!

Thank you, June!

*Beate Bartes & Ulla Slama, Co-Editors*

# President's Message

**Dear members and all,**

*Yvonne Andersson, President*

I am happy to say that during the past year we took a major step forward. In October last year we received the possibility of starting a project with support from Merck Serono. The project was to create the first ever International Thyroid Awareness Week. In August, 2007 TFI took the decision to make May 25th World Thyroid Day. It also was decided to let the International Thyroid Awareness Week run from May 25th until May 31st.

The aim of this year's week was to raise awareness about thyroid disorders in the world. Together we created information material including a patient booklet, leaflets for the different diagnosis, a patient information film and a special website – www.thyroidweek.com – in English, German, French, Spanish, Portuguese, Greek and Arabic. The Chinese version was not ready in time, but we hope it will be available next year.

Thyroid Awareness Week was launched in April with a press conference during the conference of the European Endocrine Society in Istanbul. The initiative was very well received by the journalists and medical professionals attending the conference. We received letters of recognition and support from ETA and LATS. This felt very good since it supported our aims to work with all continents of the world.

We are overwhelmed with the results from the week. There have been articles about thyroid disorders in more than 80 countries, articles in the major newspapers of the world – much more than we ever expected. We have received positive emails from patients and doctors. They proved there is a real need for information about the thyroid – what it is, where it is, what it does, what kind of disorders are connected to it and what the symptoms are.

With the World Health Organization we discussed putting thyroid disease on their list of important chronic diseases. TFI is invited to network with other organizations solving questions for the coming World Health Year 2010. We are pleased with these achievements and are proud to have the ETA working together with us on this matter for the benefit of all thyroid patients. We will be pleased if thyroid disorders becomes part of the chronic diseases focused on by the WHO along with heart disease, stroke, cancer and diabetes.

We are looking forward to another year full of developments and challenges through the work of TFI and their members. We also welcome new members as well as new ideas and projects. We welcome an extended collaboration with the medical profession groups – ETA, ATA , LATS and AOTA. ❧

*Yvonne Andersson*
*President of Thyroid Federation International*

# Thyroid Cancer Patient Organization Leadership Summit

**Toronto, August 2009**

On August 6th, for the first time, leaders of patient associations from several countries and continents, dedicated to thyroid cancer held a conference in Toronto, at the World Congress on thyroid cancer. Our exchange of experience was extremely interesting, as we work in the same field and have similar goals, although we work in many different ways, depending on local conditions and each organization's structure. This first contact was very rewarding and will certainly lead to many interesting projects and much cooperation in the future. ❧

*Beate Bartès*

*Participants: Joan Shey, Light of Life (USA), Beate Bartès, Vivre sans Thyroide (France), Sandra Licht, Light of Life (Argentina), Gary Bloom, ThyCa (USA), Yvonne Andersson, Nordic Thyroid Cooperation/TFI, Harald Rimmele, Ohne Schilddrüse Leben (Germany) and Kate Farnell, Butterfly Thyroid Cancer Trust (UK) (not pictured : Rita Banach, Thryvors, Canada)*

# Norwegian Thyroid Association

Norwegian Thyroid Association (Norsk Thyreoideaforbund, NTF) was founded in 1990 as an organization for people with hypothyroidism. It was decided in 2003 that the organization should include all thyroid diseases and NTF has since seen rapid growth – by the end of 2008 the organization had 6,124 paying members. NTF consists of an elected central board, five regional councils, 46 active local groups, contact groups for hypothyroidism, hyperthyroidism, thyroid cancer, youth and children, a central secretariat in Oslo and a medical advisory board.

The National Congress, where the board is elected, takes place every second year. At the same time The Norwegian Thyroid Award is given to a physician or institution having done outstanding research on thyroid diseases or given special interest, care or education to thyroid patients.

The member magazine of NTF is named Thyra and is published four times a year. Activity in the organization is financed by membership fees (about 37 Euro), our own national lottery and subsidies from the Health Department based on number of members and special activities arranged for members.

Since 2005, NTF has celebrated a national Thyroid Day on May 25th. NTF proposed to TFI in 2007 that this day should be an international day – World Thyroid Day. In Norway, there is one central arrangement. In addition, most of our active local groups arrange open meetings with lectures by physicians, have booth to distribute information material. The celebration of the day is a great success and gives NTF many new members all over the country each year.

NTF has been very active both in local and national media producing press releases, writing articles and giving interviews. We have created a special media course for all our representatives to turn everyone in the organization into information workers for NTF.

Bente Bakke, from the district near Oslo, has been the president of the Norwegian Thyroid Association for the past three years. During that time, she has had two cancer operations – breast and colon. She appears to recover well, but she has come to the conclusion that the work as president is too much for her. Vice president Kristin Kvalsnes will take over as acting president in September, 2009. ❧

*Bente Bakke*

# NTS — The Nordic Thyroid Patient Cooperation Network

At the Thyroid Federation International meeting in Edinburgh, 2003 there was discussion concerning the usefulness of national/regional networks within TFI.

In Norway, at the end of 2004, a group of active thyroid patient organization members took the initiative and started a thyroid patient cooperation network between northern European countries. For centuries, these countries have had similar political structures and cultural contacts. It has been interesting to exchange experiences and it may be possible to have a stronger political influence concerning the care of thyroid patients, especially as the population of each northern country may be

*(continued on page 5)*

*Passing the gravel: Nordic president Paavo Koistinen (Finland 2007-2008) and new president Yvonne Andersson (Sweden 2009-2010).*

as small as a larger city in many other countries.

In January 2005, the first Nordic meeting took place in Oslo. The Norwegian Thyroid Association selected Martha Flermoen as their first president. The president's post circulates between the Nordic countries and began with Norway (2005-2006). Finland (2007-2008) was next with Sweden (2009-2010) following. This year Yvonne Andersson from Sweden is president. She is also president of TFI. Denmark (2011-2012) will be the next country to hold the president's post.

The NTS has its own logo, five butterflies that represent the thyroid shape and the five Nordic countries—Norway, Finland, Sweden, Denmark and Iceland.

