

Department of Women's and
Children's Health

ANNUAL REPORT

2008

Introduction

During 2008 the first students from our newly started midwifery programme were awarded their degrees as midwives. To celebrate this occasion a solemn ceremony was arranged in the great hall in the main University building. The second course started in January 2009.

Uppsala University has lost its right to graduate specialist nurses, which means that our department is unable to continue its programme in pediatric nursing. We are now, together with the Faculty for Medicine and Pharmacy and other departments, planning to apply to the Swedish National Agency for Higher Education in order to regain the right to examine specialist nurses. During 2009, however, no such programme will start.

In June 2008, researchers from our department played a key-role when a Berzelius Symposium on pre-eclampsia was held in Uppsala. International and Swedish basal scientists and clinical researchers presented new and interesting data on this puzzling syndrome. The symposium took place in the University building and collected a full auditorium. The possibility to listen to and meet some of the most prominent international researchers in the field was highly appreciated by many of our young research fellows.

During 2008, a newly recruited Professor in Pediatrics, Mar Tulinius, came and left. We have met difficulties to get competent stand-ins but new processes have started to recruit two senior academic lecturers in pediatrics and one in pediatric and obstetric nursing. We are also continuing our effort to receive funding from the faculty to create an academic post in pediatric surgery.

Due to positive evaluation from the international committee behind the KoF-report, concerning our research in international health, funding for two research positions were assigned our department. The positions were announced and after evaluation Eva-Charlotte Ekström and Pia Olsson were appointed. This new economic contribution will create improved conditions for these two researchers.

Gudmar Lönnerholm retired from his professorship in 2008 but will continue his engagement in pediatric oncologic research. Gudmar Lönnerholms long standing achievement as teacher and researcher is highly appreciated. Susan Pfeifer replaced Gudmar Lönnerholm as head of the research group in pediatric oncology.

The new leadership on the hospital side for the division as well as the department of obstetrics and gynecology took up office in 2008. Hitherto, the cooperation between the new clinical leadership and our department has been characterised by mutual understanding and positive attitudes. We will do whatever is possible to preserve this new spirit of cooperation.

To be the Head of the Department of Women's and Children's Health is an important and most often inspiring task. We work within areas of utmost significance for women's and children's health in Sweden as well as in the developing world. Our research and educational activities contribute to improved health and living conditions for women and children. New challenges will always appear but can be met by our committed researchers and teachers, supported by our dedicated administrators.

Uppsala in March 2009

Ove Axelsson

Head of the Department of Women's and Children's Health

Education at the Department of Women's and Children's Health

During the year 2008 more than 600 students have participated in the broad range of programmes available at the Department of Women's and Children's Health, Uppsala University. IMCH (International Maternal and Child Health) further has 62 full-time equivalent students on a yearly basis and an additional 65 students participating in the single courses. The level of education ranges from undergraduate courses for nurses and medical students to Master's Programme in International Health.

The undergraduate/graduate courses given by the department

Obstetrics and Gynecology and Pediatrics within the Registered Nurse Programme

The Registered Midwife Programme

Obstetrics and Gynecology within the Medicine Programme

Pediatrics within the Medicine Programme

Global Medicine, which is an elective course for medical and nurse students and include a 2-week study visit to hospitals and health centres in a low-income country

Postgraduate courses for nurses

Postgraduate Education in Pediatric Nursing

Child and Adolescent Health Care, Child and Adolescent Psychiatric care, 15 credit points

Nursing Care of Children and Adolescents with General Pediatric Conditions, 15 credit points

Nursing Care of Children and Adolescents with Special Somatic Conditions, 15 credit points

Nursing Care of Children and Adolescents focusing on Specific Fields of Study, 15 credit points, including a degree project, 7,5 credit points

Nursing Care of Children and Adolescents focusing on Specific Fields of Study: degree project, 15 credit points

Other postgraduate courses

Master's Programme in International Health (2-year programme)

International Training Programme focusing on global Child Survival issues

Single courses

Fetal Monitoring

Obstetric Ultrasound

ABC-Training for Young Obstetricians and Gynecologists

Breastfeeding and Human Lactation, 7,5 credit points

Neonatal Nursing, 15 credit points

Pain in Children and Adolescents, 7,5 credit points

Violence Against Women 7,5 ECTS

Reproductive Health in a life-cycle perspective (also available within the Midwife Programme)

Global Health (also available within the Midwife Programme)

The registered Midwife Programme

In January 2007, the registered Midwife Programme was introduced and in June 2008 the first class of midwives was examined. The registered Midwife Programme is a 90 ECTS degree program including practical training and a 30 ECTS examination. The cornerstones of the education include formal training in reproductive health and obstetrics but students are also prepared for independent work within the fields of maternal health, youth health (contraceptive advice), and infertility settings. Because of the available resources at the department particular emphasis on global reproductive health and violence against women is provided. Within the program it is possible to obtain a Magister degree, which in turn is a prerequisite for future PhD studies. The evaluations from students are very good regarding academic level of lectures, the pre clinical training on phantoms and clinical education in for example women's health and childbirth care.

The Postgraduate Education in Pediatric Nursing

The postgraduate education in pediatric nursing has, during the last year, focused on providing an Internet-based education with course material, including video-taped lectures, available within the PingPong platform. The web-based course is accompanied by weekly seminars. Using reflective learning, the students share their experiences of theoretical knowledge and clinical practice once a week with each other and their teachers through the platform. As these programs are available on an advanced level, students are given the opportunity to obtain a Magister degree. Approximately half of the students have chosen to write their Magister thesis. As the postgraduate courses for nurses have failed the review by the Swedish National Agency for Higher Education, no students within this programme will start their education during 2009-2010. Preparations for a revised education of pediatric nurses are ongoing with the aim of restarting the program in 2010.

Obstetrics and Gynecology and Pediatrics within the Registered Nurse Programme

The new course in "Nursing and medical care in gynecological, obstetric and pediatric care", 12 credit points started in 2008. Both theoretical and practical teaching of nurses will be available at the department of Women's and Children's Health. The education is problem-based and uses the PingPong platform. Students are given the opportunity to write their C-thesis at the department.

