YEAR REPORT 2007

DEPARTMENT OF ENDOCRINOLOGY

INTERNAL MEDICINE

University Medical Center Groningen

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Content

1. Personnel

The members of the Department of Endocrinology and Metabolism are responsible for providing care to a large and heterogeneous group of patients with endocrine and metabolic diseases and for teaching and training students, residents in Internal Medicine, fellows training to become an endocrinologist, as well as scientific research in these fields.

In this year report we will summarize our activities during the year 2007. After its success last year, this is the second year that our year report appears in English. Reasons for this are our increasing international contacts and collaborations.

In 2007 the following persons were members of our department:

Mrs. N. Alma - Bierma (Natasja)	secretary
Dr. A.P. van Beek (André)	internist-endocrinologist
Dr. G. van den Berg (Gerrit)	internist-endocrinologist
Mrs. B.T. de Boer (Berber)	diabetes nurse specialist
Dr. R.P.F. Dullaart (Robin)	internist-endocrinologist
Mrs. W. van El, MA (Winnie)	nurse practitioner
Mrs. B. Fokkens (Baukje)	data entry assistant
Mrs. M.A. Groeneveld (Mariska)	physicians' assistant
Mrs. B.G. Haandrikman (Bettine)	medical analyst
Mrs. I. Hoekstra (Immie)	diabetes nurse
Mrs. A.N.A. van der Horst - Schrivers (Anouk)	internist-endocrinologist
Mrs. C. Janson (Carla)	diabetes nurse
Mrs. A.B. Jongbloed (Alied)	diabetes nurse
Dr. J.C. Keers (Joost)	psychologist
Dr. M.N. Kerstens (Michiel)	internist-endocrinologist
Mrs. dr. M.M. van der Klauw (Melanie)	internist-endocrinologist
Mrs. G. Kreugel, MSC (Gillian)	nursing consultant
Mrs. dr. T.P. Links (Thera)	internist-endocrinologist
Mrs. S.H. Meeuwisse - Pasterkamp (Susanne)	internist-endocrinologist in training
Mrs. C. Neperus (Carolien)	secretary
Dr. F. Perton (Frank)	laboratory analyst
Mrs. I.E. Pop (Inge)	physicians' assistant
Dr. W.J. Sluiter (Wim)	biochemist, statistician
Mrs. L.G.J. Smit (Linda)	diabetes nurse specialist
Mrs. Y.T.M. Snelders - van den Berg (Yvonne)	diabetes nurse specialist
Drs. F.A.J. Verburg (Erik Jan)	internist-endocrinologist in training
Mrs. R. Visser (Rosalie)	researcher
Prof. dr. B.H.R. Wolffenbuttel (Bruce)	internist-endocrinologist
Mrs. R. Zuur (Roelie)	diabetes nurse specialist

2. Developments in 2007

In 2007 there were several developments within our department.

UMCG organisation
The discussions within the UMCG have lead to a new organisational structure, effective January 1st, 2007. The Department of Endocrinology has found its place within the organisational cluster of Internal Medicine and related departments, as part of Sector A. This sector comprises patient care, research and teaching around the theme of Vascular and Chronic diseases.

Patient Care
The Health Insurance Companies recognized the Diabetes Rehabilitation program as an outstanding and innovative program, and agreed to partially reimburse this program.

Staff members
Mrs. Anouk van der Horst finished her training in Endocrinology, and was appointed at a permanent staff position. She finished her PhD thesis, which she will defend in March 2008.
Erik Jan Verburg started his training in Endocrinology.

PhD thesis
Members of the department were involved in several PhD theses, which were defended in 2007. In November mrs. T.T.H. Phan defended her thesis titled 'Imaging strategy in differentiated thyroid cancer (DTC)'. This thesis focussed on clinical dilemmas, which the clinician faces in the management of patients with DTC with a specific emphasis on the role of current and new diagnostic imaging and immunoassay methods (for more information see page 20).

LifeLines Cohort Study
The LifeLines Cohort Study finished the pilot phase of the project in the fall of 2007. The Medical Ethical Review Committee of the UMCG approved the final protocol for the main phase of the study, in which 130,000 adult subjects will be included during the upcoming four years. In addition to the pilot location in the city of Sneek, Friesland, one other location has opened its doors, in the city of Drachten. It is expected that in 2008 at least 5-6 new locations for screening LifeLines participants will open, an the number of research staff will increase to at least 30. The LifeLines position paper, in which the theoretical background of the project and details of its data collection have been explained, was published online in October 2007, after it was accepted for publication in the European Journal of Epidemiology.

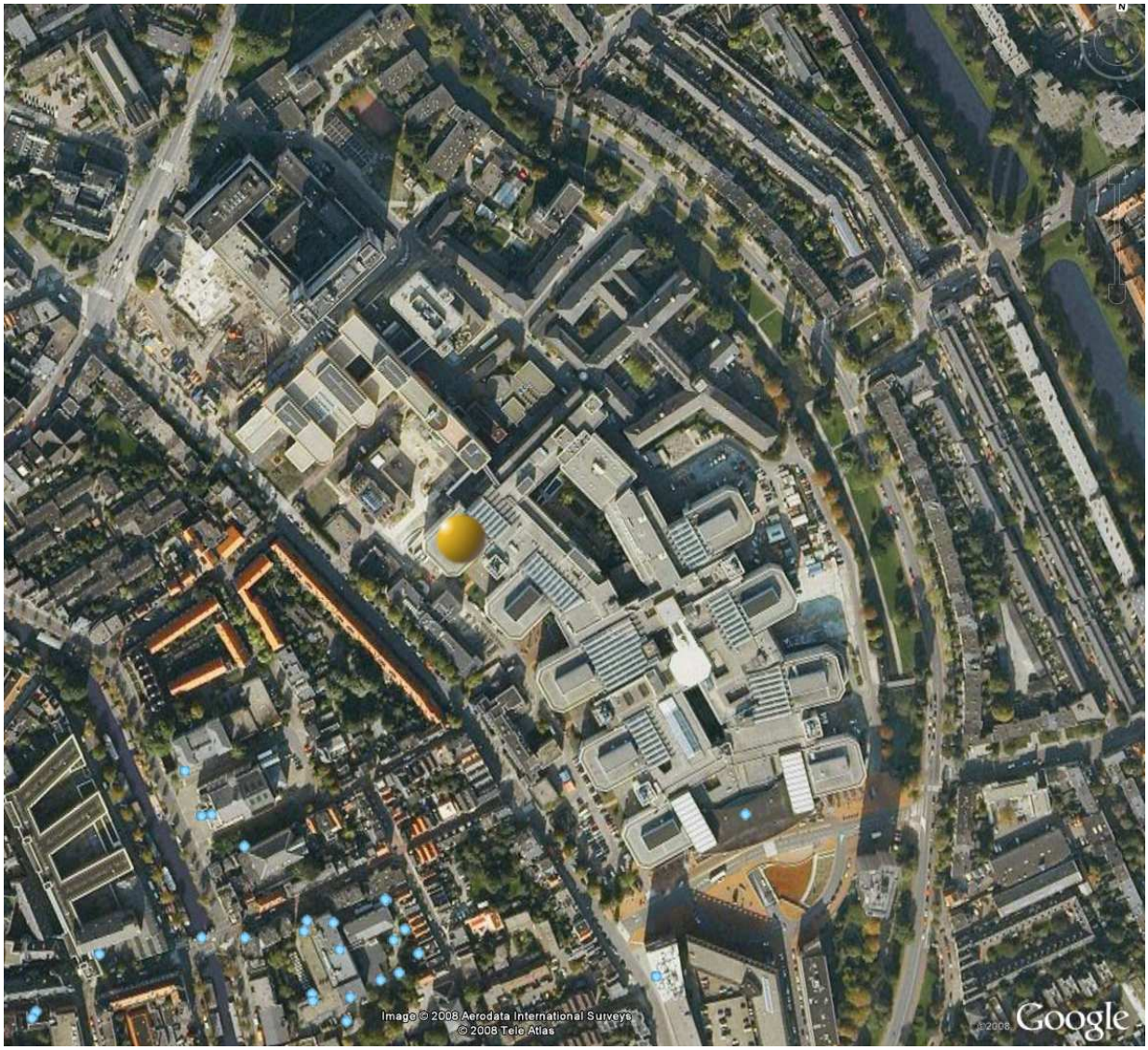

Figure 1. Google Earth picture of the UMCG. The yellow dot in the middle is the E-building. On the ground floor of this building, you can find the outpatient clinic of the Dept of Endocrinology; on the 4th floor there is the clinic ward, including the special facilities for high-dose radioactive iodine treatment