Nordisk Thyreoidea Samarbeid

NTS has, like TFI, interest in cooperation between patients and doctors as well as understanding the importance of evidence-based medicine. There have been many lectures for patients by endocrinological specialists at the meetings, such a northern Norway health study on the thyroid gland (Professor Trine Bjøro, Norwegian Radium Hospital); radioactive contamination and thyroid problems in Norway (Dr. Jon Reitan, Oncological Specialist); a study about thyroid patients in Norway (Louise Koren Dahll, Endocrinological Specialist, Thyreoideapoliklinikken, Aker Sykehus, Oslo); and an impressive story by a thyroid patient, psychologist Audhild Løhre, of her life events before her thyroid disease was diagnosed. She lost her job, driver's license, and received the diagnosis of Alzheimer's disease. Since her proper diagnosis, she has had her job and driver's license reinstated, and there was no need for a dementia care home.

In Stockholm, Sweden on November 18th, 2007 a full day meeting was held with some well known endocrinologists from Sweden talking to patients. Attending were Prof. Ernst Nyström, Dr. Ove Torring, Dr. Jan Kalissendorff and Dr. Stig Valdemarsson. The themes included hypo- and hyperthyreosis, thyroid inflammations, thyroid history, thyroid and obesity, thyroid and pregnancy, thyroid and life quality.

*Yvonne Andersson (Sweden), Bente Bakke (Norway), Ulla Slama (Finland), Kerstin Sumelius (Sweden). Back row, standing: Paavo Koistinen (Finland), Peter Lakwijk (Sweden).*

The meetings in 2008 and 2009 took place in Finland with Paavo Koistinen as president. Primarily, thyroid and pregnancy, as well as thyroid cancer diagnosis and care were discussed. A brochure about thyroid cancer has been produced by the Nordic countries.

In Finland, a network has been arranged for young thyroid patients. These include a web site in the Finnish language by the Thyroid Association of Southern Finland and a scheduled holiday camp, although there were not enough participants for it to be held.

In Denmark, they are supporting the development of a thyroid group on the Islands Faroyen. The Danish organization, with president Lis Larsen, arranged a well attended meeting with a lecture by a thyroid specialist and a thyroid association with its own web site has been started on the islands.

The NTS has produced general thyroid brochures in the many languages, including Arabic, Russian, Somalian and Vietnamese. The brochure is available free from the web site or can be found on the TFI web site.

In recent years it has been discovered that good pre-natal thyroid care has an important outcome on the pregnancy itself and the mental development of the offspring. Therefore, the Nordic thyroid organization decided at their 2007 Helsinki meeting to approach authorities about TSH screening of all pregnant women. This is not yet possible, but we hope all countries will follow the recommendations of the Endocrine Society concerning screening of patients at risk.

The Nordic Thyroid patient organization has been a positive experience. It may be helpful for other thyroid patient organizations to start similar networks between countries in close geographical areas with similar circumstances. It is not even necessary any longer to meet personally at every meeting, as it is now possible to have discussions via telephone or computer conferencing at a much less cost. ❧

*Ulla Slama, NTS Representative of Finland*

# World Health Organization

ARTICLE BY YVONNE ANDERSSON


During the International Thyroid Awareness Week Yvonne Andersson, President of Thyroid Federation International, had a meeting with Dr. Fiona Adshead, Director of Chronic Diseases and Health Promotion of the World Health Organization (WHO). This department is focusing on chronic diseases, such as heart disease, stroke, cancer, chronic respiratory diseases and diabetes.

Our aim for the meeting was to present thyroid disease as an important disease to focus on. It's extremely important to get the information out and to raise the awareness about how serious the consequences are of untreated thyroid disease. It might lead to death, or cause heart disease, but for all affected, if not well treated, thyroid disease lowers the quality of life.

There is an estimation that more than half of the patients with thyroid disorders are undiagnosed and suffer from symptoms without really knowing what it is. It effects fertility, pregnancy, depression and possibility even Alzheimer's disease.

To find people with symptoms, and to be able to diagnose them at an early stage of the disease, would be a major win for the health care systems in countries all over the world but would also improve the patient's quality of life. The cost of thyroid diseases includes the cost of examinations and medicines but most important are the costs related to sick leave time. Early detection would save costs and these funds could be used in more cost effective ways.

Thyroid disease is estimated to affect more than 5% of the world population. It should have a place among other chronic diseases which are the focus of the WHO.

TFI is invited to join a network within the WHO where organizations for chronic diseases are working together for a better future for those affected. ❧

## Enjoying a Well Deserved Dinner

*Annual TFI meeting in Thessaloniki, Greece: at the end of a long meeting, a well deserved dinner at the port of Chalkidiki.*

*From left to right: Jytte Flamsholt, Beate Bartès, Ulla Slama, Yvonne Andersson, Peter Lakwijk, Julie Bente Lasserre, Shannon Wood, Harald Rimmele, Annemaarit Lavikainen and Larry Wood.*

# The Australian Thyroid Foundation Thyroid Awareness Week 2009

BY BEVERLEY GARSIDE, PRESIDENT, THE AUSTRALIAN THYROID FOUNDATION LTD.


The ATF's annual Thyroid Awareness Week was established in 2000 and has been making a difference in thyroid disorder awareness in Australia ever since. The ATF has streamlined the annual events and focus each event on a different thyroid message – for example, Thyroid Awareness Week – Get Smart – Protect Your Baby's Brain. This message is directed at young women who are pregnant, breastfeeding or contemplating pregnancy.

Here in Australia, research shows 70% of pregnant women are iodine deficient. We all know without enough iodine the baby's development can be impaired, particularly the brain development and IQ.

Therefore, this message had to be strong, direct and aimed at the 18 - 40 year old women. The ATF sent a mailout to Obstetricians, Endocrinologists, GP's, Pharmacists, IVF Clinics and Breastfeeding Australia to raise awareness. The mailout included a letter informing the receiver of our organization, TAW, the message and why it is so important for pregnant women to take a pregnancy and breastfeeding supplement during this time which includes 250 mcgs. of iodine. Also included is the research paper, a poster to be displayed for women to see and postcard size pamphlets for waiting rooms and counter tops for women to take home.

The ATF main sponsors, Blackmores Vitamins, who developed the formula for a supplement from research and Saxa Iodised Salt sponsored this mailout for the ATF. It has been extremely well received, with many asking for more copies.