Education at IMCH

The Master's Programme in International Health is a 2-year programme that attract physicians, nurses, midwives, nutritionists as well as students with a social sciences background interested in global health issues. Yearly 25-30 participants from all over the world are selected from several hundred applications. Core courses in international

health and research methodology are followed by elective courses and completed by project planning, field work and compilation and defence of a master's thesis. Several of the students return back to their home country for field work during the second year of the program. Apart from European students we have Asian and African countries well represented, and a few from the North and South American continents. A process has been initiated to get all courses within the program reviewed by the European network TropEd – an important tool for quality control of the education program. We notice that some PhD students are recruited among skilled and successful Masters students – and we have examples where the Masters thesis is the starting point for subsequent PhD research.

The department is also involved in an European joint Master's Programme in Humanitarian Assistance, the NOHA programme, contributing with, among other components, courses on public health in humanitarian assistance.

On behalf of Sida and jointly with University of Gothenburg and the Karolinska Institute the department is running an International Training Programme focusing on global Child Survival issues. Senior colleagues with responsibilities for child health programmes from Ministries to non-Governmental programmes attend a monthly course in Uppsala and subsequent research/development work and follow-up workshop in their region. In 2008 the focus was on Africa. The design of the program is successful in stimulating processes of change, and we noted several examples of important development activities for improved child health in the reports of the participants.

Inger Sundström Poromaa
Director of Undergraduate Studies

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(from July 2008)

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Inger Sundström Poromaa	teacher representative
Lennart Nordvall	teacher representative, deputy
Matts Olovsson	teacher representative, deputy
Karin Törnblom	representative for technical/adm. personnel
Lena Moby	representative for technical/adm. personnel, deputy
(from July 2008)	
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Thomas Lundqvist	graduate student representative
Julia Aulin	student representative

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3. Gynaecological Endocrinology

Tord Naessén, MD, PhD, Associate Professor

4. National Center for Knowledge on Men's Violence against Women

Gun Heimer, MD, PhD, Professor

5. International Maternal and Reproductive Health

Birgitta Essén, MD, PhD, Associate Professor

6. International Child Health and Nutrition

Lars-Åke Persson, MD, PhD, Professor

7. Paediatric Endocrinology

Jan Gustafsson, MD, PhD, Professor

8. Paediatric Oncology

Gudmar Lönnérholm, MD, PhD, Professor

9- Paediatric Neurology

Gunnar Ahlsten, MD, PhD, Associate Professor

10- Perinatal and Neonatal Medicine and Paediatric Cardiology

Anders Jonzon, MD, PhD, Associate Professor

11- General Paediatric

Lennart Nordvall, MD, PhD, Associate Professor

12- Paediatric Surgery and Paediatric Urology

Rolf Christofferson, MD, PhD, Associate Professor

Scientific Reports

Clinical and Experimental Reproductive Biology

Matts Olovsson

Research projects

1) Preeclampsia

Pre-eclampsia is a complication that occurs in 3-5% of pregnancies. It is a potential threat against both mother and foetus. This project aims at a better understanding of the aetiology and pathogenesis of pre-eclampsia, how to predict the disease and to what extent it is associated with specific cardiovascular changes. We have shown that there are also several differences between early and late onset preeclampsia concerning placental oxidative stress, angiogenic and anti-angiogenic markers and several inflammatory markers. Our data indicates that pathogenesis differs between early and late onset disease and they should most likely be predicted, diagnosed and treated differently. Currently we are also studying potential markers such as angiotensin II to predict preeclampsia. We have also initiated a study where placental metabolism is studied in situ using MRS. Preliminary data clearly shows differences between women with preeclampsia and healthy pregnancies. Further, we have initiated a study of the relationship between preeclampsia and different types of cardiovascular changes later in life.

2) Endocrine disrupting chemicals and female reproductive health

It has been shown that several environmental contaminants such as PCB and DDT have endocrine disrupting capacity, thus meaning that they may have effects on female reproductive functions. A lot of information can be achieved from animal experiments but this is expensive, time consuming and there is also an intention to reduce the number of laboratory animal use. This as a part of an EU project, ReProTect, within ECVAM. We are working with cell culture systems to screen for potential effects of these chemicals on female reproductive functions. We use endometrial cells such as human endometrial endothelial cells in our test systems. The work is done in cooperation with several other European groups.

3) Endometriosis and endometrial angiogenesis

Endometriosis is a common gynaecological disease, occurring in about 10% of all women. The disease causes abdominal pain and reduced fertility. Together with a group from Moscow we are investigating the association between the proliferative activity in the lesions and the angiogenic activity. We have recently shown that serum and peritoneal fluid concentrations of several factors involved in the regulation of angiogenesis at least partly normalize within a week after surgical removal of the endometriotic lesions.

Angiogenesis is thought to play a pivotal role in the cycling endometrium and is regulated by a combination of systemic and local factors. Physiological angiogenesis is part of the endometrial repair and growth process following menstruation as well as at the time of embryo implantation. Endometrial pathologies such as endometriosis, hyperplasia and malignancy are all dependant on angiogenesis. We have studied the transcript profile changes induced by VEGF-A and serum withdrawal in primary human endometrial endothelial cells using oligonucleotide microarray measurement, followed by analysis using Gene Ontology and pathway analysis databases. This work is done in cooperation with a group in Cambridge.

4) Studies on embryo, fallopian tube, endometrium and the implantation process

The communication between the embryo and maternal tract seem to be important for transport through the fallopian tube and subsequent implantation. We have studied gene expression in human embryos, which has resulted in one manuscript ready for submission and one manuscript in preparation. Our study shows amazingly regulated development of the embryo which has very little communication with the maternal side. Better methodology in cryopreservation is important to

increase successrate at IVF treatment. Our data on vitrification of embryos has resulted in one submitted manuscript, one manuscript in preparation and one additional ongoing study. One PhD student, F hambiligki is working on the project.

The transport of the embryo through the fallopian tube is crucial for the reproduction. Our data show that prostaglandins are involved in the fallopian tube contractility, and that this event is hormone dependent. We have also found evidence of communication from the embryo to the maternal tract during the transport through the fallopian tube. These data was presented in K Wånggrens thesis. Cecilia Olsson's 10p project for BMA exam resulted in a new tissue culture method for studies on hormone regulation of fallopian tube in vitro and a manuscript will be finalized for submission. A new PhD student has been enrolled into the project. (A Stavreus-Evers, K Wånggren, A Rumman, L Aghajanova).