3. Health care / patient activities

Clinic Ward E4

The number of patients admitted to our ward E4 was 260, which implies a small decrease compared to 2006. This probably also is related to the fact that we share the same beds with the Acute Care ward of the Department of Internal Medicine, and a strong demand for admissions for Internal Medicine reduces the possibilities for our department. The total number of beds for admission of patients with internal medicine disease is not sufficient, and especially during the fall and winter months many of our patients have to be admitted on other departments, like Neurology, Obstetrics and Surgery. This great pressure on available hospital beds is also mirrored by the fact that after pituitary surgery, most patients now remain in the Neurosurgery ward, whereas in the past they were transferred to the Endocrinology department at the 2nd or 3rd day after surgery.
Those 260 patients stayed in the ward for a total of 1400 days, implicating a stable average stay of 5.4 days. This short admission time is the result of efficient and careful planning of hospital discharge and outpatient follow-up. Nevertheless, a significant number of patients needed a hospital stay of more than 30 days. Mostly, these were patients with severe diabetic foot problems.

Outpatient clinic

The number of outpatient clinic visit has slightly increased in 2007. The number of patients seen for the first time has increased by 17%. By the institution of ‘dedicated’ clinics for newly referred patients we were able to reduce the average waiting time for patients to less than two weeks.
Patients are referred by General Practitioners (G.P.'s), or by medical specialists within the UMCG, as well as colleagues from surrounding hospitals. All referrals are made in writing, and judged on a daily basis, so that we can give priority to those patients with the highest urgency. If needed, patients can and will be seen the same day, for instance for patients with newly-diagnosed type 1 diabetes, who have to start insulin therapy instantaneously. Also, patients who are suspected to have an endocrine tumour, or who have a thyroid nodule will be seen within a period of 1-2 weeks, in order to start their diagnostic work-up and treatment as soon as possible.
Our access time could be improved further when all patients would keep their appointment. Too frequently we observe that patients do not show up for their initial or follow-up visit, and this time lost puts other patients later in the waiting list. For this reason we have started to make telephone calls to all patients who do not show up for their appointment, in order to reduce future 'no-shows'.

Table 1. Patient care activities of the department of Endocrinology

Year	Clinic admissions	Outpatient clinic visits	First consultations outpatient-clinic
2000	326	8796	494
2001	278	8198	512
2002	281	8360	570
2003	330	8815	642
2004	315	9720	761
2005	322	10148	705
2006	283	9631	812
2007	260	9761	958

Outpatient care for people with diabetes mellitus is carried out together with our colleagues from the Department of General Internal Medicine. Dr. M.N. Kerstens is the coordinator for diabetes care. Since

the beginning of September 2006, diabetes care is offered based on a 'One Stop' principle. This means that all care providers can be found within the same location, i.e. the first floor of the A-wing of the Triade building (entrance 23). Here a patient can be seen by the internist, diabetes nurse specialist, dietician, podotherapist. There is a facility for making retinal photographs, and for drawing blood for laboratory determinations. We are very happy that in the same clinic an Information Post of the Dutch Diabetes Patient Association (Diabetesvereniging Nederland) can be found.

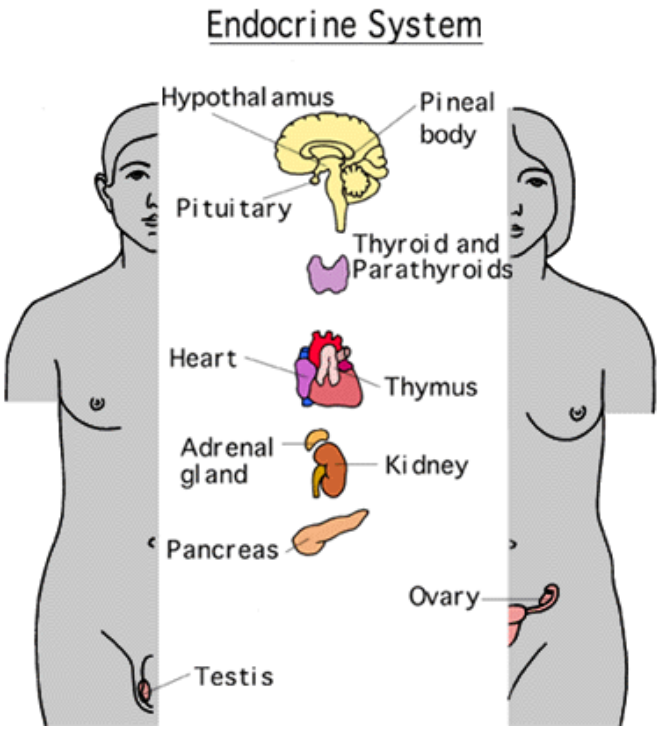

Figure 2. The Endocrine System

Topreferent care

As there are many endocrine glands and metabolic diseases, an endocrinologist takes care of a group of patients with a large variation of diseases. Several groups of patients are referred to our department because of specific disease problems. These include:

* thyroid carcinoma
* thyroid dysfunction and goitre
* pituitary tumours
* adrenal diseases (tumours, phaeochromocytoma, disturbances steroid synthesis)
* endocrine tumour syndromes (MEN1, MEN2, VHL, Neurofibromatosis etc)
* pregnancy in diabetes
* diabetic complications, including diabetic foot problems
* insulin pump therapy.

There is an extensive collaboration with the endocrinologists working in the hospitals in the four northern provinces (Friesland, Groningen, Drenthe, Overijssel) of The Netherlands. Some of our patients come from distant parts of our country, and may travel up to 300 km for their appointment at the outpatient clinic!

Multidisciplinary patient care

We have multidisciplinary groups of physicians for the care of the above-mentioned patients suffering from thyroid carcinoma, pituitary diseases, diabetic foot problems and Turner's syndrome. These teams get together weekly or sometimes monthly to discuss patient problems and the multidisciplinary treatment of complex patients. For diabetic foot patients there is a combined outpatient clinic once monthly on Wednesday afternoon, in addition to the separate clinics held at the Dept of Orthopaedics, the Dept of (Vascular) Surgery, and the Diabetes Centre. For patients with pituitary problems, there is a weekly multidisciplinary outpatient clinic on Friday afternoon. For patients with metabolic diseases, like inborn errors of metabolism or mitochondrial diseases, there is a dedicated 'metabolic' clinic on Monday morning. Adult patients with Turner's syndrome are periodically checked at the combined outpatient clinic, which is staffed by an endocrinologist and a gynaecologist.
Dr. Links is responsible for the Multidisciplinary Thyroid Team, dr. van den Berg and dr. van der Klauw for the Pituitary Outpatient Clinic, prof. Wolffenbuttel for the Diabetic Foot Collaboration and dr. Kerstens and dr. van Beek for the multidisciplinary Turner Team.
Also there is intensive interaction with the Department of Oncology related to the treatment of patients with other endocrine tumours.

All these activities are not possible without the assistance of a dedicated staff of administrative personnel. These include Monique Gelms, Hinny Sikkema, Anita Scholtens, Joke Smink, Ada Schaaf, Berber Ellens, Wiesje Suurhoff, Nihaila Sillé, Fenna Diepenbroek-Beulakker, and also all the ladies responsible for the letters to G.P.'s regarding our patients.

4a. Diabetes mellitus / Diabetes Care

Integrated diabetes care

The UMCG supports the concepts of the Dutch Diabetes Federation, which are summarized in a specific Standard of Care for the Treatment of Diabetes. Integrated care means for us:
1. Optimal medical treatment and care.
2. Education and learning to master skills and knowledge, needed for optimal self-management.
3. The process in which the person with diabetes experiences and improves his position in society.