ATF president, Beverley Garside and our Principal Medical Advisor, Professor Creswell Eastman, who headed the research studies, spoke to the media during TAW which was organized by Ogilvy PR Health, who very kindly promote our messages and raise awareness on our behalf free of charge.

The ATF encourages all Thyroid Federation International groups to organize a similar campaign to promote the importance of women taking a supplement including iodine during pregnancy and breastfeeding. Future generations will benefit from the message and all groups will raise awareness of their organization's services. ❧


**2008 TFI Annual Meeting in Greece:**
*From left to right: Jytte Flamsholt (Denmark), Beate Bartès (France), Harald Rimmele (Germany), Yvonne Andersson (Sweden), Nancy Patterson (USA), Larry Wood (USA) and Annemaarit Lavikainen (Finland).*

# New Treatment Modalities for Refractory Thyroid Carcinoma

ARTICLE BY DR. MARTIN SCHLUMBERGER, SERVICE DE MÉDECINE NUCLÉAIRE ET D'ONCOLOGIE ENDOCRINIENNE; FACULTÉ DE MÉDECINE PARIS-SUD ET INSTITUT GUSTAVE ROUSSY, VILLEJUIF, FRANCE

*Dr. Schlumberger*

## Introduction

Metastatic thyroid carcinoma is uncommon. It is often slowly progressive and available treatment modalities of refractory disease were poorly effective and potentially toxic. For these reasons, most patients were submitted only to follow-up and few therapeutic trials have been carried out.

During the past two decades, the improved knowledge of molecular abnormalities responsible for thyroid carcinoma has guided the development of new treatment modalities in patients who are refractory to standard treatments. Kinase inhibitors that inhibit angiogenesis and several transduction pathways, including the MAP kinase pathway are effective in differentiated and in medullary thyroid carcinoma. They provide clinical benefits in more than half of the patients, and patients with refractory thyroid cancer should be encouraged to participate to therapeutic trials with these new compounds.

The present review describes patients who may benefit from these new treatment modalities, molecular abnormalities found in thyroid cancer samples and recently published results of trials.

## Patients

Thyroid cancers of follicular origin are histologically classified as papillary (75-80%), follicular (5-10%) or anaplastic (2-5%). Medullary thyroid cancer that derives from C cells accounts for 5-10% of all thyroid cancers.

The large majority of papillary and follicular thyroid cancers are cured after initial treatment and 20 year survival is above 90%. Distant metastases occur in less than 10% of patients, and 131I radioiodine treatment induces a complete remission in one third of these patients who will have a normal life expectancy. In patients who are refractory to radioiodine treatment, median survival is 3-6 years after the discovery of distant metastases, and response to cytotoxic chemotherapy is infrequent (< 20%), being partial and transient.

Anaplastic thyroid cancers are aggressive. The combination of surgery, cytotoxic chemotherapy (doxorubicine-cisplatine) and external radiation therapy to the neck and mediastinum induces a local control in more than half of patients and a long term survival in 20% of patients; favorable results are obtained in patients with disease confined to the neck, but treatment does not improve survival of patients with distant metastases.

Patients with medullary thyroid carcinoma (MTC) are treated with surgery either before the appearance of disease in subjects with the hereditary form of the disease (1/3 of cases) that allows a cure, or in patients with clinical disease among whom only 1/3 will achieve a cure. In patients with metastatic disease, cytotoxic chemotherapy is poorly effective.

## Genetic Abnormalities in Thyroid Cancers

In papillary thyroid cancers, rearrangements of the RET gene and point mutations of the BRAF and the RAS genes are found in 80% of tumors and activate the MAPK (Mitogen-Activated Protein Kinases) pathway.

Germline activating point mutations of the RET gene are responsible for the hereditary MTC, and somatic RET mutations are found in 2/3 of sporadic MTC.

These genetic abnormalities induce the transformation of normal cells into tumor cells, and induce tumor progression. Their inhibition may induce cancer stabilization or regression.

Genetic abnormalities found in follicular carcinomas include the PAX8-PPAR rearrangement and RAS point mutations.

In poorly differentiated and in undifferentiated thyroid carcinomas, p53 mutations are frequently found, and the MAPK and Phosphatydilinositol 3 Kinase pathways are frequently activated.

Tumor angiogenesis allows tumor cells to survive and proliferate. Many factors are involved in the development of tumor vascularization, among which the VEGF (vascular endothelial growth factor) has a central role. VEGF binds

*(continued on page 9)*

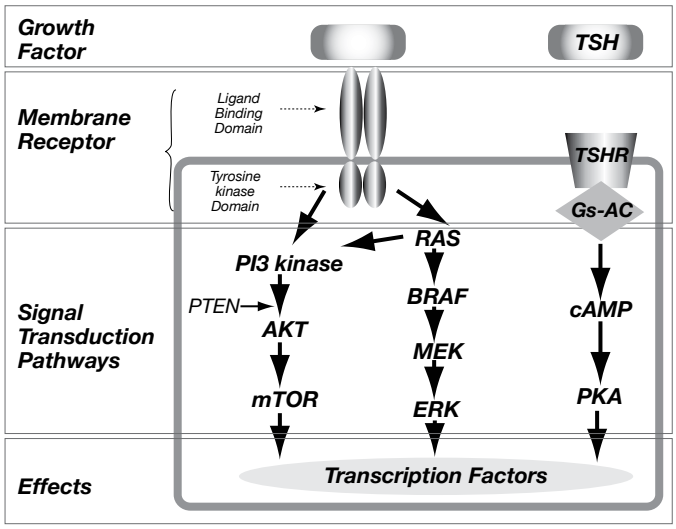



**Figure 1:** *Signal transduction pathways. The MAP kinase pathway is activated in tumor cells from papillary thyroid carcinoma, due to the presence in over 80% of cases of either a RET rearrangement or a point mutation of RAS or BRAF gene. In MTC, a germline activating point mutation of the RET gene is found in hereditary cases, and a somatic RET mutation is found in more than half of sporadic tumors. The MAP kinase pathway activation is responsible for both cancer occurrence and progression (oncogenic addiction). Inhibition of this pathway will stop tumor progression or will induce tumor regression. Other tyrosine kinases are inhibited, including VEGF receptors in endothelial cells, and this will induce an anti-angiogenic effect. The clinical response is the result of the combination of these effects.*

to receptors with tyrosine kinase activity on endothelial cell membrane (VEGFR) of vessels. In thyroid tumors, both VEGF and VEGFR are overexpressed.