The development of the endometrium is crucial for embryo implantation. The development is regulated by steroid hormones. Our data show that not only the classical hormones, estrogen and progesterone is important, also thyroid hormone play a role in endometrial receptivity. All data showing the distribution and function of thyroid hormone in the human ovary is submitted. All samples for Frida Hussein's first study on the role of thyroid hormone in the human endometrium are collected.

Paracrine, juxtacrine, and autocrine interactions through growth factors and cytokines are important for all phases of the human implantation process. Our group have studied several factors such as LIF, HB-EGF, Ghrelin and IGF1. The studies on endometrium have resulted in one 10p project, T Allhammar, BMA and one master thesis, A Rumman, BMA. These studies show the presence, regulation and function of ghrelin and its receptor in the receptive endometrium. One study Muc16 in the endometrium is accepted for publication in *Biology of reproduction*, January 2008. The first study on IGF1 receptor shows the importance for IGF1 receptor for embryo development is summarized for the first manuscript. The second study on the role of IGF1 for ovulation has resulted in a 10p project for Lisa Rådström BMA. The uterine tissue is not yet analyzed. Using cell culture models we show that down regulation of Muc16 for implantation and that mifepristone inhibits embryo attachment.

The transport of water is important for endometrial function. We have shown that AQP1 in endometrium from women with menorrhagia compared to control women, which shows different expression of AQP1 in blood vessels between these two groups, is published. Anna Hildenbrand's second publication on AQP1 in the endometrium is submitted. Further studies using cell culture models are ongoing. Anna Hildenbrand held her half time seminar in November 2007.

5) Unexplained infertility

For women with unexplained infertility, there are reasons to believe that endometrial factors can be involved. Today, we lack good diagnostic tools for these women, and the treatment could be more efficient. Our studies show that LIF and its receptors (LIFR and gp130) and inhibitor (SOCS1) in endometrium from fertile and infertile women is submitted. This study shows that it is more common with low LIFR expression concomitantly with high SOCS1 expression in endometrium from women with unexplained infertility compared to fertile controls. A similar study on HB-EGF and its receptors showing lower HB-EGF expression in endometrium from infertile women is accepted for publication in *Reproductive Sciences*.

Genetic variations might influence endometrial receptivity and infertility treatment. Signe Altmäe has published her first paper in her Tartu-project and statistical evaluation is ongoing for her second study. Almost all data is analyzed in the Tissue Factor study, the manuscript is planned for submission 2008. One additional study on sex steroid hormones is ongoing and has resulted in an abstract accepted for the congress in *Gynecologic Endocrinology* in Florence 2008.

Low folat levels have been related to fertility problems. Data from Tiina Syvänen's and Cecilia Vanhainen's master thesis's show that it is more common with the polymorphism in the MTHFR 677 TT in women with unexplained infertility compared to the general population. Statistical analysis of 10 different genes involved in the folate metabolism in relation to infertility is ongoing.

These studies are performed in collaboration with colleagues in Hungary, Italy Estonia, UK and USA.

6) *Postpartum depression*

Postpartum depression (PPD) affects approximately 10% of all mothers within one year of delivery. It seems as though some women are more prone to be affected, whether this is due to biological, psychological or social factors. There is growing evidence for a role of estrogen, progesterone, leptin and adiponectine, as well as of several gene polymorphisms in the pathogenesis of PPD. Seasonal variation for this condition has only been reported in one small study so far. A questionnaire containing the Edinburgh Postnatal Depression Scale (EPDS) as well as several other variables was given to all the women who gave birth in Uppsala's university hospital during the period May 2006 - May 2007, in order to complete (a) 5 days, (b) 6 weeks and (c) 6 months after delivery. Blood samples were collected from 533 women. The fact that 2.332 women (65% of all eligible women, 92% of those that consented to the study) responded to a least one of the three questionnaires, gives the unique opportunity to unveil and confirm several epidemiological associations. Biochemical and genetic analyses could give further insight in the pathogenesis of PPD, as well as the identification of markers that could help health professionals to promptly identify women at risk. This of paramount importance not only for the mental health of the new mother, but also for the normal psychosocial development of her infant, and well being of her whole family. In a recently submitted paper we could show that lower serum leptin levels at delivery are associated with higher risk for the development of postpartum depressive symptomatology.

7) *Ovarian cancer*

Prognostic factors for epithelial ovarian cancer in FIGO-stages I-II. We have studied the relevance of p53, bax, p21, p27, PUMA och c-MYC, EGFR, VEGF-R, VEGF and PTEN as prognostic factors. A future project within genomics has been planned. We have also published a paper about borderline ovarian tumours and ovarian cancer in Sweden in 1960-2005.

8) *Relationship between the use of IUD and PID*

Case-control study of serious infections in the Fallopian tube in women >35 during 2001-2004 and the relationship to the use of intrauterine device (IUD). Dr Ingrid Wikström coordinates the study where users of IUD are compared with non-users among women with serious pelvic inflammatory disease. Data from patient files have been collected, statistics done and preparation of manuscripts initiated.

9) *Improvement of organised cytological screening by self-sampling*

Women not attending organised cytological screening program are offered testing of vaginal smear obtained using a novel self-sampling device. We have shown that there is a high prevalence of oncogenic HPV in women not attending organised cytological screening and that about half of the women not attending the organised cytological screening program actually performs the self-sampling. The results have been presented in several publications, abstracts and presentations.

10) *Reproduction and psyche*

Women suffer twice as often from mood and anxiety disorders than men. These gender differences are not apparent before menarche and gradually disappear when women are aging. Hence, the most pronounced gender differences in prevalence rates for anxiety disorders and major depression are found during the fertile life of women. Even if genetic, interpersonal and social factors are taken into account for these gender specific differences, a biologic neurohormonal component remains, where ovarian steroids (estradiol and progesterone) and metabolites of ovarian steroids (neurosteroids) are

likely to play a role.