Our care is based on International Guidelines, summarized in the Dutch NDF/CBO guidelines. These guidelines preferably are based on evidence coming from clinical practice and controlled clinical trials. In case insufficient evidence exists, we have adopted our diagnostic and treatment protocols on the basis of the vast experience of our staff. The medical responsibility resides with the physician, but our Diabetes Management Team includes diabetes nurse specialists, dieticians, a podotherapist, a psychologist, and a social health worker. We offer integrated diabetes care on two locations of the UMCG. Our regular outpatient clinic can be found in the Triade building (Entrance 23) at the Hanzeplein, in the middle of the city of Groningen. The other location harbours the Diabetes Rehabilitation program, and is situated within the Centre for Rehabilitation Beatrixoord. Together these locations form the University Diabetes Centre, the only Diabetes Knowledge and Expertise Centre in the northern part of The Netherlands.

The diabetes nursing staff consists of:
mrs. Nella A. Groenewegen, head nurse; mrs. Berber T. de Boer, Carla Janson, Immie Hoekstra, Alied Jongbloed, Linda Smit and Roelie Zuur, diabetes nurse specialists; Winnie van El, nurse practitioner; Gillian Kreugel, Msc, nursing consultant. Yvonne Snelders supported the diabetes care in the Academic General Practice.

There are extensive collaborations between the medical staff of the Endocrinology Department and care providers within the UMCG and outside the UMCG, including regional hospitals, medical specialists, and G.P.'s in the province of Groningen.

Multidisciplinary treatment programs are available for several groups of patients:

1. Patients with limited or no secondary complications

For patients in this category, emphasis is placed on diabetes education, learning how to handle diabetes and how to prevent the development of complications. Patients are seen three times per year by the diabetes nurse specialist, and once or twice by the endocrinologist

2. Patients with long term complications

The care for this patient group is coordinated by the internist-endocrinologist. They follow these patients with a frequency of at least three to four times a year, and all patients will visit the diabetes nurse specialist at least once a year, with support regarding all aspects of care, including intensified diabetes education.

3. Specific patient groups

For specific groups of patients we have an individual and dedicated counselling program.

a. Teenagers & adolescents

Yearly, teenagers of 15 and 16 years old are referred for continuation of their care from the out-patient clinic for children to the out-patient clinic for adults. To prevent the teenagers being unprepared in the new situation, an information afternoon is organised by a children's diabetes nurse specialist and a diabetes nurse specialist of the out-patient clinic for adults.

During this afternoon, the diabetes nurse specialist and teenagers are introduced to each other, extensive information is given and questions are answered. The information contained what the teenagers can expect in the new situation and what to do with questions or in case of emergencies. The afternoon ends with a tour around the clinic for outpatients. Most teenagers take their parents along. All teenagers get a combined appointment with the internist-endocrinologist and the diabetes nurse.

b. Pregnancy

It is widely known that optimal glycaemic control is necessary to minimise the development of congenital abnormalities or perinatal complications in the newborn babies. This takes a lot of effort. Patients with a wish to become pregnant are offered an intensified outpatient program supported by low-threshold phone, fax or e-mail contact to obtain normal HbA1c levels (HbA1c ≤ 6.5% on at least two occasions) before pregnancy. Folic acid supplementation is started at least two to three months before becoming pregnant.

The patients who have become pregnant and patients with gestational diabetes are treated, in a multidisciplinary cooperation, by an internist-endocrinologist, diabetes specialist nurse, gynaecologist, dietician and ophthalmologist. Treatment and follow-up protocols are available, and they have been standardized according to local and (inter)national guidelines.

Figure 3. The Netherlands consists of 12 provinces. Most patients we see come from the northern provinces, but some of them may even come from Limburg or Zeeland (300 km travel distance!)

4. Newly referred patients

There is an extensive program for patients who are newly referred by their G.P. or by another medical specialist. In this program, sometimes referred to as a 'diabetes carrousel', both the endocrinologist, diabetes nurse specialist and dietician participate. There is considerable attention for improvement of the skills and knowledge, which a person with diabetes needs for optimal self-management. If needed, other specialists like psychologist or podotherapist can be consulted.

The patients we care for in our Diabetes Centre come from all around The Netherlands, even from the southern provinces of Limburg and Brabant. However, the majority of them live in one of the four

(or five if you include Flevoland) northern provinces: Groningen, Friesland, Drenthe or Overijssel. Their treatment is based on formalized treatment protocols, which include the majority of advices and guidelines issued by the Dutch Diabetes Federation. Our clinical care would be very much facilitated when we would have the availability of an Electronic Patient File.

5. Diabetes Rehabilitation

In the Rehabilitation Centre Beatrixoord, we provide an intensive multidisciplinary diabetes education and rehabilitation program. Eligible for this program are patients with complex diabetes-related problems, as well as problems related to self-management and acceptance of the disease. Half of the patients come from the outpatient clinic of our own hospital, whereas the other 50% are referrals from internists in the surrounding hospitals in the north of The Netherlands. Some patients even come from provinces like Zeeland and Limburg (figure 3).

The program comprises several days of outpatient education in small-sized groups, with focus on practical aspects of diabetes acceptance, self-management and rehabilitation. Patients not only learn to define the problems they have with diabetes management, but also learn to attack them. For instance, the presence of 25 m swimming pool and a dedicated training and gymnastics facility will ensure that all patients can experience effects of exercise and training, and by doing this learn how to adjust their insulin dose and cope with varying blood glucose levels.
Long term results of the program are excellent, as described by our psychologist Joost Keers, who defended his thesis on this topic in 2005. Permanent improvement of diabetes control as well as health-related quality of life, but above all improved self-management skills have been the most important achievements. For this reason, the Association of Rehabilitation Physicians and the Dutch Diabetes Federation have rated this program 'a high quality and indispensable asset'. After long negotiations with governmental bodies, we received in 2007 official approval of this program, and subsequently a considerable coverage of the program by health care insurance companies.

The following people form the team responsible for the Diabetes Rehabilitation Program:
Mrs. Rita Wesselius, team coordinator; Mrs. Linda Faber, mrs. Ingrid Stoelinga, mrs. Madelein Schotman, diabetes nurse specialists; Mrs. Marianne van Dijk, dietician; Mrs. Brigitta Joosen, en Mrs. Renske Bouman, physiotherapists; Mr. Guus van Bochove, movement scientist; Mrs. Heike Mesch, psychologist; Mrs. Tilly Söder and mrs Janet Waijer, social welfare; Mrs. Franka Waterschoot, ergotherapist.
They are supported by Mrs. Janine Kramer and mrs. Elsa Pieterman-Slagter, secretaries; Mrs. Hennie Meijer, assistant. In addition mrs. Brenda Hermse has the function of coordinating all planning related to outpatient care.

The medical aspects of Diabetes Rehabilitation as well as consultations for General Internal Medicine problems are performed by the medical staff of the Department of Endocrinology. Diabetes care for patients admitted to other wards within the Rehabilitation Centre is supported by the endocrinologist and the diabetes nurse specialists.

6. Obesity

An obesity rehabilitation program, which started in 2005, is available for patients with diabetes or metabolic syndrome and complicated obesity. The program aims to change lifestyle patterns by means of an intensive long-term program. Approximately 20 patients have been treated in this year. An internist-endocrinologist, diabetes nurse, dietician, psychologist, physiotherapist are involved in this multidisciplinary program. Experiences in this program are also used for the future development of an obesity treatment centre.

4b. General Endocrinology

New developments

Turner's syndrome is a genetic anomaly that results from complete or partial absence of one X chromosome and is the most frequently occurring chromosomal abnormality in females. Adults with Turner's syndrome have an increased risk of developing multiple co-morbidities such as cardiovascular diseases, hypothyroidism, diabetes mellitus, osteoporosis, gastrointestinal disorders, hearing loss and the attendant problems of estrogen deficiency and infertility. Therefore, a multidisciplinary approach is needed for early detection and adequate treatment of the various problems that may affect adult women with this syndrome.
In September 2006, a specialized outpatient clinic for patients with Turner's syndrome has been started by the departments of Endocrinology and Gynaecology. In agreement with clinical guidelines that have been issued in recent years, patients visit this facility once a year and are examined at each visit by both the endocrinologist and the gynaecologist. The team is also staffed by social workers experienced with the specific psychosocial problems that Turner patients may be facing. In addition, patients are referred to the Cardiologist and Ear, Nose & Throat specialist for periodic evaluation once every 3 years, or more frequently if indicated. At present, the Turner outpatient-clinic is open to other patients from the northern region.