## New Treatment Modalities for Thyroid Cancer

Small molecules used in thyroid cancer patients inhibit tyrosine kinases of VEGFR in endothelial cells, and are anti-angiogenic. Furthermore, some molecules also inhibit kinases of the MAP kinase pathway in tumor cells (Figure 1). These agents are used in refractory cancers both papillary and follicular and in MTC, because the same pathways are activated in these various tumors. These small molecules are administered as pills, taken orally every day at home. Results are available for 4 compounds in refractory papillary and follicular thyroid carcinoma :

Axitinib (AG-013736, Pfizer) inhibits VEGF receptors. In 60 patients, a partial response was observed in 16 and a stabilization longer than 4 months in 23 patients.

Sorafenib (BAY 43-9006, Bayer) inhibits VEGFR, PDGFR, RET and BRAF. In 27 patients, a partial response was achieved in 7 and a stabilization in 16. In another study in 58 patients with refractory papillary thyroid cancer, only 3 partial responses were achieved.

Motesanib (AMG 706, Amgen) inhibits VEGFR, PDGFR and c-Kit. In 93 patients, it induced a partial response in 14% and a stabilization of the disease longer than 6 months in 35 %.

Sunitinib (SU11248, Pfizer) inhibits VEGFR and RET. In 31 patients, it induced a partial response in 4 and a stabilization of the disease in 21 patients.

These clinical trials have clearly demonstrated the efficacy of these drugs in refractory thyroid cancers. Several randomized trials are ongoing (with vandetanib, see below) or will be activated in the near future (Sorafenib).

In patients with a refractory medullary thyroid carcinoma, several trials have been performed:

Vandetanib (ZD6474, Astra-Zeneca) inhibits VEGFR, EGFR and RET. In 30 patients with the hereditary form of the disease with a germline RET mutation, a partial response was obtained in 6 patients and a stabilisation longer than 6 months in 22 other patients. A randomized trial versus placebo is in progress.

XL-184 (Exelixis) inhibits VEGFR, RET and MET. In 17 patients, it induced a partial response in 9 and a stabilization of the disease for more than 3 months in the 8 other patients. A randomized phase III trial versus placebo is in progress.

Motesanib in 91 patients induced a partial response in 2 and a stabilization of the disease for more than 6 months in 43 patients.

Sorafenib in 5 patients, induced a partial response in 2 and a symptomatic improvement in all.

These trials have clearly shown that all these kinase inhibitors are effective in MTC patients. However, other kinase inhibitors (gefitinib that inhibits EGFR, and imatinib that inhibits c-KIT and PDGFR) have no efficacy.

Several other molecules will enter clinical trials in the near future for refractory differentiated or medullary thyroid carcinoma.

## Toxicities

The most frequent side effects of these molecules are fatigue, diarrhea, nausea, anorexia, hypertension, skin toxicities (folliculitis, photosensitisation with vandetanib, hand-foot syndrome with sorafenib) and may lead to a

*(continued on page 10)*

dose reduction or even to treatment withdrawal. Thyroxine need increases in most patients, and this should lead to a careful control of serum TSH level during treatment.

### Perspectives

These new treatment modalities induce a clinical benefit (sum of complete responses, partial responses, stabilizations) in more than half of the patients with refractory disease. This is significantly better than that observed with cytotoxic chemotherapy. Patients with refractory disease should thus be encouraged to participate to these trials for two main reasons: these compounds have an efficacy that is better than that of any other treatment modality; second, this is the only way to improve the treatment results of this rare disease.

Because this is a long term treatment, because significant toxicities may occur and because many patients experience only a stabilization of their disease, only patients in whom a clear progression of the disease has been documented should be offered to participate to trials.

The TUTHYREF (TUmeurs de la THYroïde REFractaires) network, composed of 20 teams was created in France in 2008 and endorsed by the INCa (the French Institut National du Cancer), should facilitate the access of patients with refractory thyroid cancer to these innovative treatments. ❧

*Correspondence:*
*Martin Schlumberger*
*Institut Gustave Roussy (IGR) et Université Paris-Sud*
*39 rue Camille Desmoulins 94805 Villejuif cedex*
*E-mail: schlumbg@igr.fr*

*Prof. Schlumberger is one of the medical advisors of the French association, "Vivre sans Thyroïde", www.forum-thyroide.net*

# New Formulation of Eltroxin creates a lot of Problems for Danish Thyroid Patients

At the end of 2008 GlaxoSmithKline (GSK) decided to change their T-4-product Eltroxin in Denmark. No notice was given, neither to the doctors or the patients. Just a small red text on the Eltroxin-box saying "new formulation same effect". The box that only the patient sees, not the doctor.

For your information we have no choice of T4-product in Denmark. GSK is the only supplier on the Danish Market.

The Danish patients organization, Thyreoidea Landsforeningen (TL) immediately contacted (GSK) but they did not seem very interested in a dialogue with the patients. TL began to investigate the matter and was very surprised to find out that no Danish doctor was informed about the new formulation – no GPs or endocrinologist.

We contacted the Danish Health Authorities and they had not heard of the change either. GSK had made an application to change the formulation some years ago and it had been accepted by the authorizes but no notice was given from GSK when they decided to supply the new formulation.

Itm is one thing to not inform the patients' organization but to not inform doctors is another thing. Doctors need to know what they prescribe to patients and when there is a change in it.

Through our relations with Thyroid Federation International we found out that GSK had done the same in New Zealand in 2007 and more than 700 patients had problems with the new formulation. GSK in Denmark still claims not to have been aware of the problems in New Zealand.

Some of the approximately 100,000 patients in Denmark using T4 began to have problems with the new Eltroxin. Some experienced a change in their TSH – still within the normal range but enough for some patients not to feel well. Other symptoms are the classical symptoms for low thyroid function.

TL decided to contact the media and when newspapers started to write about it we began to receive more information from GSK! They wrote to all doctors and pharmacies and together with the Danish Health Authorities they recommended that every patient have a blood test taken after some weeks use of the new formulation. A new dosage may be necessary.