The overall aims of these studies is to investigate how reproductive hormones influence mood and anxiety in women, how reproductive events affect mood disorders in women, and vice versa, how mood disorders affect reproduction in men and women. Our studies investigate the interactions between ovarian steroids and mood/anxiety during various aspects of a woman's fertile life such as young women with adverse mood effects from combined oral contraceptives, pregnant and postpartal women, women with severe premenstrual symptoms, postmenopausal women on estradiol treatment and involuntary childless couples.

The study designs span from prevalence studies on psychiatric disorders to human experimental studies on anxiety/fear and to neuroimaging studies where functional magnetic resonance imaging is used to evaluate activation of parts of the central nervous system known to be involved in anxiety and/or fear. Furthermore, part of the proposed study is also aiming at elucidating possible harmful effects of progesterone metabolites. During 2008, these studies resulted in 10 publications and one thesis (Kristiina Kask).

11) *Regulation of transport, development and implantation of the human pre-embryo*

Functional Fallopian tubes and endometrium is essential for human reproduction.

The mechanisms behind active tubal transport in vivo and their correlation to fertility are still, to a large extent, unknown. Transport of the spermatozoa and later the pre-embryo is aided by muscular contractions in the wall of the Fallopian tube and by cilia in the tubal mucosa. The regulation of muscular activity is under the influence of adrenergic nerve, sex steroids oxytocin, nitric oxide and prostaglandins. However, the hormonal regulation of the muscular activity in the Fallopian tube has not been fully studied. Sex hormones and gonadotrophins are involved in regulation especially of reproductive organs. Their effect in the Fallopian tube has not been extensively studied. Growth hormone, thyroid stimulating hormone, thyroid- and parathyroid hormone and ghrelin is involved in regulation of metabolism in many tissues throughout the body. They might also be of importance for regulation of the Fallopian tube, endometrium and embryo. This has to my knowledge not earlier been extensively studied.

Sex steroids are also involved in the regulation of the ciliary activity in the Fallopian tube. This regulation is only partly investigated and further studies are needed to gain more knowledge.

The Fallopian tube is believed to be involved in development of the pre-embryo and its conditioning for later implantation in the endometrium. Very little is known about the interaction between the embryo and Fallopian tube. During In vitro-fertilization some pre-embryos will not be used for treatment of the couples. These embryos can be used for in-vitro studies of pre-embryo development and implantation. Selection of pre-embryos with the best implantation ability is based on morphological parameters. Follicular fluid might contain markers for embryo implantation and successful pregnancy and might in the future aid the selection of embryo for transfer to the patient.

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3. V. Bourlev, A. Larsson and M. Olovsson. (2006) Elevated levels of fibroblast growth factor-2 in serum from women with endometriosis. *Am J Obstet Gynecol.* Mar;194(3):755-9.
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European Union, 300 000 SEK

The Swedish Research Council 300 SEK

The Council for Working Life and Social Research 1 340 000 SEK

Dissertations

Kristina Kask

Obstetrical Research

Ove Axelsson

During 2008 Karin Stålberg presented her thesis “Prenatal Ultrasound and X-ray - Potentially Adverse Effects on the CNS”. The thesis consists of four different papers and uses epidemiological methods, including case control studies (two papers), a cohort study (one paper) and a randomised controlled trial (one paper). The following conclusions could be drawn: No overall increased risk for childhood brain tumours was found after prenatal abdominal x-ray exposure. The risk estimate was almost doubled, but not statistically significant, for primitive neuroectodermal tumors (PNET). Prenatal ultrasound exposure had no significant association with schizophrenia or other psychosis. Exposed men tended to have a higher incidence of schizophrenia but other factors might have influenced the results. Childhood brain tumors were not associated with prenatal ultrasound exposure. This holds true for all brain tumors as well as for separate subtypes. Trimester of exposure and number of ultrasound examinations had no impact on risks. Second trimester ultrasound scanning did not seem to affect school performance in teenagers. Boys exposed at anytime during pregnancy had a tendency towards lower schoolgrades in general.

Other projects aiming towards doctoral thesis are in good progress. Maria Jonsson will probably defend her thesis in 2009. She has presented interesting data on the use and misuse of oxytocin. Oxytocin is a potent drug that can cause fetal birth asphyxia through negligent stimulation of labour. It can also give maternal circulatory side effects when administered in connection with caesarean sections. Maria Jonsson has also identified risk factors for fetal metabolic acidosis at birth. One is misinterpretation of cardiotocographic (CTG) registrations during delivery.

Eva Bergman focuses on methods to improve antenatal identification of IUGR fetuses through self-estimation of the symphysis-fundus distance in combination with the concept “relative growth”. 2008 has been a year of collection of new data. The fruitful collaboration with statisticians from the University in Gothenburg continues.

Hashem Amini is involved in a project aiming at improving antenatal diagnosis of fetal anomalies with help of magnetic resonance imaging. He has also published data on false positive ultrasound diagnosis of fetal anomalies and investigated shortcomings of the Swedish Birth Defects Register concerning fetal anomalies.

Maria Palm has collected a biobank of blood and urine samples from women with uncomplicated pregnancies. She will study biological processes, such as oxidative stress, inflammation and angiogenesis, during normal pregnancy.

A new research fellow, Johanna Belachew, will continue our previous efforts to improve diagnosis of placental remnants with ultrasound in the postpartum period. This time 3-D ultrasound will be used.

Associate professor Ulf Hanson has begun a multi-centre randomized trial on treatment of gestational diabetes.

Members of the group

Ove Axelsson	Professor
Ulf Hanson	Associate professor
Solveig Lindeberg	Associate professor
Helle Kieler	Associate professor
Eva Gerdin	Associate professor
Dan Hellberg	Associate professor
Staffan Nilsson	Visiting professor
Karin Eurenus	M.D, Ph.D
Peter Lindgren	M.D, Ph.D
Karin Zetterström	M.D, Ph.D
Ajlana Mulic-Lutvica	M.D, Ph.D
Karin Stålberg	M.D, Ph.D
Hashem Amini	Research fellow
Maria Jonsson	Research fellow
Maria Palm	Research fellow
Eva Bergman	Research fellow
Johanna Belachew	Research fellow

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Dissertations

Karin Ståhlberg

Agencies that support the work/Funding

The Swedish Council for Working Life and Social Research (FAS)	400.000 SEK
The Regional Research Foundation Uppsala-Örebro	1.000.000 SEK
The Uppsala County Research Foundation	100.000 SEK
Other foundations	500.000 SEK

Gynecological Endocrinology

Tord Naessen

I: HRT and effects on postural balance function: *'Non-vertebral 'Osteoporotic' fractures - a Brain disease or a Bone disease?'* was the title of a leader accompanying our article in 'Menopause' 2007.