The Department of Endocrinology has a track record for the diagnostics and treatment of (neuro)endocrine tumours, in close collaboration with the Departments of Medical Oncology, Nuclear Medicine and Molecular Imaging, Genetics, Radiology, Pathology, Gastroenterology, Surgical Oncology and Clinical Chemistry, As a consequence, the UMCG is a referral centre for non-hereditary as well as hereditary neuroendocrine tumours (MEN1, MEN2, VHL).
Several innovative PET methods have been used such as 18F-DOPA and 11C-5-HTP for imaging of medullary thyroid cancer, phaeochromocytoma, carcinoids and islet cells tumours and 124I and 11C-methionin for papillary and follicular thyroid cancer. Ongoing research supports these developments in better staging of disease and applying new therapies. The Endocrinology department has participated in several national and international clinical trials with new targeted drugs like imatinib and vandetanib in patients with medullary thyroid cancer, and new trials are coming.
Next year we will start a national project for screening of pancreatic neuroendocrine tumours in Multiple Endocrine Neoplasia type 1 and Von Hippel-Lindau disease employing imaging with endoscopic ultrasound and 11C-5-HTP PET. This project is supported by the Dutch Cancer Society.

For the diagnostics of catecholamine excess a rapid sensitive and highly selective automated method for plasma free metanephrine and normetanephrine is available on the Department of Clinical Chemistry (Dr. I.P. Kema). This quick method enables the routine quantification of catecholamines and their metabolites for daily patient care, but also creates possibilities to perform more in-depth analyses of the biochemical activities of neuroendocrine tumours.

Finally, selective adrenal venous sampling (AVS) is currently the gold standard technique for differentiation between the main subtypes of primary hyperaldosteronism. Since 2007, this important diagnostic facility is available in the UMCG.

5. Teaching

The fields of Endocrinology, Diabetes and Metabolism are important parts of the medical curriculum. Hormones play a pivotal role in the maintenance of all biochemical processes in the human body. Endocrine diseases can have several consequences for the functioning of organs like the eyes, the cardiovascular system, kidneys, skeleton and the musculoskeletal system. Therefore, our department participates in all teaching activities for students in the Bachelors phase of the School for Medical Sciences, the school for Dentistry and the Life Sciences cluster, and clinical training for the students in the Masters phase. The lectures are both patient demonstrations as well as theoretical lectures on endocrine physiology and pathology, including diabetes mellitus, thyroid diseases, Addison's and Cushing's disease, and pituitary development and pathophysiology.

In addition, staff members act as coach in the medical professionalization program (Year 2) as well as mentor or tutor for students in the first clinical year (Year 4), when students follow the introduction period in the clinic. Staff members are also involved in educational research projects for individual students from the UMCG but also from abroad..

Every year, the department organises a two-week period specifically devoted to Endocrine Pathology. Students discuss major endocrine diseases based on actual patient cases, and follow patients in the outpatient clinic. Staff support also has been provided to the yearly ISCOM, International Student Congress of Medical Sciences by chairing oral and poster sessions

Staff members also participate in the teaching programs of surgeons, urologists, oncologists, obstetricians and nurse practitioners, as well as specialised programs in the training of nurses.

6. Postgraduate education

The members of the department of Endocrinology actively participate in all kinds of postgraduate education activities for general practitioners and medical specialists, like the scientific meetings of the Dutch Association for Endocrinology (NVE) and the Dutch Association for Diabetes Research (NVDO). .

On May 27, the department organised a mini-symposium on the new guidelines for thyroid cancer. Over 70 participants extensively discussed these new guidelines, and their implementation in clinical practice.

On September 17, prof. Wolffenbuttel participated as a chairperson and speaker in a satellite symposium during the Annual meeting of the European Association for the Study of Diabetes. Topic of the symposium, which was organized by Eli Lilly, was 'Optimal glycaemic control in diabetes'.

On October 2, the department participated in the yearly Endocrinology Teaching Evening which is specially organised for General Practitioners. Topics of the evening were Adverse metabolic effects of corticosteroids, management of diabetes during corticosteroid therapy, the incidentaloma of the adrenal gland, and a patient case discussion featuring a patient with hypertension caused by phaeochromocytoma. The Powerpoint presentations of this course can be found on the department's website.

On October 4, dr. G. van den Berg was co-organizer of the yearly meeting on Pituitary Diseases, which is held in the Grand Hotel Karel V, Utrecht.

There is intensive collaboration with the company Pronounce, editor of several diabetes-related journals. One of these activities is the Netherlands Journal of Diabetology, a peer-reviewed journal, which aims to improve knowledge on diabetes mellitus and its treatment, by special attention for clinical and scientific developments. The journal publishes original articles, case reports, reviews, book reviews and brief summaries of important international papers. For more information see www.diabetes.nl/ntd.htm.

Another form of collaboration with Pronounce and the Postgraduate Education Institute (Wenckebach Institute) of the UMCG resulted in an e-learning program for nurses. By use of this program, nurses working in hospitals but also pharmacy assistants and other health care providers can learn the latest information on diabetes mellitus, its pathophysiology and treatment, with this diabetes training program, according to the blended learning possibilities. This approach uses an electronic education program (Digidiabetes) followed by a practical training, given by a diabetes nurse specialist. The practical training, of three hours, was given twice in 2007.
New e-learning modules covering aspects like dyslipidaemia and hypertension are in preparation.

7. Training for Internal Medicine and Endocrinology

The Department of Endocrinology participates in the training program MD's becoming internists, and offers these trainees a 4 months program which consists of outpatient clinics, clinical care for hospitalised patients and in-clinic consultations for patients with endocrine diseases and diabetes mellitus.

The Department of Endocrinology is one of the 8 academic training centres for clinical endocrinology in the Netherlands (AERA: Aandachtsgebied Endocrinologie, Nederlandse Internisten Vereeniging), and is licensed as a European training centre as well (UEMS). This training to become board-certified Endocrinologist in The Netherlands consists of a 18 to 24 months' program, during which the endocrinology fellow is trained in out-patient, clinical and consultative care of patients with all major endocrinological diseases (thyroid disorders including thyroid carcinoma, adrenal diseases including congenital adrenal hyperplasia, pituitary diseases, gonadal insufficiency, secondary hypertension including phaeochromocytoma, disorders in calcium homeostasis and osteoporosis), dyslipidaemias and premature atherosclerosis, diabetes mellitus, including insulin pump treatment and pregnancies in patients with diabetes and genetic metabolic diseases. This endocrinology training includes clinical stays in the Department of Paediatric Endocrinology, Gynaecological Endocrinology and Assisted Fertility, Nuclear Medicine and Molecular Imaging, and the Laboratory Centre. On a regular basis, multidisciplinary meetings are organized with respect to care for patients with endocrine diseases and metabolic disorders, pituitary disorders, thyroid carcinoma and pathology.

At present, dr. R.P.F. Dullaart coordinates the Endocrinology teaching program. All staff members contribute to the training program. In 2007 two MD's, mrs. Susanne Meeuwisse-Pasterkamp and mr. Erik-Jan Verburg followed the Endocrinology training program.

In April 2007 two regional study days incorporated in the Internal Medicine training program have been organized by prof. Wolffenbuttel in collaboration with dr. Jaap Huisman (internist-endocrinolgist, Enschede) and dr. Anton Franken (internist-endocrinologist, Zwolle). The topic of this day was 'General Endocrinology', with a focus on thyroid and adrenal diseases, and osteoporosis.

8. Scientific research

The research of the Department of Endocrinology is part of the Kidney Centre and the Cardiovascular Centre of the Research Institute GUIDE (Groningen University Institute for Drug Exploration). The mission of GUIDE is to promote and execute innovative drug development research which is based on a thorough and detailed understanding of the pathophysiology of diseases, and the development of new (ways of administration of) drugs. New techniques like genomics, proteomics and bioinformatics play a major role in this development.

