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ETA Symposium



EUGOGO

European Group of Graves' Orbitopathy

Final programme and abstracts

Graves' Orbitopathy Teaching Course

Mainz, Germany,
28-29 September 2012

www.eugogo.eu



University Eye Clinic
Department of Ophthalmology
Johannes Gutenberg University Medical Centre

Welcome

Dear colleagues,

Welcome to the international **ETA TEACHING COURSE ON GRAVES' ORBITOPATHY** organized by the European Group on Graves' Orbitopathy "EUGOGO" in Mainz, Germany, September 28-29, 2012.

A multidisciplinary approach in which endocrinologists, ophthalmologists, orbital surgeons and basic scientists combine forces has been the philosophy behind the foundation of EUGOGO. The group is currently composed of 12 centers in eight European countries, and in accordance with our philosophy each center is represented by specialists in internal medicine and ophthalmology. A further requirement of EUGOGO membership is that each participating center must have combined thyroid-eye clinics in which the patient is seen simultaneously by physicians from both disciplines.

During this sixth EUGOGO teaching course and the second taking place in Mainz, Germany, an excellent international multidisciplinary faculty with varying expertise will share with you the latest data of this complex thyroid-related autoimmune disease. More than four hours will be reserved for grand rounds with live demonstrations and practical assessment of patients with thyroid eye disease. Index cases will be presented and extensively discussed within small multidisciplinary groups.

Looking forward to welcoming you in Mainz, on behalf of the Executive Committees of the ETA and of EUGOGO, please receive our best personal regards

Susanne Pitz

George J. Kahaly

**University
Medical Centre**
of the
Johannes Gutenberg
University Mainz

**University
Eye Clinic**
Auditorium 101



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Organisation

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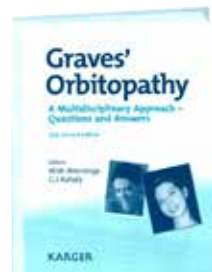
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**Registration fee [200 Euro]
includes**

Scientific programme,
Get Together buffet,
coffee breaks,
and EUGOGO book

Graves' Orbitopathy

A Multidisciplinary
Approach -
Questions and
Answers
2nd, revised
edition



Accreditation

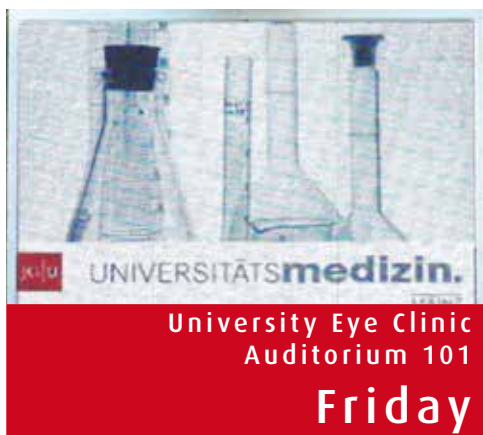
For German participants:
the teaching course has been accredited
with a total of **15** credits by the Akademie
für Ärztliche Fortbildung in Rheinland-Pfalz
– please bring 2 EFN barcodes.

EACCME credits

The Course has been accredited by the
European Union of Medical Specialists.

All participants will receive a certificate of
attendance.

Programme



Sept 28, 2012

12:00 – 13:00

Registration

13:00 – 13:15

WELCOME ADDRESS

Prof. Dr. Norbert Pfeiffer

President of the Johannes Gutenberg University Medical Centre
and Chairman of the Department of Ophthalmology