We study effects of endogenous and exogenous sex hormones on bone mass and fracture risk. Over 50% of all fractures have normal DEXA. Our results indicate that menopausal hormone replacement therapy (HRT) positively affect the brain and improve postural balance function.

Significance: If HRT can affect the brain and improve postural balance this might explain the rapid dynamic between HRT exposure and reduced fracture risk, the paradoxically stronger reduction in hip fracture risk when HRT is initiated soon, compared with late, after menopause and might also explain that it seems hard to show substantial effects on hip fracture risk after treatment with bisphosphonates.

II. Effects of endogenous and exogenous sex steroids on the artery wall, prevalent cardiovascular disease (CVD), prediction of CVD / death evens in women and men and effects on breast tissue.

We evaluate the significance of subtle differences in sex hormone levels (within the 'normal ranges') with regard to prevalent CVD and coming risk of CVD and death in elderly women and men. Endogenous hormone levels are analyzed in 1016 samples from a population-based study, the PIVUS study. We also study hormonal effects on human breast tissue.

Effects of ultra-low estrogen dose therapy in elderly women

To our knowledge we were the first group to report systemic effects of real 'ultra-low' doses (7.5µg/24h) of estrogen with systemic effects on bone markers, bone mass and serum lipid levels.

In early 2009, we will start a RPC-study on low-dose hormone replacement therapy, initiated soon after menopause, with regard to effects on the artery wall composition (arterial ageing).

Significance: There is a need to better understand effects of HRT with regard to age at start of therapy, especially effects of HRT when started soon after menopause, i.e. at ages when HRT is mostly needed and prescribed for treatment of climacteric symptoms.

III: We propose a new principle for non-invasive ultrasound assessment of the artery wall with regard to arterial aging and screening for cardiovascular disease (CVD).

With increasing age and development of atherosclerosis the dimension of the artery wall intima layer increases whereas that of the media layer decreases. Thus, differential directions of changes in these two artery wall layers will reduce the usefulness of the present 'Gold-standard' for non-invasive assessment of the artery wall the Carotid IMT assessing the intima+media complex. We therefore use and propose a new principle for assessment of the artery wall; separate assessment of the artery intima and media layers and the use of the Intima/Media thickness ratio.

We currently evaluate the strength of the method to predict incidence of CVD events and death, within the PIVUS-75 study. Up to date we have investigated over 640 subjects of estimated 750.

The method/principle is also used in evaluations of effects on the artery system in women with SLE, young subjects with previous history of major depression and in studies on pre-eclampsia in pregnancy.

Significance: We consider the principle superior to present 'gold-standard', (Carotid-IMT) with regard to prevalent CVD, tentatively also for prediction of CVD events and for monitoring effects of interventions against atherosclerosis/CVD.

IV: Long term estrogen therapy and preservation of brain tissue and function.

We study effects of long-term estrogen therapy on mental function, total and relative brain volumes (esp. hippocampal region) with MRI. By using Positron Emission Tomography (PET), we study whether HRT can preserve the local estrogen synthesis in the brain (aromatase enzyme function) and reduce the normal age-related increase in amyloid deposits (PIB).

Significance: If HRT, initiated soon after menopause, can preserve cognitive function, brain tissue, local estrogen production and reduce the normal age-related increase in amyloid deposits (PIB) this could generate ideas for preventive strategies against some forms of age-related cognitive decline / dementia.

V: Premenstrual syndrome (PMS or PMDD).

The normal variations sex steroids during the menstrual cycle give in some women a negative effect on mood and temper, especially in the form of increased irritability and depressed mood (PMS). We study differences in the brain sensitivity to changes in sex hormone levels in women with and without a diagnosis of PMDD (PMS). The methods used include studies with Positron Emission Tomography (PET).

Significance: to better understand the relation between hormones and symptoms in PMS, a disorder affecting many women with consequences for the individual, her family- and professional life.

VI: Basic regulation of the menstrual cycle and the dysregulation in PCOS

We investigate follicular fluid (FF) from women w and w/o a diagnosis of PCOS and after ovarian stimulation regimens during IVF. We assess and compare concentrations of FF hormones and the product/precursor ratios (illustrating specific enzyme activities). Methods used include Liquid Chromatography Tandem Mass Spectrometry (LS-MS/MS).

Significance: the results are expected to have implications for a better understanding of anovulation in e.g. PCOS and for improvement of the success rate in IVF.

Members of the group

Tord Naessen	Associate Professor, Senior Univ. Lecturer
Olle Eriksson	MD, PhD
Dmitrijus Kirilovas	MD, PhD
Kenny Rodriguez	MD, PhD
Gunilla Hallberg	Research student
Tansim Akhter	Research student
Jona Kristiansdottir	Postgraduate student
Marita Larsson	Research Nurse

Agencies that support the work

- The Medical Faculty, Uppsala University,, the Amersham Foundation: - 280.000:-
- 'Hjärt- och Lungsjukas Förening': 100,000:-
- Selander's Foundation: 100,000:-

• **Important research accomplishments during recent years:**

- Development and validation of a non-invasive method for in vivo-assessment of the aromatase activity (active aromatase) in gynecological endocrinology with regard to the ovary and the brain, using PET-technology.
- Currently applied in our investigations on effects of long-term postmenopausal hormone therapy on the aging process and a potential for preservation of the local production of estrogen in the brain.
- Treatment with exceptionally low-doses of estrogen at high age, seems to have substantial systemic effects; in our studies on bone marker, bone density and the serum lipid profile.
- This knowledge is part of the base for our current investigation regarding effects of endogenous levels of serum sex hormone levels and cardiovascular status and future risk of CVD.
- Later therapeutic interventions with ultra-low doses might be started.
- PMDD-PET
- Differences in in brain regional specific blood flow and ¹¹C-5HTP activity evaluated.
- That postmenopausal hormone therapy might reduce fracture risk, in part, via mechanisms other than bone mass, i.e. through the brain, by improving postural balance function.
- We have used assessment of postural balance function in two of our published articles, in one article to be submitted and in one currently being analyzed.
- *The last publication was accompanied by an Editorial in the journal 'Menopause'. 'Nonvertebral 'osteoporotic' fractures: a brain disease or a bone disease?'*
- Suggesting a new principle for non-invasive assessment of the carotid artery wall. This principle seems superior compared to the present 'Gold-standard', carotid-IMT.
- We have validated this principle and it has been applied in three of our published studies.
- Currently used in evaluation within the PIVUS and PIVUS-75 studies.
- Will be applied with regard to women with SLE, and pre-eclampsia and in long-term users of hormonal contraceptives.
- *Presentation of the principle was chosen as 'Late Breaking News' at the NAMS meeting in Nashville, TN, 2006.*