Research programs

Program I: Endocrine tumours and dysfunction

1. Thyroid cancer: diagnosis and treatment

topic: *Use of rhTSH in the follow-up of patients with differentiated thyroid cancer*
researcher: mrs. A.C.M. Persoon
supervisor: dr. T.P. Links, prof. dr. P.L. Jager
promotor: prof. dr. B.H.R. Wolffenbuttel
thesis: Spring 2009

topic: *Imaging of differentiated thyroid cancer*
researcher: mrs. T.T.H. Phan
supervisor: dr. T.P. Links
promotor: prof. dr. R. Dierckx, prof. dr. B.H.R. Wolffenbuttel, prof. dr. P.L. Jager (Canada)
thesis: November 26, 2007

topic: *Hürthle cell carcinoma and RET/PTC rearrangements*
researcher: mrs. M. de Vries
supervisor: prof. dr. R.M.W. Hofstra, dr. T.P. Links

topic: *Medullary thyroid cancer: distinction and treatment of progressive disease*
researcher : H.H.G. Verbeek
supervisor : dr. T.P. Links, prof. dr. R.M..W. Hofstra, prof. dr. J.T.M. Plukker

2. Pituitary tumors

topic: *Radiotherapy of pituitary tumours*
researcher: A.C.M. van den Bergh, radiotherapist
promotor: prof. dr. J.A. Langendijk, prof. dr. B.H.R. Wolffenbuttel
co-promotor: dr. R.P.F. Dullaart
thesis: September 3, 2008

topic: *Quality of life after treatment for pituitary adenoma and Cushing's disease*
researcher: drs. M. Sattler (radiotherapist)
supervisor: dr. A.P. van Beek
promotor: prof. dr. B.H.R. Wolffenbuttel, prof. dr. J.A. Langendijk

3. Neuro-endocrine tumours

topic: *Carcinoid tumours*
researcher: A.N.A. van der Horst - Schrivers
collaborator: dr. I.P. Kema (Clinical Chemistry), dr. A.H.M. Wijmenga, dr. T.P. Links
promotor: prof. dr. E.G.E. de Vries, prof. dr. P.H.B. Willemse
thesis: March 2008

topic: *Imaging in neuroendocrine tumours*
researcher : H.B. Fiebrich
supervisor: dr. A.H. Brouwers, dr. T.P.Links
promotor: prof. dr. E.G.E. de Vries

topic: *Optimal treatment of phaeochromocytoma: a multicentre randomized trial*
Research proposal for ZonMW

Program II: Diabetes / Lipids / Vascular

1. Pathophysiology, genetics and treatment of diabetes and diabetes-related complications

a. The role of endogenous and exogenous AGEs in the development of diabetic complications
b. Genomics and proteomics of diabetic complications
c. Etiology and treatment of type 1 diabetes
d. Genetic predisposition for type 2 diabetes
e. Gene-environment interaction in the development of type 2 diabetes

This research programs are carried out by the Department of Endocrinology (dr. R.P.F. Dullaart, dr. T.P. Links, prof. dr. B.H.R. Wolffenbuttel) in close collaboration with the Dept's of General Internal Medicine and Nephrology:
Dr. S.J.L. Bakker, dr. A.J. Smit, dr. J.C. ter Maaten, prof. dr. R.O.B. Gans.
ir. C.J.A.L. Mentink, Maastricht, successfully defended his thesis in this program in 2006.
Mrs. H. Lutgers is expected to defend her thesis in the fall of 2008.
The projects on genetics of type 2 diabetes are part of the research carried out in the LifeLines Cohort Study.

topic: *The role of CETP and HDL metabolism on cardiac risk*
researcher: mrs. S.E. Borggreve
promotor: prof. dr. B.H.R. Wolffenbuttel, prof. dr. P.E. de Jong, prof. dr. J.L. Hillege
co-promotor: dr. R.P.F. Dullaart
thesis: October 8, 2008
support: Dutch Heart Foundation

topic: *Lipid transfer proteins: consequences for cellular cholesterol efflux and cardiovascular risk in diabetes mellitus*
researcher: R. de Vries
promotor: prof. dr. B.H.R. Wolffenbuttel
co-promotor: dr. R.P.F. Dullaart, dr. A. van Tol
thesis: November 2008
support: Diabetes Research Foundation (DFN)

In the latter two projects, there is a close collaboration with dr. A. van Tol, Department of Cell Biology

and Genetics, and mrs. dr. G. Dallinga - Thie, Department of Internal Medicine, both of the Erasmus Medical Centre Rotterdam.

2. Metabolism, obesity and metabolic syndrome

topic: *Thyroid (dys)function, metabolic syndrome and incident cardiovascular disease*
researcher: A. Roos
promotor: prof. dr. B.H.R. Wolffenbuttel
co-promotor: dr. A. Berghout (internist, Rotterdam), dr. S.J.L. Bakker (internist), dr. T.P. Links
thesis: 2009

topic: *Lifestyle modification in obese infertile women: hormonal-metabolic parameters and body-fat distribution*
researcher: mrs. J.G. Dolfing, gynaecologist, W.K.H. Kuchenbecker, gynaecologist
supervisor: dr. A. Hoek, dr. D.H. Schweitzer (internist, Voorburg)
promotor: prof. dr. B.H.R. Wolffenbuttel
thesis: 2009

topic: *The effects of obesity and weight reduction on inflammatory markers and site-specific adipocyte function in prediabetes*
researcher: F.A.J. Verburg
promotor: prof. dr. B.H.R. Wolffenbuttel
co-promotor: dr. A.P. van Beek
thesis: 2010

3. Diabetes psychology and quality of care

topic: *Diabetes education: effects of self-adopted therapy goals and partner behaviour*
researcher: mrs. M. Schokker
supervisor: dr. T.P. Links, dr. J. Bouma, dr. J.C. Keers
promotor: prof. dr. R. Sanderman, prof. dr. B.H.R. Wolffenbuttel
thesis: 2010

topic: *What helps patients to keep their medication plan? Compliance vs self-management.*
researcher: mrs. R. Visser
supervisors: dr. J.C. Keers, dr. P. Denig

topic: *Optimising outpatient diabetes care by integrated treatment and screening for psychosocial problems. (Medical Technology Assessment reseach).*
reseacher: dr. J.C. Keers
supervisors: dr. T.P. Links, dr. W.J. Sluiter
scientific report: 2007

topic: *GIANTT: assessing pharmacotherapeutic care for patients with type 2 diabetes*
researcher: J. Voorham
promotor: prof. dr. F. Haaijer-Ruskamp, prof. dr. B.H.R. Wolffenbuttel
co-promotor: dr. P. Denig
thesis: 2010

topic: *'Diabetes VerjaarDAG': Implementation of yearly counselling by a diabetes nurse specialist*
researcher: mrs. C. Annema
supervisor: G. Kreugel, prof. dr. B.H.R. Wolffenbuttel

topic: *Care improvement for diabetic patients with chronic renal failure (CRF)*
researcher: W. van El
supervisor: dr. C.F.M. Franssen (nephrologist), dr. J.C. Keers, dr. M.N. Kerstens, dr. T.P. Links

topic: *INOBESE, The influence of the needle length on long term glycaemic control in insulin using obese diabetic subjects*
researcher: G. Kreugel
supervisor: prof. dr. B.H.R. Wolffenbuttel

Program III. General endocrinology

1. Osteoporosis

topic: *The use of ultrasound of the calcaneus in predicting bone mineral density in patients with high risk of secondary osteoporosis*
researcher: mrs. A.C. Heijckmann, internist-endocrinologist, Veghel
promotor: prof. dr. A.C. Nieuwenhuijzen Kruseman, prof. dr. P. Geusens (rheumatologist, Univ Hosp Maastricht), prof. dr. B.H.R. Wolffenbuttel
thesis: December 17, 2008

topic: *Prospective study on the effects of cessation of bisphosphonate treatment in patients with primary osteoporosis.*
Research proposal to ZonMW

2. Thyroid

topic: *Amiodarone effects and side effects*
researcher: S. Ahmed
supervisor: dr. T.P. Links
promotor: prof. dr. I.C.van Gelder, prof. dr. D.J. van Veldhuizen

Imaging strategy in differentiated thyroid cancer

Summary of the thesis of mrs. T.T.H. Phan, defended November 2007.
http://irs.ub.rug.nl/ppn/305032321

This thesis focuses on clinical dilemmas, which the clinician faces in the management of patients with DTC with a specific emphasis on the role of current and new diagnostic imaging and immunoassay methods. Chapters 1 and 2 give a short introduction in the diagnostics, therapy and follow-up of patients with DTC, and an overview of current nuclear imaging methods.