Prof. Dr. Luigi Bartalena

Secretary of the European Thyroid Association

Dr. Petros Perros

Chairman of Eugogo

13:15 – 15:00

PATHOGENESIS / ASSESSMENT OF GRAVES' ORBITOPATHY

Chair: Jacques Orgiazzi, France / Antonella Boschi, Belgium

13:15 – 13:35

Pathogenesis

Simon Pearce, UK

13:35 – 13:55

Assessment of clinical activity

Jane Dickinson, UK

13:55 – 14:15

Assessment of clinical severity and optic neuropathy

Carol Lane, UK

14:15 – 14:35

Assessment of eye muscle motility

Anja Eckstein, Germany

14:35 – 14:55

Imaging

Wibke Müller-Forell, Germany

15:00 - 15:30
Coffee Break

15:30 – 17:30

MANAGEMENT OF GRAVES' ORBITOPATHY

Chair: George J. Kahaly, Germany / Chantal Daumerie, Belgium

15:30 – 15:50

Thyroid treatment

Petros Perros, UK

15:50 – 16:10

Selenium and anti-oxidative measures

Claudio Marcocci, Italy

16:10 – 16:30

Intravenous steroids

Luigi Bartalena, Italy

16:30 – 16:50

Non-steroid immunosuppressants

Mario Salvi, Italy

16:50 – 17:10

Orbital decompression surgery

Susanne Pitz, Germany

17:10 – 17:30

Eye Muscle / Lid surgery

Nicola Curro, Italy

Programme



Sept 28, 2012

17:45 – 18:00

INDEX CASE PRESENTATION

Katharina Ponto

18:00 – 18:45

INDEX CASE DISCUSSION

in 4-5 groups à 25 participants
+ 2 ophthalmologists / 2 endocrinologists

19:00 – 19:30

STATE-OF-THE-ART LECTURE

Chair and introduction: Petros Perros

History and philosophy of EUGOGO

Wilmar Wiersinga, The Netherlands

19:30 – 21:00

**Get Together
in Foyer**



8:00 – 10:00

GRAND ROUNDS

with 10 groups, 10 patients,
1 Ophthalmologist and 1 Endocrinologist/group, 20 min/patient

10:30 – 12:30

GRAND ROUNDS

(2nd round)

10:00 - 10:30
Coffee Break

12:30 – 13:00

FEEDBACK + FAREWELL

Luigi Bartalena / Petros Perros / Susanne Pitz

Abstracts

PATHOGENESIS / ASSESSMENT OF GRAVES' ORBITOPATHY

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Pathogenesis and genetics of Graves' orbitopathy

GRAVES' ORBITOPATHY (GO) IS characterized by an immune-mediated inflammation of the orbital structures. It is believed that expression of the thyrotropin receptor (TSHR) on orbital pre-adipocytes leads to aberrant targeting of the anti-thyroid immune response to the orbit. Inflammatory cytokines are released attracting a lymphocytic infiltrate and causing glycosaminoglycan accumulation in the extraocular muscles, leading to inflammation and proptosis. More recently, recruitment of circulating fibrocytes, a form of mesenchymal progenitor cell, has been implicated.

Several genetic variants have been proposed to have a role in GO, such as MHC or CTLA4 molecules, although GO rarely seems to 'run true' even in families with several members who have hyperthyroid Graves' disease. More likely, the accumulation of several genetic variants leads to a more severe autoimmune phenotype in GO, and none of these variants has thus far been confirmed to be specific for GO. Nevertheless, polymorphisms in pathways relating to insulin resistance (eg. PPAR γ), which is a common association of GO, are currently being explored and may provide additional pathogenic insights in the fullness of time.

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Assessment of clinical activity

GRAVES' ORBITOPATHY (GO) IS the commonest cause of orbital disease with an inflammatory component. With a basic knowledge of both orbital anatomy and the pathogenesis of GO it is easy to understand how it's typical constellation of features originate. These features can be considered as primary or secondary. Primary features are those due directly to the disease process affecting a tissue e.g. restrictive myopathy. Secondary features occur due to the interaction of the affected tissue and the anatomical configuration of the tissues e.g. corneal ulceration or dysthyroid optic neuropathy, and are less likely to be florid at presentation. Most patients with GO present in a fairly typical manner: they have evidence of bilateral disease, upper eyelid retraction, proptosis, and soft tissue inflammation, with or without muscle restriction. However the presentation can be quite heterogeneous: for example GO may be very asymmetrical, or secondary features may be evident at presentation. The reasons for the heterogeneity are poorly understood, but probably include bony anatomical configuration, speed of onset of the inflammatory process, and/or pre-existing vascular compromise.

The heterogeneity of presentation can sometimes make GO difficult to diagnose. Of equal, or perhaps greater, importance is the considerable overlap between symptoms and signs of GO and those of other orbital conditions, which include malignancies. Hence the clinician requires a constant awareness of when patients should be investigated further, particularly with orbital imaging.