Original works (not abstracts) 2006 - 2008: Group Gynecological Endocrinology /Tord Naessen

Citation index: over #1350 citations since 1996.

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National Centre for Knowledge on Men's Violence Against Women

Research and Education

Introduction

The National Centre for Knowledge on Men's Violence Against Women (NCK) works by order of the Swedish Government with education, research, development, information and the compilation of research findings in the area. Women subjected to violence are treated at the centre's outpatient clinic at Uppsala University Hospital. The centre also supports women subjected to violence via a national hotline.

Scientific Reports

Violence against women in a medical perspective

Research leader: Gun Heimer

The research at the National Centre for Knowledge on Men's Violence Against Women is mainly concerned with violence against women in a medical perspective, with violence during pregnancy and rape as the principal areas of interest. The studies are concerned with physical, sexual and psychological violence alike. Violence against women is a serious problem in all parts of the world representing a grave threat against women's health and therefore also, regrettably, a growing future field of research.

Members of the group

Gun Heimer, Professor, MD, PhD
Kristina Stenson, CPM, PhD
Mariella Öberg, Postgraduate student
Steven Lucas, MD, PhD
Elisabeth Mattsson, CPM, PhD

Publications 2007–2008

1. Stenson, Kristina och Heimer, Gun: *Partner abuse experienced by female health staff: Relevance to awareness and action when meeting abused women patients*. Women's health issues December 2007.
2. Alander, Ture; Heimer, Gun; Svärdsudd, Kurt; Agréus, Lars: *Abuse in Women and Men with and without Functional Gastrointestinal Disorders*. Digestive Diseases Sciences 2007.
3. Heimer, Gun; Stenson, Kristina: *Vården har en nyckelroll I att avslöja våld och hjälpa kvinnor*. Läkartidningen 2008:7
4. Heimer, Gun; Stenson, Kristina: *Prevalence of experiences of partner violence among female health staff: relevance to awareness and action when meeting abused women patients*. Womens Health Issues March–April 2008

Undergraduate Teaching

The undergraduate courses at NCK, in cooperation with the Department of Women's and Children's Health, all have an interdisciplinary content including medical perspectives on men's violence against women. They are aimed both at students and at professionals in different fields of work where abused women are likely to be found, i.e. health professionals, social workers, policemen etc. During 2008 four different courses, each comprising 7,5 hp, were held. Apart from these courses, NCK held recurring lectures in the programmes for Nurses, Midwives and Physicians.

NCK also teaches about Men's Violence Against Women in the programmes at Uppsala university for the following professions:

- Lawyer
- Physiotherapist
- Police officer
- Psychologist

Awards and Appointments

1. Heimer, Gun: The Swedish Crime Victim Compensation and Support Authority's Teaching award. The award was given for that "*she in her teaching, with the help of her clinical experience, manages to visualise violence against women as a question of gender equality, of women's health and, not least, as a question of crime victims*".

Website

www.nck.uu.se

International Maternal and Reproductive Health

Birgitta Essén

Members of the group

Birgitta Essén	M.D., Associate Professor, Senior Lecturer
Beth Maina Ahlberg	Adjunct Professor
Gunilla Aneblom	RNM, Ph.D.
Anna Berglund	M.D., Ph.D.
Pauline Binder	Ph.D. student
Magdalena Bjerneld	Ph.D. student
Kim Dickson	Ph.D. student
Maria Ekstrand	Ph.D. student
Eva-Charlotte Ekström	Ph.D.
Elisabet Eriksson	Ph.D. student
Annida Esscher	Ph.D. student
Elisabeth Darj	M.D., Associate Professor
Martha Garrett	Ph.D.
Waheedul Hoque	Ph.D. student
Malin Jordal	Ph.D. student
Colomba Kokusiima Mbekenga	Ph.D. student
Margareta Larsson	RNM, Associate Professor, Senior Lecturer
Gunilla Lindmark	M.D., Professor emerita
Emma Lindström	Ph.D. student
Projesetine Muganyizi	Ph.D. student
Barni Nor	Ph.D. student
Viveca Odland	M.D., Adjunct Professor
Pia Olsson	RNM, Ph.D.
Andrea Pembe	Ph.D. student
Christine Rubertsson	RNM, Ph.D.
Mattias Rööst	Ph.D. student
Tanja Tydén	RNM, Professor
Karin Törnblom	Administrator

More than a third of the ill-health in women is related to their reproduction. Research must address both individual and structural factors contributing to these health problems, as well as the health interventions and programs that can be effective to alleviate the suffering, both in low- and high-income countries.

Maternal health care is a core component of health care. Studies address the quality of high-risk referrals in rural Tanzania and delivery care in Sri Lanka. Experiences of parents during the postpartum period are analyzed in Tanzania giving basis for improved support. In Bolivia and Rwanda, cases of severe maternal morbidity (near miss) are compared to cases of maternal death in order to identify mechanisms due to delays in deciding to seek medical help, for reaching obstetric facility and receiving adequate care.

Maternal and perinatal mortality in a migration perspective is another research topic. To explore public health issues in low-income countries and in what way these experience could be adopted among a migrant population in more high-income settings is a challenge. Not only medical factors, but socio-cultural factors and communication are thus explored. The research is linked to the Immigrant Well Woman Clinic, at the Department of Women's Health, Akademiska sjukhuset.