In chapter 3 the additional value of *higher-dose (370 MBq) 131I diagnostic scanning* was assessed in patients with a negative low-dose (74 MBq) 131I diagnostic scan, and compared with Tg measurements and post-treatment scan in 158 patients. In only 2.5%, with possibly relevant uptake at the higher-dose diagnostic WBS, treatment would not have been given if the higher-dose diagnostic WBS had not been performed. In 154/158 patients, the high dose diagnostic WBS had no additional value.

Mediastinal uptake of 131I on post-treatment WBS is a frequent problem. Misinterpretation for metastatic tumor tissue can lead to unnecessary additional treatment with 131I or surgical exploration. We proposed in chapter 4 a flow-chart based on our experiences and the literature to assist clinicians dealing with this problem. From our data, mediastinal uptake of 131I was present in approximately 10% of the patients, irrespective of age. Our survey illustrated that serum Tg levels, risk status of the patient, and presence of the thymus on radiological examinations are important clinical parameters in the treatment decision making.

The *performance of bone scan* in comparison with FDG PET in the detection of bone metastases in DTC was evaluated in chapter 5. In eight of 24 (33%) patients with clinical or biochemical evidence of disease, bone metastases were present. In five of eight patients the bone lesions were visible on the bone scan as well as on the FDG PET scan, in three of these eight bone metastases were only identified on bone scans. Our data suggest that bone scan is still valuable in the detection of bone metastases in DTC and therefore can not be replaced by FDG PET.

In patients with elevated Tg, a 'blind' treatment with high dose 131I is applied more often followed by a post-treatment 131I scan which also serves as a diagnostic tool. However, patients without 131I uptake on their post-treatment scans are exposed to high radiation and high TSH levels. Improvement of diagnostic imaging for the detection of recurrent or metastatic disease and a better (anatomical) localization by using an *advanced imaging technique with 124I-PET(/CT)* would allow more selective application of 131I therapy and might avoid unnecessary high dose treatments. In this feasibility study, described in chapter 6, *124I-PET* was superior to low dose diagnostic 131I scans, and adequately predicted findings on subsequent high dose post-treatment 131I scans. In combination with the high resolution and the possibilities to combine with CT, 124I-PET is an important diagnostic tool to improve clinical decision making.

Because of increased protein metabolism and transport in cancer cells radiolabeled amino acids can be applied. In 20 DTC patients with biochemical evidence of recurrent disease the feasibility of *11C-methionine (MET) PET* in comparison to FDG PET was evaluated (chapter 7). In 5, uptake was only observed on the MET PET, confirmed in one by MRI. In six, patients concordant uptake was observed on both PET scans. This the first study which demonstrates that imaging using radiolabeled amino acids is feasible in thyroid cancer.

Finally, we evaluated, as described in chapter 8, 94 of 346 (27%) DTC patients with undetectable Tg at the moment of 131I ablation and compared their outcome to patients with detectable Tg (or TgAb). It was shown that patients with initially negative Tg and TgAb have a similar prognosis as all DTC patients. It also showed that it is feasible to follow Tg and TgAb levels, even in those patients who were initially negative for these biomarkers at ablation. Important finding was that when patients developed Tg or TgAb positivity during follow-up, the disease-free survival was significantly shorter as compared to those with persistently negative Tg and TgAb.

LifeLines

The risk to develop multifactorial diseases is determined by risk factors that frequently apply across disorders (universal risk factors). To investigate presently unresolved issues on etiology of and individual's susceptibility to multifactorial diseases, research focus should shift from single determinant–outcome relations to effect modification of universal risk factors.
Researchers of the UMCG have developed a model to investigate universal risk factors of multifactorial diseases, based on a single risk factor, a single outcome measure, and several effect modifiers.

Modifiers and determinants

Outcome measures can be disease overriding, such as clustering of disease, frailty and quality of life. "Life course epidemiology" can be considered as a specific application of the proposed model, since risk factors and effect modifiers of multifactorial diseases typically have a chronic aspect. Risk factors are categorized into genetic, environmental, or complex factors, the latter being a combination ("endophenotype") of multiple factors. The proposed research model of multifactorial diseases assumes that determinant-outcome relations differ between individuals because of modifiers, which can be divided into three categories: risk-factor modifiers; outcome modifiers; generic modifiers.
A study to assess disease risk during life requires phenotype and outcome measurements in multiple generations with a long-term follow up. The latter will also enable to separate genetic and environmental factors. Traditionally, representative individuals (probands) and their first-degree relatives have been included in this type of research. We put forward that a three-generation design is the optimal approach to investigate multifactorial diseases. This design has statistical advantages (power and precision, multiple informants, separation of non-genetic and genetic familial transmission, direct haplotype assessment, quantify genetic effects), enables unique possibilities to study social characteristics (socioeconomic mobility, partner preferences, between-generation similarities), and offers practical benefits (efficiency, lower non-response).

Concepts

LifeLines is a cohort study to investigate universal risk factors and their modifiers for multifactorial diseases: LifeLines. This study will result in better understanding of the causes and prognosis of burden of disease over lifetime and may ultimately result in optimal tailored treatment of individual diseases and disease overriding preventive strategies. Specific research questions will focus on risk factors and modifiers (genetic, environmental and complex factors) for single and multiple diseases. Rather than co-morbidity, LifeLines focuses on co-determinants.
Secondary aims include the assessment of the prevalence and incidence of multifactorial diseases and their risk factors in individuals as well as in families. The burden of disease for the society will be quantified in terms of care needed.
LifeLines is an observational follow-up study in a large representative sample of the population of the northern provinces of the Netherlands covering three generations. Firstly, a random sample of persons aged between 25 and 50 years are invited to participate. Subsequently these probands invite their family members if present to take part as well (parents, partner, parents in law, children), resulting in a three-generation study.
The core of the LifeLines project consists of dedicated data collection and biological sample storage, including genetic samples ("biobank"). All participants receive a number of questionnaires and a basic medical examination and are followed for many years with extensive standardized measurements.
A cohort study, in contrast to a case-control study, enables the prospective investigation of risk factors, which is crucial in the study of environmental and other time varying exposures, as well as interactions between environmental risk factors. For genetic studies a case-control design is often more appropriate, but in such a design it is virtually impossible to investigate gene-environment interactions.

Number of participants

The LifeLines project will include 165.000 participants: anticipated to consist of approximately 45.000 probands, 30.000 partners, 55.000 parents (in law) and 35.000 children. This number is based on balancing costs and practical limitations with sufficient number of incident diseases. When estimating the number of events one has to realize that sick individuals are less likely to participate. Following the adjustment for this “Hawthorne effect” as suggested by the UK Biobank,40 after five years the expected numbers of some common multifactorial diseases in this cohort are 1000 individuals with myocardial infarctions, 500 with stroke, 2000 with depression. Based on a prevalence of 20% to 40% of the risk factors of interest, and estimated relative risk around 1.2, these numbers are sufficient to identify statistically significant associations. Newly developed statistical methods to analyze combinations of (genetic) risk factors will improve the effectiveness for these databases.

However, the main objective for LifeLines is to investigate effect modification, or interaction in statistical terms. By performing stratified analyses or introducing more additional terms into a regression model, each with its own variation, the required number of participants increases substantially. This is only partly compensated by the fact that these analyses will typically use continuous measures as outcome (endophenotype). The power calculations for these analyses are strongly influenced by the interaction ratio, which is often not known.

Methods of data collection are matched with other ongoing biobank studies (P3G consortium), which enables combining datasets to construct large study populations. LifeLines participates in the BBMRI consortium (www.biobanks.eu).

Figure 4. The 3 Northern provinces of The Netherlands, area of the LifeLines Cohort Study, viewed from the air by Google Earth.

For more information readers are referred to the website www.lifelines.nl.