This presentation will discuss these concepts and draw out both typical and atypical presentations of GO, highlighting particularly unusual features such as lack of upper eyelid retraction, divergent strabismus or unilateral disease. Several cases which illustrate these points will be presented.

Abstracts

PATHOGENESIS / ASSESSMENT OF GRAVES' ORBITOPATHY

Carol Lane

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Assessment of Clinical Severity and Dysthyroid Optic Neuropathy

CLINICAL SEVERITY IS determined by the functional or cosmetic defect caused by GO. It is determined by visual impairment, ocular exposure and ocular motility restriction and can be divided into the following 3 categories:

1. Sight-threatening GO: Patients with dysthyroid optic neuropathy (DON) and/or corneal breakdown. This category warrants immediate intervention.
2. Moderate-to-severe GO: Patients without sight-threatening GO whose eye disease has sufficient impact on daily life to justify the risks of immunosuppression (if active) or surgical intervention (if inactive).
3. Mild GO: patients whose features of GO have only a minor impact on daily life insufficient to justify immunosuppressive or surgical treatment.

Dysthyroid optic neuropathy is a sight threatening complication of GO. It may be defined as impairment of optic nerve function caused by compression or stretch of the optic nerve due to infiltration of orbital tissues by inflammatory cells and glycosaminoglycan deposition. It is observed in up to 5% of patients with GO, though criteria for diagnosis remain elusive. Optic disc swelling, an RAPD, loss of visual acuity or colour vision, visual field defects and apical crowding are important diagnostic features.

Wiersinga W, Perros P et al. Consensus Statement. Clinical assessment of patients with Graves' orbitopathy: the European Group on Graves' orbitopathy recommendations to generalists, specialists and clinical researchers. *European Journal of Endocrinology* 2006; 155:387-389.

Lane CM, Boschi A. Management of Very Severe Graves' Orbitopathy (Dysthyroid Optic Neuropathy and Corneal Breakdown) in Wiersinga WM, Kahaly GJ (eds): *Graves' Orbitopathy: A Multidisciplinary Approach – Questions and Answers*. Basel, Karger, 2010, pp159-166.

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Assessment of ocular motility

DIPLOPIA AND COMPENSATORY head are the result of extraocular muscle fibrosis and the most commonly indications for prism correction and eye muscle surgery. Muscle fibrosis is mostly not limited to one muscle. It often affects both, the medial and inferior rectus in varying degrees on both sides. The choice of which eye to treat and which dimension first is very important. It is important to concern primary and secondary action of each muscle, when planning eye muscle surgery.

Evaluation of motility to assess and follow up GO:

For assessment and follow up of GO diplopia and ductions have to be examined. Diplopia is classified in: no diplopia, diplopia with horizontal or vertical gaze but not in straight gaze, intermittent diplopia in straight gaze, constant diplopia in straight gaze and fixed eyes. Ductions can be graded in four directions using the Hirschberg principle, or quantified with the Goldmann Perimeter, a modified motility meter or Kestenbaum glasses. When diplopia occurs in straight gaze and cannot be corrected with head tilt the squint angle has to be measured with the alternating prism cover test to prescribe Fresnel prisms, when fusion occurs after prism corrections.

Evaluations prior to surgery: Orthoptic assessment before surgery should include the following procedures: measurement of squint angle, ductions and field of binocular single vision. The squint angle (fixation of the eye with better excursions) should be measured in primary position by using the alternating prism cover test (far distance: 5 m and near distance 30 cm). In complex situations squint angle should be measured in all 9 directions of gaze: by using Maddox screen or Harms tangent screen in 2½ m. Cyclodeviation should be evaluated at the Harms tangent screen or cycloferometer in primary position and 9 direction of gaze, especially if the squint angle cannot be compensated with vertical and horizontal prisms alone. Ductions should be measured as mentioned above. The Field of binocular single vision can be assessed at the Maddox screen or Harms tangent screen in 2½ m.

Evaluations after surgery: Field of binocular single vision should be assessed postoperatively. If diplopia occurs in primary of reading position – squint angle should be measured for prism correction or to send the patient to further surgical correction.