Maternal nutrition is essential for reproductive outcome. Studies in Bangladesh, Indonesia and South Africa focus on the effects of supplementation in pregnancy to increase birth-weight and protect against toxic effects of arsenic in water. A study in South Africa focuses on exclusive breastfeeding to improve child HIV-free survival.

Gender-based violence is a major health problem. The researchers at IMCH are collaborating with several universities for support to victims. In Nicaragua and Bangladesh the consequences for the newborn of violence during pregnancy are studied, in Tanzania attitudes to violence in all sectors of the community and the legal system. In Sweden, several projects focus on medical and socio-cultural factors related to honour violence, female genital cutting and surgery 'designer vaginas'.

STI and HIV are threats to young people when beginning their sexual life. IMCH studies behaviours and attitudes among adolescents in Uganda, Nicaragua, South Africa and Sweden as well as the access to contraception and abortions. The impact of information from the churches is studied in South Africa.

Public Health in Humanitarian Assistance is given attention at IMCH with research directed to experiences and training needs of health care workers.

Information seeking training is provided through the Inform program, a specialized program offered to collaborating partners.

The research is approached in an interdisciplinary way involving gynaecological and obstetrical issues, nursing, and epidemiology with public health aspects. These also include political, legal, social, and cultural aspects of medicine as well as theoretical frameworks in social anthropology.

Collaborating centres

Department of Public Health, Lund and Umeå University

University of Donetsk, Ukraine

University of Sri Jayawardenepura, Colombo, Sri Lanka

Aadhar Research Institute, Jaipur Rajasthan, India

ICDDR,b Dhaka, Bangladesh

Muhumbili University of Health and Allied Sciences (MUHAS) Dar-Es-Salaam, Tanzania

Makerere University, Kampala, Uganda

Malmö Högskola

National University of Rwanda (NUR)

Reproductive Health Research Unit, Johannesburg, South Africa

University Western Cape, South Africa
Medical Research Council, South Africa
Health Systems Trust, South Africa
University of Zambia
Centre Muraz, Burkina Faso
University of Leon, Nicaragua

Key words: maternal health care, maternal nutrition, gender based violence, migration, STD and HIV/AIDS, contraception, abortions, youth health, public health in humanitarian assistance, information seeking

Publications 2006-2008

2008

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2007

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Agencies that support the work

Swedish International Development Cooperation Agency (Sida)	3 130 000
Swedish Council for Working Life and Social Research (FAS)	904 000
EU	120 000
Livsmedelsverket	300 000
The Swedish Programme for ICT in Developing Regions (Spider)	380 000
Swedish South Asian Studies Network (SASNET)	150 000
International Network for the Availability of Scientific Publications (INASP)	404 500

Dissertations

Maria Ekstrand

International Child Health and Nutrition

Lars Åke Persson

The research programme International Child Health and Nutrition focuses on strategies for improved child survival, on interventions against child malnutrition and undernutrition, and on equity in child health and survival.

Global child survival chances have been considerably improved since the 1960s. However, during the last decade the improvement has slowed down. A persistent problem in many countries is a high neonatal mortality. This is addressed in a collaborative project in the entire Quang Ninh province in Vietnam, where a community-based cluster randomised trial is testing a facilitation approach for improved neonatal health and survival (the NeoKIP trial, Neonatal health Knowledge Into Practice, trial registration number ISRCTN44599712). A few of the baseline reports are already published and three PhD students are active in this project. Sida is the main funder of this project.

It is estimated that almost 15% of global under-five deaths could be prevented by exclusive breast feeding during the first six months of life. In a situation with high prevalence of HIV infection among pregnant women feeding options as well as an optimal provision of and use of health services remain a challenge. In a collaborative project in South Africa infant feeding is studied in the perspective of prevention of mother-to-child transmission of HIV (PMTCT). One PhD student defended his thesis along these research lines in 2008, and another one is starting up, financed by a Links grant from Swedish Research Council.

In an extensive prenatal intervention trial in Matlab, Bangladesh, effects of food and micronutrient supplements are investigated in a short- and long-term perspective. In this project, that has got the acronym MINIMat (Maternal and Infant Nutrition Interventions in Matlab, trial registration number ISRCTN16581394), effects are studied on infant mortality, foetal and child growth, micronutrient status, immune function, morbidity and psycho-motor development. Currently the cohort of children pass the age of 5 years and participate in a follow-up on body composition, blood pressure and metabolic markers in order to address research questions related to the DoHAD hypotheses (development origin of health and disease). The mothers are also being followed into the next pregnancy. We collaborate with, among others, the research institution ICDDR in Bangladesh, and research groups at London School of Hygiene and Tropical Medicine, Institute of Child Health, London, University of California at Davis and Cornell University in Ithaca, US. Data from the cohort are currently used by 4 PhD students at our department, and funding is provided from, among others, the Swedish Research Council and Sida.

Equity in child health and survival is focused in studies in Vietnam and Nicaragua, where trends in child survival are analysed and reasons to differentials in child health between population groups. The health consequences – also for children – of violence against women have been studied in Nicaragua and Bangladesh that was reflected in a PhD thesis in 2008. Health and living conditions of street children in Kenya are documented in another project. Grants have been provided by Sida for these studies.

We have contributed with epidemiological expertise in population-based studies on arsenic in tube wells in Bangladesh. Due to the newly discovered arsenic catastrophe in that country we took the initiative to epidemiological studies on health consequences of arsenic contamination of drinking water. The research activities are closely linked to mitigation activities for safe drinking water. We have provided evidence that prenatal arsenic exposure is associated with morbidity and mortality of the offspring in infancy. We collaborate with ICDDR, Bangladesh and with the department of Metals and Health, Karolinska Institutet. Two PhD students work on these issues.

We are coordinating a research network of Swedish researchers and their international collaborating partners, who focus research on global child health issues – especially research on knowledge implementation into practice for improved survival. The network has the acronym RICH (Research on Improved Child Health). More on the website of the network <http://www.richnetwork.se/>.