9. Activities outside the UMCG

Contacts with patient societies
Our department has extensive contacts with several societies of patients, which results in a continuous stimulation to further improve patient care. Staff members of the Department give presentations for regional patient groups. Twice yearly a structured mutual discussion with the Diabetesvereniging Nederland is organized. From the beginning of 2005, prof. Wolffenbuttel is one of the medical advisors of the Dutch Association for Addison and Cushing Patients (NVACP, Nederlandse Vereniging voor Addison en Cushing Patiënten).
Dr. Links is advisor of the foundation "BETER", that supports organization of care for patients with hereditary endocrine cancer syndromes.

Specific activities
Several members of the department participate in national and international study or research-groups, amongst others the Dutch Adrenal Collaborative (www.bijniernetwerk.nl)

Dr. G. van den Berg Dutch is representative within The Northern European Neuro-Endocrine Group (NENEG).

Dr. T.P. Links is president of the Dutch national Working Group for Von Hippel Lindau's disease, member of the Working Group on Thyroid Carcinoma of the Comprehensive Cancer Centre North Netherlands (IKN), and chairperson of the CBO Guideline Group for Differentiated Thyroid Cancer.

Prof. dr. B.H.R. Wolffenbuttel is Editor-in-chief of the scientific Netherlands Journal of Diabetology, a peer-reviewed scientific journal in the Dutch language, which appears four times a year. He is also a member of the Board of the journals International Diabetes Monitor and International Growth Monitor, as well as Expert Opinion in Pharmacotherapy. He is chairman of the Foundation for the Dr. F. Gerritzen Price, a foundation which every year rewards a price to the best scientific PhD thesis in the field of diabetes mellitus.

Dr. J.C. Keers and mrs. W. van El are members of the Education board of the Dutch Diabetes Research Foundation.

Mrs. Gillian Kreugel is a member of the scientific committee of the EADV (Dutch Association of Diabetes specialist nurses) and a member of ‘Diabetes Network Groningen’.

Addendum 1 - Conferences

Endocrinology Grand Rounds	weekly (Tuesday 9 - 10.30)
Endocrine Case Conference	weekly (Friday 9 - 10)
Internal Medicine Patient Discussion	every two weeks (Tuesday 16.45 - 17.30)
Thyroid Carcinoma Consultation	monthly (Friday 11 – 12.30)
Diabetic Foot Rounds	weekly clinical rounds (Monday) 1x monthly (Friday)
Pituitary Case Conference	every two weeks (Tuesday 12 - 13)
Multidisciplinary Diabetes Consultation	once monthly (Thursday, 16.30 - 17.30)
Endocrine Pathology Case Conference	once every 2 months (Friday 9 - 10)
Vascular Medicine Research meeting	every two weeks (Tuesday 16.45 -17.30)
Endocrinology Journal Club	monthly (Friday 9 - 10.30)
Regional Case and Research Conferences	6-8 times a year

Addendum 2 - Multidisciplinary teams

Thyroid
Dr. T.P. Links, Endocrinology
Prof. dr. J.T.M. Plukker, dr. L. Jansen, Oncologic Surgery
Dr. A. Brouwer and colleagues, Nuclear Medicine
Dr. F. Burlage, Radiotherapy
Dr. P. C. Jutte, Orthopedics
Dr. M. Coppes, Neurosurgery
Dr. A. Muller Kobold, Clinical Chemistry
Staff members of Endocrinology

Pituitary
Dr. G. van den Berg, Endocrinology
Dr. M.M. van der Klauw, Endocrinology
Dr. E. Hoving, Neurosurgery
Dr. J.W. Pott, Ophthalmology
Dr. A.C.M. van den Bergh, Radiotherapy
Dr. L. Meiners, Neuroradiology
Staff members of Endocrinology

Diabetic foot
Staff members of the Departments of (Vascular) Surgery, Orthopaedics, Dermatology, Rehabilitation, Plastic Surgery and Internal Medicine / Endocrinology

Turner team
Dr. M.N. Kerstens, Endocrinology
Dr. A.P. van Beek, Endocrinology
Mrs. dr. A. Hoek, Gynaecology
Mrs. dr. W.M. Bakker- van Waarde, Paediatrics
Mrs. E. Lont, Nursing
Mrs. H.J. Huisinga, Social Support
Mrs. A. Elliot-Pascal, Social Support

Addendum 3 - Publications 2007

PhD Thesis

Mrs. E. Beeks.
Functional correlates of the alpha adducin polymorphism.
Promotor: prof.dr. P. de Leeuw; co-promotor: *Dr. M.M. van der Klauw*, RUG; dr. A. Kroon.
July 6, 2007

Mrs. I.M.J.G. Eijkelenberg.
Key factors of change processes in shared care. Viewpoints of managers, care providers and patients.
Promotores: prof. dr. C. Spreeuwenberg, *prof. dr. B.H.R. Wolffenbuttel.*
September 5, 2007

Mrs. T.T.H. Phan.
Imaging strategy in differentiated thyroid cancer.
Promotor: prof. dr. R.A.J.O. Dierckx, *prof. dr. B.H.R. Wolffenbuttel*, prof. dr. P.L. Jager; co-promotor: *Links TP*. http://irs.ub.rug.nl/ppn/305032321
November 26, 2007

Mrs. A.C. Heijckmann.
Bone mass and fractures in patients at risk for secondary osteoporosis.
Promotor: prof. dr. A.C. Nieuwenhuijzen Kruseman, prof. dr. P. Geusens, Hasselt, *prof. dr. B.H.R. Wolffenbuttel, RUG*; co-promotor: dr. M.S.P. Huijberts.
December 19, 2007

International peer-reviewed publications

Alvarez-Llamas G, Szalowska E, de Vries MP, Weening D, Landman K, Hoek A, *Wolffenbuttel BHR*, Roelofsen H, Vonk RJ. Characterization of the human visceral adipose tissue secretome. Mol Cell Proteomics 2007; 6(4): 589-600

Beek AP van, van den Bergh ACM, *van den Berg LM*, *van den Berg G*, *Keers JC*, Langendijk JA, *Wolffenbuttel BHR*. Radiotherapy is not associated with reduced quality of life and cognitive function in patients treated for nonfunctioning pituitary adenoma. Int J Radiat Oncol Biol Phys 2007; 68(4): 986-91

Bergh ACM van den, *van den Berg G*, Schoorl MA, *Sluiter WJ*, van der Vliet AM, Hoving EW, Szaó BG, Langendijk JA, *Wolffenbuttel BHR*, *Dullaart RPF*. Immediate postoperative radiotherapy in residual nonfunctioning pituitary adenoma: beneficial effect on local control without additional negative impact on pituitary function and life expectancy. Int J Radiat Oncol Biol Phys 2007; 67(3): 863-9

Borggreve SE, Hillege HL, Dallinga-Thie GM, de Jong PE, *Wolffenbuttel BHR*, Grobbee DE, van Tol A, *Dullaart RPF* on behalf of the PREVEND Study Group. High plasma cholesteryl ester transfer protein levels may favour reduced incidence of cardiovascular events in men with low triglycerides. Eur Heart J 2007; 28(8): 1012-8

Dallinga- Thie GM, *Dullaart RPF*, van Tol A. Concerted actions of cholesteryl ester transfer protein and phospholipid transfer protein in type 2 diabetes: effects of apolipoproteins. Curr Opin Lipidol 2007; 18(3): 251-7

Dullaart RPF, Dallinga- Thie GM, van Tol A. Plasma phospholipid transfer protein activity, a determinanant of HDL kinetics in vivo. Clin Endocrinol 2007; 67: 316-20

Dullaart RPF, *de Vries R*, Dikkeschei LD, *Sluiter WJ*. Higher plasma leptin largely explains increased C-reactive protein levels in women. Eur J Clin Invest 2007; 37(3): 231-3

Dullaart RPF, *Oomen PHN*, *Sluiter WJ*. Circulating vascular endothelial growth factor is unaffected by acute hyperglycemia and hyperinsulinemia in type 1 diabetes mellitus. Eur J Intern Med 2007; 18(3): 193-5

Dullaart RPF, *de Vries R*, Dallinga-Thie GM, van Tol A, *Sluiter WJ*. Plasma cholesteryl ester transfer protein mass and phospholipid transfer protein activity are associated with leptin in type 2 diabetes mellitus. Biochim Biophys Acta 2007; 1771(1): 113-8