GSK has now invited the board of Thyreoidea Landsforeningen to a meeting to talk about the problems – and we hope it will prevent the same thing from happening elsewhere in the world. ❧

*Bente Julie Lasserre*
*Past vicepresident of Thyreoidea Landsforeningen and Thyroid Federation International*

# Iodine Nutrition in Brazil: Where do we stand?

ARTICLE BY GERALDO MEDEIROS-NETO

## Introduction

Since colonial times Iodine Deficiency Disorders have been a major cause of goiter in the Brazilian population, having been described by several scientific expeditions that ventured deep into Brazil's hinterland. But although goiter is a visible and easily detectable anomaly, the most serious sequelae of Iodine Deficiency Disorders is Brain Damage to fetus and infants. Indeed, several reports confirm that mild to severe iodine deficiency induces some degree of brain defects, with post-natal sequelae such as mental deficiency, abnormal neurological signs and deaf mutism. [1]

Thus, several countries in Europe introduced iodized salt in order to prevent the consequences of Iodine Deficiency. Only in 1953 were the first steps taken in Brazil following the introduction of iodized salt, albeit restricted to areas recognized as iodine deficient. This legal ruling posed an almost impossible task for the health authorities and the salt industry. How possibly could distribution of iodized salt only to areas defined as "endemic" be organized, while other areas of the country were to continue using non-iodized salt?

## Further Legislation on Salt Iodination

After three years this situation was recognized as logistically unworkable and in 1956, iodized salt was made widely available to Brazil's population as a whole. The Ministry of Health was charged with the task of importing potassium iodate for distribution to the salt mills. Again the whole strategy of adding iodine to salt was hampered because, in brief, small salt mills never added potassium iodate to the salt they produced, in spite of receiving this iodine source from the Health Authorities. Successive national surveys of schoolchildren were conducted in 1955 (24.6% of the Brazilian children were goitrous), and again in 1975 (when 14.7% of the children had palpable goiters). This latter figure indicated that approximately 10 million Brazilians were likely suffering from iodine deficiency (out of a population of 60 million).

Thus, another law was enacted by the House of Representatives determining that the amount of iodine in salt for human consumption was to be set at 10mg Iodine/kg salt. Moreover, this new law transferred the onus of purchasing potassium iodate to the salt industry. Obviously, this was ineffective because each State of the Republic of Brazil was then responsible for the surveillance of salt supplied for human use by checking samples of salt on the market and also at salt mills, although this was seldom done.

## Creation of Task Form to Save the Iodination Programme

The situation was so badly conducted that in 1982 the "National Institute for Food and Nutrition (INAN)" of the Ministry of Health decided to create a Working Task Force to solve the problem. This new task force included members of the Salt Industry, Health Authorities, and expert consultants from the Universities of Pernambuco and São Paulo (GMN). The Committee decided that the solution would be to provide Potassium Iodate free of charge to the salt mills, but the industry would have to agree a system of close surveillance whereby samples of salt would be periodically tested both on the market and on the production line. If below or above legal concentrations of Iodine/kg were detected, the salt mills would be fined and possibly closed down.

Therefore, between 1982 and 1992, it can be assured that the Brazilian population had received iodine through an effective salt iodination programme, coordinated by the INAN Committee, with full cooperation of the salt industry. About seven thousand samples of salt were analyzed each year, and INAN published the results annually in an internal bulletin.

## Salt Iodination Programme Interrupted

In 1992, there was a legal dispute based on the fact that supplying the salt industry with free potassium iodate was illegal according to the 1974 law. Therefore, during the preceding three years most of the salt consumed by the Brazilian population was not iodized. The largest salt mills, however, continued to add iodine to their salt at their own expense. In 1994-1995, a Third National Survey in schoolchildren was conducted and aside from goiter prevalence iodine urinary excretion was assayed. Four deficient areas and

*(continued on page 12)*

116 moderately deficient villages were detected. This work indicate that iodine deficient was still present mostly in the impoverished area of Northeast Brazil. Finally, in 1995, a new law was approved by the House of Representatives and the Senate, and signed by the President of the Republic of Brazil. The law simply stated that all salt for human use should be iodinated according to the limits and rules set forth by the Ministry of Health. During the same period, it was agreed that surveillance and monitoring should be conducted by the National Agency for Sanitary Surveillance (ANVISA). The limits for salt iodination were set at 40 to 60 mg Iodine/kg of salt.

## New Limits for Salt Iodination

In 1998, ANVISA decided to increase the concentration of iodine in the salt for human use to 40-100 mg Iodine/kg of salt. The rationale was to provide a broader range so as to avoid salt producers from introducing less (<40$\mu$g) or more (>100 $\mu$g/L) iodine to salt. In either circumstance, the salt industry would be fined accordingly.

For the ensuing five years (1998-2003), the Brazilian population was subjected to excessive iodine nutrition due to the relatively high content of iodine in the salt. This was confirmed by the studies linked to the Thyromobil Project in 2001. [2] In this field work, it was confirmed that schoolchildren were receiving excessive iodine nutrition. Indeed, almost 86% of all children examined excreted more than 300 $\mu$g Iodine/L of urine. Moreover, close to 50% of all salt samples (collected at homes) contained more than 60 mg Iodine/kg of salt. Therefore, in 2003, the ANVISA agency decided to lower the iodine concentration of salt for human use to 20-60 mg Iodine/kg of salt.

## Effects of Excessive Iodine Intake on the Population

Excessive iodine intake for a prolonged period of time may be harmful. The WHO states that iodine excess may increase the prevalence of chronic autoimmune thyroiditis (in individuals with a genetic trait linked to autoimmunity) and also lead to iodine-induced hyperthyroidism mainly in the elderly (who frequently present thyroid nodules). Thus, Camargo et al [3] confirmed that the prevalence of chronic autoimmune thyroid disease (Hashimoto's thyroiditis) was elevated in an urban population in São Paulo, after 5 years of excessive iodine nutrition (1998-2004). A total of 16.5% of women (all ages) had clinical signs, ultra-sonographic hypoechogenicity and positive anti TPO antibodies, which, taken together, are considered to strongly indicate chronic autoimmune thyroiditis. Men were also affected (4% of all men) by Hashimoto's thyroiditis.