Abstracts

PATHOGENESIS / ASSESSMENT OF GRAVES' ORBITOPATHY

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Imaging

MOST ADULT PATIENTS presenting an exophthalmus suffer from thyroid orbitopathy (Graves' orbitopathy – GO -), mainly diagnosed by endocrinological and/or ophthalmological findings. Nevertheless neuroimaging of these patients with computed Tomography (CT) and magnetic resonance imaging (MRI) plays an important role in differential diagnosis and especially interdisciplinary management of the disease. Although very quick and cheap indication for CT should be justified due to radiation burden to the lens, but MRI represents the method of choice. Imaging demonstrates not only morphological changes of the different involved orbital compartments, but may help in defining statements concerning the acuity/recurrence of the disease. Classical criteria of Graves disease are presented in primary diagnosis and in the course of the disease (e.g. demand of surgical intervention), as well as some common and rare differential diagnosis.

Abstracts

MANAGEMENT OF GRAVES' ORBITOPATHY

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THYROID TREATMENT IN GO

DYSTHYROIDISM HAS A detrimental effect on the course of GO, especially hypothyroidism. One of the principal objectives therefore is to achieve euthyroidism rapidly and maintain it. In the small proportion of cases of GO presenting with hypothyroidism, this is relatively simple through the introduction of levothyroxine. Anti-thyroid drugs and thyroidectomy appear to be neutral with regards to the course of the orbitopathy, while radioiodine (especially when given to smokers and during the active phase of the eye disease) has a small but definite detrimental effect on the eyes, which can be prevented by a short course of oral steroids. Total thyroid ablation (total thyroidectomy followed by radioiodine ablation) may have a small beneficial effect, though the evidence is yet not compelling. All treatments of thyrotoxicosis induce a phase of thyroid instability with a significant risk of fluctuations in thyroid function lasting several months. It is crucial that patients are followed up carefully every 2-3 months, or more frequently if necessary, with assessments of clinical and biochemical thyroid function. Sensible and proactive decisions about thyroid medication are essential to achieve and maintain euthyroidism. Patient compliance with medication is crucial and frequently problematic, thus necessitating close engagement between patient and endocrinologist.

Abstracts

MANAGEMENT OF GRAVES' ORBITOPATHY

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Selenium and anti-oxidative measures in GO

ANIMAL AND HUMAN studies suggest that increased ROS generation and the consequent oxidative damage may contribute to the pathogenesis of Graves' orbitopathy (GO). These findings have been the rational for the use of antioxidants in the management of GO. A small non-randomized study investigated the effects of 3-month treatment with antioxidants (nicotinamide and allopurinol) in patients with moderately severe GO. Favorable results, particularly on soft tissue involvement were reported. Recently, a large multicenter, randomized, double blind, placebo-controlled study has evaluated the effect of selenium on the course of mild GO. Selenium is a trace mineral which is incorporated as selenocysteine into several selenoproteins, mostly enzymes, in which selenium acts as a reduction oxidation center and functions as an antioxidant. This study has shown that a 6-month course with sodium selenite (100 µg twice daily) was associated with a significant improvement of the quality of life and of eye manifestations compared with patients treated with placebo. In addition, a lower rate of worsening was also observed in patients given selenium. The beneficial effect of selenium persisted in the 6 months after treatment withdrawal. The patients included in the study were living in marginally selenium-deficient areas. Whether selenium administration will be of benefit in patients living in selenium-sufficient areas and whether patients with more severe GO will also benefit from selenium supplementation associated with immunosuppressive therapy remain to be established.

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Intravenous steroids for Graves' orbitopathy (GO)

MEDICAL MANAGEMENT OF GO is largely unsatisfactory, owing to the lack of drugs acting on GO pathogenic mechanisms. Glucocorticoids (GCs) remain the first-line treatment for moderate-to-severe and active GO, based on their genomic and non-genomic actions, leading to anti-inflammatory and immunosuppressive effects. While oral GCs are effective, the intravenous (iv) route is associated with better outcomes and tolerability. ivGC treatment regimens are extremely heterogeneous (Marcocci et al., EJE 2012), but a popular regimen is based on 12 weekly infusions with a cumulative dose of methylprednisolone (MP) of 4.5 grams (Kahaly et al., JCEM 2005). Recently, EUGOGO completed a multicenter, randomized clinical trial of 159 patients randomly assigned to three different cumulative MP doses (about 2.25 grams, 5 grams and 7.5 grams) (Bartalena & EUGOGO, unpublished). The results of this study showed that the highest dose provided a more favorable overall ophthalmic outcome, compared to the intermediate and the lowest doses. Differences were, however, modest and mainly confined to the improvement in ocular motility. Both the high and the intermediate doses caused a similar decrease in the Clinical Activity Score. The highest dose was associated with a slightly greater toxicity. Major adverse events were also observed using the lowest dose, underscoring that this treatment requires a careful selection of patients and a strict follow-up to be performed in specialized centres. The results of this study may suggest that the cumulative dose of ivGC be tailored to the patient, reserving the highest dose to patients with most severe forms of GO.