Dullaart RPF, *de Vries R*, van Tol A, *Sluiter WJ*. Lower plasma adiponectin is a marker of increased intima-media thickness associated with type 2 diabetes mellitus and with male gender. Eur J Endocrinol 2007; 156(3): 387-94

Groot JWB de, *Links TP*, *Sluiter WJ*, *Wolffenbuttel BHR*, Wiggers T, Plukker JTM. Locoregional control in patients with palpable medullary thyroid cancer: Results of standardized compartment-oriented surgery. Head Neck 2007; 29(9): 857-63

Groot JW de, Zonnenberg BA, van Ufford-Mannesse PQ, *de Vries MM*, *Links TP*, Lips CJ, Voest EE. A Phase II Trial of Imatinib Therapy for Metastatic Medullary Thyroid Carcinoma. J Clin Endocrinol Metab 2007; 92(9): 3466-9

Heijckmann AC, Huijberts MS, De Vries J, Menheere PP, Van Der Veer E, Kruseman AC, *Wolffenbuttel BHR*, Geusens P, Drent M. Bone turnover and hip bone mineral density in patients with sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 2007; 24(1): 51-8

Hes FJ, van der Luijt RB, Janssen AL, Zewald RA, de Jong GJ, Lenders JW, *Links TP*, Luyten GP, Sijmons RH, Eussen HJ, Halley DJ, Lips CJ, Pearson PL, van den Ouweland AM, Majoor-Krakauer DF. Frequency of Von Hippel-Lindau germline mutations in classic and non-classic Von Hippel-Lindau disease identified by DNA sequencing, Southern blot analysis and multiplex ligation-dependent probe amplification. Clin Genet 2007; 72(2): 122-9

Horst-Schrivers AN, Post WJ, Kema IP, Links TP, Willemse PH, Machteld Wymenga AN, de Vries EG. Persistent low urinary excretion of 5-HIAA is a marker for favourable survival during follow-up in patients with disseminated midgut carcinoid tumours. Eur J Cancer 2007; 43(18): 2651-7

Jager CM de, de Heide LJ, *van den Berg G*, Wolthuis A, van Schelven WD. Acromegaly caused by a growth hormone-releasing hormone secreting carcinoid tumour of the lung: the effect of octreotide treatment. Neth J Med 2007; 65(7): 263-6

Jong WH de, Graham KS, van der Molen JC, *Links TP*, Morris MR, Ross HA, de Vries EG, Kema IP. Plasma free metanephrine measurement using automated online solid-phase extraction HPLC tandem mass spectrometry. Clin Chem 2007; 53(9): 1684-93

Kreugel G, Beijer HJM, Kerstens MN, ter Maaten JC, Sluiter WJ, Boot BS. Influence of needle size on metabolic control and patient acceptance. Eur Diabetes Nursing 2007; 4(2): 51-5

Lely AT, Krikken JA, Bakker SJL, Boomsma F, *Dullaart RPF*, *Wolffenbuttel BHR*, Navis G. Low dietary sodium and exogenous angiotensin II infusion decrease plasma adiponectin concentrations in healthy men. J Clin Endocrinol Metab 2007; 92(5): 1821-6

Meerwaldt R, Lutgers HL, *Links TP*, Graaff R, Baynes JW, Gans ROB, Smit AJ. Skin autofluorescence is a strong predictor of cardiac mortality in diabetes. Diabetes Care 2007; 30(1): 107-12

Meinardi JR, *Wolffenbuttel BHR*, *Dullaart RPF*. Cyclic Cushing's syndrome: a clinical challenge. Eur J Endocrinol 207; 157(3): 245-54

Oosterhuis JK, *van den Berg G*, Monteban-Kooistra WE, Ligtenberg JJ, Tulleken JE, Meertens JH, Zijlstra JG. Life-threatening Pneumocystis jiroveci pneumonia following treatment of severe Cushing's syndrome. Neth J Med 2007; 65(6): 215-7

Pauw RG, van der Werf TS, van Dullemen HM, *Dullaart RPF*. Mediastinal emphysema complicating diabetic ketoacidosis: plea for conservative diagnostic approach. Neth J Med 2007; 65(10): 368-71

Persoon AC, Jager PL, *Sluiter WJ*, Plukker JT, *Wolffenbuttel BHR*, *Links TP*. A sensitive Tg assay or rhTSH stimulated Tg: what's the best in the long-term follow-up of patients with differentiated thyroid carcinoma? PLoS ONE 2007; 2(8): e816

Phan HT, Jager PL, Plukker JT, *Wolffenbuttel BHR*, Dierckx RA, *Links TP*. Detection of bone metastases in thyroid cancer patients: bone scintigraphy or 18F-FDG PET? Nucl Med Commun 2007; 28(8): 597-602

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Roos A, Bakker SJ, *Links TP*, Gans ROB, *Wolffenbuttel BHR*. Thyroid function is associated with components of the metabolic syndrome in euthyroid subjects. J Clin Endocr Metab 2007; 92(2): 491-6

Vries R de, Groen AK, *Perton FG*, Dallinga- Thie GM, van Wijland MJA, Dikkeschei LS, *Wolffenbuttel BHR*, van Tol A, *Dullaart RPF*. Increased cholesterol efflux from cultured fibroblasts to plasma from hypertriglyceridemic type 2 diabetic patients: Roles of pre beta-HDL, phospholipid transfer protein and cholesterol esterification. Atherosclerosis 2007; 196(2): 733-41

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Voorham J, Haaijer-Ruskamp FM, Stolk RP, *Wolffenbuttel BHR*, Denig P; Groningen Initiative to Analyze Type 2 Diabetes Treatment Group. Influence of elevated cardiometabolic risk factor levels on treatment changes in type 2 diabetes. Diabetes Care Epub 2007 Dec 10.

Stolk RP, Rosmalen JG, Postma DS, de Boer RA, Navis G, Slaets JP, Ormel J, *Wolffenbuttel BHR*. Universal risk factors for multifactorial diseases: LifeLines: a three-generation population-based study. Eur J Epidemiol Epub 2007 Dec 13

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Bos MB, de Vries JH, *Wolffenbuttel BHR*, Verhagen H, Hillege JL, Feskens EJ. [The prevalence of the metabolic syndrome in the Netherlands: increased risk of cardiovascular diseases and diabetes mellitus type 2 in one quarter of persons under 60]. Ned Tijdschr Geneeskd 2007; 151(43): 2382-8

Links TP, Huysmans DA, Smit JW, de Heide LJ, Hamming JF, Kievit J, van Leeuwen M, van Pel R, de Klerk JM, van der Wal Y. Guideline “Differentiated thyroid carcinoma”, including diagnosis of thyroid nodules. Ned Tijdschr Geneeskd 2007; 151(32): 1777-82

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Noordzij MJ, de Heide LJ, *Links TP*, Jager PL, *Wolffenbuttel BHR*. [Four patients with incidentalomas of the thyroid discovered on 18-fluoro-deoxyglucose positron-emission tomography (FDG-PET)]. Ned Tijdschr Geneeskd 2007; 151(42): 2337-41

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Letters

Kerstens MN, *Dullaart RPF*. Comment on: Holt HB, Wild SH, Postle AD et al (2007) Cortisol clearance and associations with insulin sensitivity, body fat and fatty liver in middle-aged men. Diabetologia 2007; 50(9): 2023-4

Wolffenbuttel BHR. Doubts as to the cardiovascular safety of rosiglitazone
Ned Tijdschr Geneeskd 2007; 151(40): 2236-7; author reply 2237.

Bilo HJ, Logtenberg SJ, de Grauw WJ, Kleefstra N, *Wolffenbuttel BHR*. Time to move from serum creatinine to eGFR. Diabet Med 2007 May;24(5):571-2; author reply 572-3

Kerstens MN, *van Beek AP*, Hoek A, Bakker-van Waarde WM. Turner syndrome in adulthood. Ned Tijdschr Geneeskd 2007; 151(42): 2354-5; author reply 2355.

Chapters in books

Nobels F, Mathieu C, Heine RJ, *Wolffenbuttel BHR*. Diabetes mellitus. In: Ned Leerboek Endocrinologie, 2007

Several abstracts and (poster) presentations on national and international congresses and symposia.