In conclusion, the excessive nutritional iodine intake (from 1998-2004) may be considered an environmental factor conducive to a high prevalence of both Hashimoto's thyroiditis and iodine-induced hyperthyroidism.

## Conclusions

The salt iodination programme has come a long way since the first flawed efforts in 1955. According to the latest WHO report by de Benoist et al, [4] the Americas have shown a marked improvement in iodine nutrition since 2003, with less than 10% of the whole population presenting urinary iodine excretion of less than 100 $\mu$g Iodine/L. Nevertheless, Brazil is listed as a country in which iodine intake is more than adequate (or even excessive) with a median urinary iodine intake greater than 200 $\mu$g I/Lindicating that susceptible groups within the population might be exposed to the risks of excessive nutritional iodine. It is envisaged that upon completion of the PNAISAL programme we will have an excellent tool at our disposal to determine the concentration of iodine in salt for human use. Continuous monitoring and surveillance will be necessary to keep our children and the population as a whole on an adequate iodine supply through salt. ❧

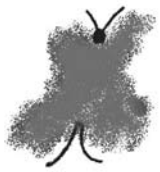
## References

1. Medeiros-Neto GA and Knobel M. Iodine deficiency disorders. In: DeGroot LJ, Jameson JL, editors. Endocrinology. 6th Ed, New York, Elsevier, 2008.
2. Rossi AC, Tomimori E, Camargo RY, Medeiros-Neto G. Searching for iodine deficiency disorders in schoolchildren from Brazil: the Thyromobil project. Thyroid 2001; 11:661-3.
3. Camargo RYA, Tomimori EK, Neves SC, Rubio IGS, Galrão AL, Knobel M, Medeiros-Neto G. Thyroid and environment: exposure to excessive nutritional iodine increases the prevalence of thyroid disorders in São Pauli, Brazil Eur J Endocrinol 2008; 159:292-299.
4. De Benoist B, McLean E, Andersson M, Rogers L. Iodine deficiency in 2007: global progress since 2003. Food Nutr Bull 2008; 29:195-202.

*Contact Information:*
*Geraldo Medeiros-Neto*
*Lab. Molecular de Tireóide (LIM-25)*
*Faculdade de Medicina da*
*Universidade de São Paulo*
*Av. Dr. Arnaldo, 455 – 4° A – sala 4345*
*01246-903 São Paulo, SP*
*e.mail: medneto@uol.com.br*

# Brand Hopping …

## It might not be without risk.



ARTICLE BY PROF. DR. MED. M. DIETLEIN, DEPARTMENT OF NUCLEAR MEDICINE, UNIVERSITY HOSPITAL COLOGNE, GERMANY

Levothyroxine (T4) is the slightly active prohormone of the biologically 3 times more active triiodothyronine (T3), produced by the peripheral 5′ deiodasis in the target organs. Via a negative feedback mechanism, a decrease of free T4 will stimulate the pituitary gland to increase its production of "Thyroid Stimulating Hormone" (TSH) – and inversely, a high T4 concentration will lower the TSH. Today, the TSH value is the most sensitive laboratory value to evaluate the thyroid function. However, TSH changes will only be entirely tangible 4 to 6 weeks after a change in the LT4 dosage.

Thyroid hormones influence the growth and the function of nearly all organs of the body, and even a slight variation of the TSH, in the upper or in the lower reference range, may have serious consequences, for example during pregnancy (retardation of the fetal cerebral maturation, resulting in a lower IQ, if the TSH of the mother is too high), in elderly patients (cardiac arrhythmia, atrial fibrillation, threefold increase in cardiovascular mortality if the TSH is too low), and in the follow-up of differenciated thyroid carcinoma (higher risk of recurrence in high-risk patients if the TSH value remains detectable).

The bioequivalence evaluations on various brands of levothyroxine, aimed at demonstrating therapeutic consistency between preparations, must be considered with reservations, because these tests are performed on healthy subjects (not on thyroid patients), with a small amount of samples and with supra-physiological doses. The target value in these tests is not TSH, but total T4 – however, variations in the total T4 of 12.5% remained undetectable. (Blakesley et al. 2004, Thyroid 14:191-200). Variations in bioavailability have a linear effect on the total T4 concentration in the serum, but an exponential effect on the TSH value. As the test persons remain with an empty stomach for a long period before and after the administration of the LT4 test doses, and receive standardized meals, possible differences in the bioavailability, due to delayed dissolution and resorption, will remain undetected. However, variations in time of intestine resorption are an important criterion in patient care, when the delay between the administration of the LT4 medication and breakfast is cut down to 15 minutes.

In the USA, the FDA (Food and Drug Administration) has tightened the criteria for levothyroxine generic drugs, and narrowed the admitted variation in bioavailability (confidence interval) from 90-110% to 95-105% (Burman et al. 2008, Thyroid 18: 487-490). Furthermore, the various levothyroxine brands in the USA are rated BX (not interchangeable) or AB (interchangeable with ...). Variations in bioavailability between 90 and 110% lead to TSH variations out of the reference range (Eisenberg and DiStefano2009, Thyroid 19: 103-110).

For the German market, the comparison between the levothyroxine brands from three manufacturers showed significant differences in the TSH level (Wenzel and Mehrländer 1988, Dtsch Med Wochenschr 113:53-58). Later, a randomized double-blind cross-over study with two drugs from two manufacturers, showed significant differences in total T4 over 10 hours and in the TSH change after 14 days (Krehan et al. 2002, Med Klinik 97:522-527). According to this study, these two levothyroxine brands cannot be interchanged without TSH follow-up in Germany.

Which are the other facts with an influence on bioavailability that we know? After storing levothyroxine tablets at a temperature of 25°C for 24 month, they contain approx. 90% of the original active ingredient (Eisenberg und DiStefano 2009, Thyroid 19: 103-110). When levothyroxine powder is heated to 90°C for 15 minutes, it is not inactivated (Wortman et al. 1989, Clin Chem 35: 90-92). Various food (plant fibers, liver extract, soy bean extract, walnuts, coffee) and many drugs (aluminum and magnesium hydroxide, magnesium and calcium carbonate, sucralfate, charcoal, colestyramine, colestinol, iron sulfate, non-selective beta-blockers, hydantoin and proton pump inhibitors – for the latter, the data are contradictory) may reduce the bioavailability of levothyroxine – the possible alteration of intestine absorption by coffee has been documented recently (Benvenga et al. 2008; Thyroid 18:293-301). Surprisingly, taking LT4 at bedtime leads to higher T4 levels in the blood and to a stronger effect on the TSH value compared with taking in the morning (Bolk et al. 2007, Clin Endocrinol. 66:43-48).