Abstracts

MANAGEMENT OF GRAVES' ORBITOPATHY

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Non-steroid immunosuppressants

B-CELL CONTRIBUTIONS TO human autoimmune disease have recently been emphasized due to the therapeutic benefit of B-cell depleting therapies. B cells are involved in the production of autoantibodies, but by also CD4+ T-cell activation and control of T-cell function and inflammation, through cytokine production. Although autoantibodies alone may not initiate autoimmune disease, their relationship with the disease course suggests that they are central to the mechanisms of disease pathogenesis. In addition to antibody production, B cells are important antigen presenting cells. Rituximab (RTX) has been used off-label in various autoimmune disorders and effectively depletes mature and memory CD20+ B cells, but not long-lived plasma cells. This has provided the rationale of its use in GD, since blockade of pathogenic autoantibody generation might bring about Graves' hyperthyroidism remission and in active GO. Although caution is suggested before proposing RTX as a novel therapeutic tool in this disease, data collected show that RTX does significantly affect the inflammatory activity and severity of GO. Recently, we have reported that low dose of RTX (100 mg) caused effective peripheral B cell depletion and induced long term remission of GO, without further treatment. The amelioration of GO was similar to what has been reported with much larger doses of RTX. This study is potentially interesting also from the point of view of the safety concerns in using higher doses of a potent immunosuppressive agent like RTX. We envisage that the optimal strategy for controlling the progression of a disease like GO would be to pursue B-cell depletion shortly after diagnosis and not as an additional therapeutic option when standard immunosuppression has failed.

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Orbital decompression surgery

IS THERE AN ideal timing for orbital decompression?

What are different approaches?

What results can be reached by addressing what bony structure of the removal of fat tissue?

Do results differ depending on disease severity?

The presentations aim at giving a comprehensive overview over techniques, effectiveness and typical complications as well as perioperative management.

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Eye Muscle / Lid surgery

GRAVES' ORBITOPATHY (GO) is an autoimmune disease characterized by inflammation, oedema and infiltration of the extraocular muscle and of the orbital connective/adipose tissue with mononuclear inflammatory cells, followed by deposition of glycosaminoglycans and fibrosis(1). Diplopia is a common and disturbing symptom in patients affected by moderate and severe forms of orbitopathy, which significantly affect patients' quality of life. It is caused by fibrosis of the extraocular muscles and consequent restrictive strabismus. Frequently worsening or new onset diplopia are observed after decompressive surgery because of imbalanced dislocation of extraocular muscles. Surgical correction of diplopia consist of lengthening or shortening procedures on extraocular muscles that are adopted in the inactive phase of the disease and in any case after orbital decompression surgery. Another common sign of GO is eyelid retraction caused mainly by fibrosis of eyelid retractors (superior eyelid retraction) or by proptosis (inferior eyelid retraction). Aesthetic and functional implication are associated with eyelid retraction. Correction of this sign of GO consist of elongation of eyelid retractors and is the final step in the surgical rehabilitative path of GO patients because it is mandatory to deal with decompressive and strabismus surgery first.

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Mainz

Capitol of the Rhineland Palatinate

Nestling at the confluence of the Rhine and Main rivers, Mainz has many faces.

Known to the Romans as Moguntia during their many years of occupation and as Mayence during its years under Napoleon, Mainz is a modern bustling university town with its own unique history and atmosphere.