*(continued on page 14)*

**Brand Hopping** *(continued from page 13)*

Due to the fact that the results of bioequivalence evaluations for levothyroxine are questionable (tests on healthy persons, small samples, unrealistic doses), three medical societies in the USA (American Thyroid Association, Endocrine Society, American Association of Clinical Endocrinology) issued a „Joint statement" recommending to follow-up the TSH value after switching brands (Thyroid 2004, 14:486). Similar recommendations were given by German studies (Dietrich et al. 2008, Dtsch Med Wochenschr 133: 1644-1648). But these recommended TSH tests will nullify the moderate saving of approx. 1.80 EUR per year which can be obtained by prescribing the cheapest levothyroxine 100 µg instead of the same drug from another manufacturer (difference per tablet approx 0.5 cents). An additional TSH test will cost the health insurances between 10 and 25 EUR. And such TSH measurements may become necessary even more often, several times a year, if drug prices vary and if one tries to prescribe always the cheapest brand (Reiners 2007, Ärztezeitung).

### Conclusion

The balancing act between economic necessities (discount agreements, „aut-idem" regulation) and optimum medical care (same galenics, same accuracy of dosage) remains delicate. Needless to say that discrepancies in bioavailability may result from many other causes (e.g. storage conditions, delay between LT4 intake and other medications / dietary supplements, timing of the LT4 intake, patient compliance ... or when the supplier changes the formula of his medication). Some groups of patients, strongly depending on a very precise adjustment of their thyroid function, can be clearly defined, i.e. pregnant women with a medicamentally compensated thyroid hypofunction, patients treated for differenciated thyroid cancer, or elderly patients, for whom a TSH decrease to the lower threshold range, induced by their medication, will increase the risk of cardiovascular mortality. ❧

# "Transnational" French-Canadian Patient Information Meeting

### Montréal, 2009

For the first time, two TFI member organizations from two different countries organized a patient information meeting in common. Beate Bartès, president of the French association "Vivre sans Thyroide", with a bulletin board leveraged the trip to Canada to collaborate with Ashok Bhaseen, president of the Thyroid Foundation of Canada, to organize a joint patient information meeting in Montreal, in the French language. This meeting took place in Montreal's university hospital, CHUM, by the kind curtsey of the Hospital on August 1st, 2009.

Dr Hortensia Mircescu, Medical Advisor to Thyroid Foundation of Canada, who had kindly agreed to be a Speaker for the conference, provided an excellent update on thyroid problems. It was an interactive session, where patients asked question on various issues. This conference provided a good platform for an exchange of experience, gaps in understanding of the disease and to also receive various information material related to the issues on managing the disease.

*Julie Marin (TFC), Dr. Elvira Villazon (TFC), Beate Bartès (Vivre sans thyroide), Dr. Hortensia Mircescu (TFC), Ashok Bhaseen (TFC)*

Due to the holiday season, and an excellent sunny day, the audience was small, but captive – and we hope to provide similar conferences on a yearly basis for the benefit of patients who encounter thyroid related issues. We hope that those who are interested in benefitting from a similar conference will let us know in advance (register for the meeting in advance) so that more people can take advantage of knowing and understanding the issues. ❧

*Ashok Bhaseen*

# Thyroid Dysfunction and Pregnancy

ARTICLE BY CAMILLA SCHALIN-JÄNTTI, M.D., PH.D., SENIOR ENDOCRINOLOGIST

Thyroid dysfunction is associated with reduced fertility while untreated maternal thyroid dysfunction increases the risks for miscarriage, preterm delivery and low birth weight. The prevalence of hyperthyroidism complicating pregnancy is 0.1-0.4% and that of overt and subclinical hypothyroidism 0.3-0.5% and 2-3%, respectively. Graves disease accounts for the majority of hyperthyroidism complicating pregnancy.

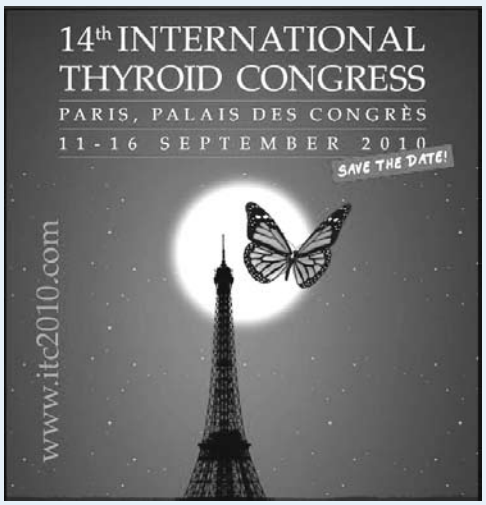
Thyroxine is essential for the normal development of fetal brain, lungs and skeleton. When suboptimally treated, maternal hypothyroidism has been associated with cognitive deficits in the offspring. The fetal thyroid is able to produce thyroxine approximately from gestational week 20 onwards. This explains why the fetus is especially dependent on adequate maternal thyroxine production and transportation during early pregnancy. Accordingly, hypothyroxinaemia during early pregnancy and prolonged maternal hypothyroidism should especially be avoided, as both timing and severity of fetal hypothyroxinaemia are critical.

The thyroxine requirement increases during pregnancy. The healthy maternal thyroid is able to compensate for the increased need by producing approximately 50% more thyroxine during pregnancy. Approximately 1-2% of pregnant women are receiving thyroxine replacement therapy. Their dose must be adequately increased (by an average of 25 – 50 ug) and monitored according to TSH levels measrued at intervals of 6-8 weeks throughout pregnancy. According to a recent large cohort study of 2497 Dutch women, pregnancy loss was associated with higher early pregnancy TSH levels also in apparently healthy women. The association extended to pregnant women with TSH in the normal range, implying a continuous relationship between TSH concentration and risk of child loss.

Thyroid peroxidase (TPO) antibodies, a marker of chronic autoimmune thyroiditis, are present in 5-15% of pregnant women. Autoimmune thyroiditis is also associated with miscarriage and preterm delivery. In these women, thyroid function may deteriorate during pregnancy. Another recent study demonstrated that thyroxine treatment was able to reduce these risks.

Ideally, thyroid dysfunction should be treated and ruled out before pregnancy. Adequate treatment of thyroid dysfunction during pregnancy greatly decreases the risk of complications. To accomplish this, adequate screening for and diagnosis of thyroid dysfunction before or during early pregnancy is essential. To date, the consensus is to screen S-TSH in all women at high-risk for thyroid disease. The S-TSH results must, however, be interpreted with caution. The S-TSH reference range during normal pregnancy is clearly lower than the usual reference range (0.4–4.0 mU/l) and in most countries trimester-specific reference ranges are not yet available. A matter of debate is whether S-TSH and S-TPOAb in the future should be routinely screened in all pregnant women. ❧

*Camilla Schalin-Jäntti*
*M.D., Ph.D., Senior Endocrinologist*
*University of Helsinki, Division of Endocrinology, Department of Medicine*
*camilla.schalin-jantti@hus.fi*




### 14th International Thyroid Congress

September 11th to 16th, 2010
Paris, France
www.itc2010.com

### 15th Annual TFI Meeting

September 8-9, 2010 (to be confirmed)
Paris, France

# TFI Member Organizations

**AUSTRALIA**
*Australian Thyroid Foundation*
Beverley Garside (President)
The Australian Thyroid Foundation Ltd.
Suite 2, 8 Melville Street
Parramatta, NSW 2150 Australia
info@thyroidfoundation.com.au
www.thyroidfoundation.com.au

*Thyroid Australia*
Cornelia Cefai (President)
333 Waverley Road
Mount Waverley, VIC, 3149
Australia
support@thyroid.org.au
www.thyroid.org.au

**BRAZIL**
*Instituto da Tiróide*
Geraldo Medeiros-Neto, MD, MACP (President)
Rua Teodoro Sampaio, 352 - conj. 64
05406-000 São Paulo, SP
medneto@uol.com.br
www.indatir.org.br

**CANADA**
*Thyroid Foundation of Canada*
*La Fondation canadienne de la Thyroïde*
Ashok Bhaseen (President)
1669 Jalna Blvd. Unit 803
London, ON N6E 3S1 Canada
a.bhaseen@thyroid.ca
www.thyroid.ca

**DENMARK**
*Thyreoidea Landsforeningen*
Lis Larsen (President)
Strandkrogen 4A
3630 Jaegerspris, Denmark
lis_l@doktor.dk
www.thyreoidea.dk

**FINLAND**
*Thyroid Foundation of Finland*
Dr. Ulla Slama
Vettmossvagen 57
Narpes, Finland
ullslama@tawi.fi
www.kilpirauhasliitto.fi

**FRANCE**
*Association Vivre sans thyroïde*
Beate Bartès (President)
2, av d'Expert, Léguevin, 31490
France
info@forum-thyroide.net
www.forum-thyroide.net

**REPUBLIC OF GEORGIA (EU)**
*Georgian Union of Diabetes and Endocrine Associations (GUDEAS)*
Prof. Ramaz B. Kurashvili (President)
Georgian Medical Diagnostic Centre
5, Ljubljana Str., Tbilisi, 380059
Republic of Georgia (EU)
diabet@access.sanet.ge

**GERMANY**
*Ohne Schilddrüse Leben e. V.*
Harald Rimmele (President)
Rungestraße 12
10 179 Berlin, Germany
info@sd-krebs.de
www.sd-krebs.de

*Schilddrüsen Liga Deutschland e.V.*
Barbara Schulte (President)
Ev. Krankenhaus Bad Godesberg
Waldstrasse 73, 53177 Bonn, Germany
info@schilddruesenliga.de
www.schilddruesenliga.de

**ITALY**
*Associazione Italiana Basedowiani e Tiroidei*
Emma Bernini (President)
c/o Centro Minerva
Via Mazzini 6, 43100 Parma, Italy
aibat@asmn.re.it
www.endocrinologia.re.it/aibat.htm

**JAPAN**
*Thyroid Foundation of Japan*
Dr Fumito Akasu (President)
CBON Queen Building, 4th Floor
Roppongi 7-18-12
Minato-ku, Tokyo 106-0032 Japan
www.hata.ne.jp/tfj/

**MEXICO**
*La Asociación Mexicana de Tiroides*
Carlos M Duncker, MD (President)
Zacatecas 230, Quinto Piso
Colonia Roma, C.P. 06700
México, D.F., México
amet@tiroides.org
www.tiroides.org

Thyroid Federation International

**THE NETHERLANDS**
*Schildklierstichting Nederland*
Joke van Galen (Deputy President)
Stationsplein 6
3818 LE Amersfoort
The Netherlands
info@schildklier.nl
www.schildklier.nl

**NORWAY**
*Norsk Thyreoideaforbund*
Bente Bakke (President)
Fr. Nansens plass 9, NO-0160, Oslo
Norway
post@stoffskifte.org
www.stoffskifte.org

**RUSSIA**
*Thyroid Foundation of St. Petersburg*
Prof. Elina G. Gasparyan (President)
"Professor" Medical Centre
42 Chaykovsky Street
St. Petersburg 191123, Russia
gasparyan@peterlink.ru

**SWEDEN**
*Svenska Sköldkörtelföreningen*
Yvonne Andersson (President)
Postbox 10256
SE-43423 Kungsbacka, Sweden
info@skoldkortel.se
www.skoldkortel.se

*Sköldkörtelförening i Stockholm*
C/O Nina Oksa
Byälvsvägen 215
SE-12847 Bagarmossen, Sweden
Info@skoldkortelforeningen.se
www.skoldkortelforeningen.se

**UNITED KINGDOM**
*The Thyroid Eye Disease Charitable Trust*
Dr. Colin Dayan (Chair)
P.O. Box 2954, Calne
SN11 8WR U.K.
ted@tedct.co.uk
www.tedct.co.uk

**UNITED STATES OF AMERICA**
*Graves' Disease Foundation*
Peter Filocamo (President)
400 International Drive
Williamsville, NY 14221
gravesdisease@gmail.com
www.ngdf.org