European Thyroid Association

aiming to *promote knowledge* in the thyroid field (fundamental and clinical)
and *improve knowledge* of the thyroid gland and its diseases



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or scan the QR code

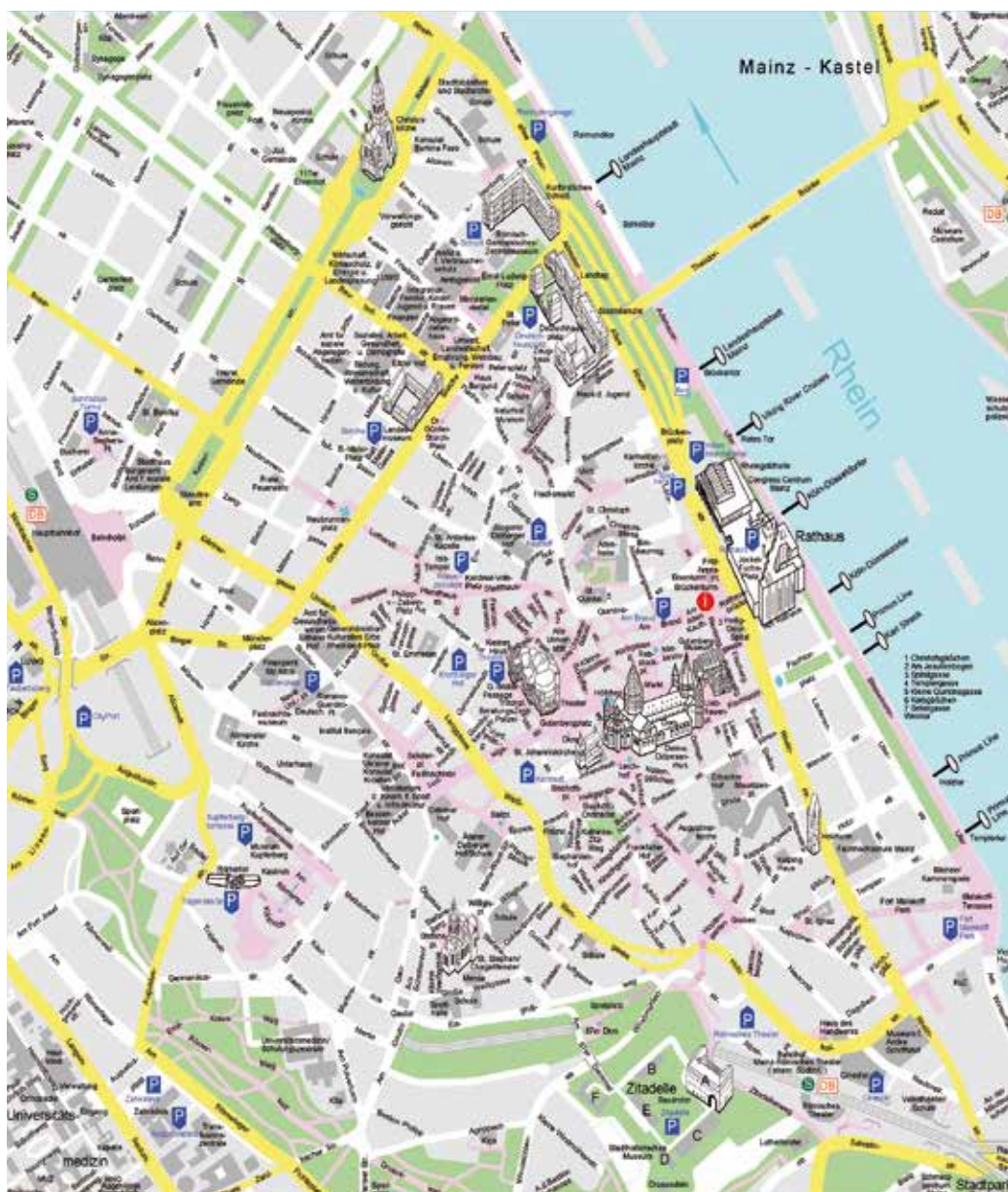
If you are in
thyroidology,
you need to be
in the ETA!



EUGOGO

European Group of Graves' Orbitopathy

Contributing towards the education,
teaching and training of health
professionals involved in the care
of patients with Graves'
Orbitopathy and improving patient
management through collaborative
scientific basic and clinical
research.



Mainz inner city