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Agencies that support the work/Funding

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Paediatric Endocrinology

Jan Gustafsson

Growth and metabolism during fetal life, infancy and childhood

During fetal life glucose is the most important nutrient. Following birth the newborn must produce its own glucose particularly for the brain. Part of our research is directed on mechanisms behind glucose production and lipolysis during pregnancy and in the newborn infant. Both infants born small and large for gestational age are at risk to develop metabolic disease later in life. In our group metabolic studies are performed by use of stable isotope labelled compounds and gas chromatography-mass spectrometry. Recent results have pointed out a mechanism behind the increased fetal weights in women with overweight or adiposity. A methodology combining microdialysis and stable isotope technique has been developed and is presently used for studies of glucose metabolism in the brain. In a collaborative project with the university of Cambridge energy substrate production in pregnancy and birth outcomes are studied in women with different degrees of insulin sensitivity.

By use of Swedish registers research concerning growth and intellectual performance in subjects born preterm are ongoing. In a longitudinal study visual function in infants born very preterm (<32 w) are studied. The recruitment of a 3 years cohort has been completed and results of follow up at 2 and 4 months corrected age on visual motor function have been evaluated. Prematurity is associated with several medical problems, one of which is retinopathy. This is also studied in a national collaborative project.

Two long term projects related to growth hormone therapy have been finished and published during the last year, one on the effect of growth hormone on statural growth in healthy short children and the other on the effect of individualized growth hormone dosing.

Since several years our group studies endocrine disease in Down syndrome (DS). In a recent investigation neonatal thyroid function in DS individuals has been studied and work on long term effects of early growth hormone treatment is ongoing.

Neonatal and childhood care and nutrition

Two thesis projects related to neonatal care and nutrition are ongoing. The effect of kangaroo care on immature newborn infants is studied as well as motor performance in very preterm infants before and after implementation of the Newborn Individualized Developmental Care and Assessment Program. Further, a study on effects of feeding regimens on catch-up growth in premature and full-term infants born small for gestational age have been finished during the last year.

Adequate nutrition is crucial for growth and development. Thus, eating disorders influence development. In collaboration with the department of Child Psychiatry a project on endocrine, metabolic and somatic consequences of anorexia nervosa is ongoing since several years. Among the studies performed so far are investigations of anthropometrical predictors of anorexia nervosa, studies of energy substrate production and of the risk for cardiac disease. Weight loss at presentation and weight gain during treatment influences metabolism. The somatic restitution can be followed by measurements of growth and weight gain and by analyses of hormones and nutritional

factors.

Overweight and obesity during childhood is an increasing problem in society. In collaboration with the Pediatric Obesity Unit at the University Children's Hospital research on energy balance in children and adolescents with overweight/obesity is ongoing.

Virus infections and type 1 diabetes

In the research on relations between virus infections and type 1 diabetes focus has been on in vitro studies of isolated human pancreatic islet cells following infection with different strains of enteroviruses. Infections with these viruses activate genes which may start an autoimmune process.

Present lines of research within this project are related to the innate immune response in virus infected human pancreatic islets and picornavirus infection at onset of type 1 diabetes. The question whether celiac disease may precede the development of type 1 diabetes is another line of research within the project.

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Dissertations

Fredrik Ahlsson presented his thesis "Born large for gestational age – epidemiological and metabolic studies".

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Paediatric Oncology

Susan Pfeifer

Leukemia – factors determining drug response (G. Lönnerholm, B-M. Frost, J. Palle)

We chair a study where all Nordic centres for pediatric oncology participate. Fresh bone marrow samples from children with newly diagnosed leukemia are sent by courier to Uppsala for test of *in vitro* sensitivity against a panel of clinically important anti-cancer drugs. Our results show that drug sensitivity at diagnosis can predict treatment failure in subsets of patients with ALL. Patients with well-defined genetic aberrations show characteristic patterns in drug sensitivity profiles. We collaborate closely with groups at Dept of Clinical Pharmacology (*in vitro* sensitivity test, gene expression profiling), Dept of Medical Sciences (genome wide analysis for identification of functional polymorphisms that affect drug response in acute leukemia) and Dept of Genetics and Pathology (sub-microscopic mutations in childhood acute leukemia).

Funding: Lions 100.000, ALF 200.000, Childhood Cancer Foundation 200.000 SEK.

Late effects after bone marrow transplantation (P. Frisk, J.Arvidson)

An increasing number of patients with hematologic malignancies are treated with bone marrow transplantation (BMT). The patients receive high doses of chemotherapy and often total body irradiation to eradicate their own bone marrow. This intensive treatment may cause a plethora of late effects, including cardiovascular complications. The therapy-related 'direct' cardiotoxicity has long been acknowledged. Recent data suggest that subjects who have undergone BMT may also be highly susceptible to development of the so called metabolic syndrome, which includes obesity, insulin resistance, hyperlipidemia, and hypertension, which may 'indirectly' lead to late cardiovascular morbidity.

We are currently investigating cardiac and metabolic status in a number of patients who underwent BMT more than 10 years ago and in an equal number of healthy controls.

In addition, these same patients will be offered a questionnaire regarding HRQoL and sexual functioning, and these data will be compared with data from a large cohort of survivors from childhood cancer.

Funding: Lions 100.000 SEK, Childhood Cancer Foundation, 75.000 SEK

Comparison of different regimens concerning intrathecal prophylaxis in children after allogeneic hematopoietic stem cell transplantation (Arvidson J, Frost B-M Uppsala in cooperation with Rubin J, Gustafsson B et al, Karolinska University Hospital – Huddinge).

In a pilot study we compared outcome regarding CNS relapse of leukemia after bone marrow transplantation with or without post-SCT intrathecal therapy. We now follow up with a larger study, including many more patients from different centra, with the same endpoints.

Procedural pain and psychosocial issues in children and adolescents with cancer (G. Ljungman, L Hedén Uppsala)

The effects of midazolam, morphine, paracetamol and ibuprofen are examined in four separate double blind RCTs in parallel groups with intervention vs placebo. 50 children are included in each of the 4 different studies. Children, parents, and nurses will report children's anxiety, distress, and pain on VAS.

Co-workers: Professor Louise von Essen, Dept of Public Health and Caring Sciences Uppsala University. Lena Högborg, RN, PhD student, Dept of Women's and Children's Health, Uppsala University.

Funding: The project started in 2005 and is since then funded by the Swedish Children's Cancer Foundation and the Swedish Cancer foundation. Total funding MSEK 2.8; 0,7 MSEK for 2008.

In addition to being a part of the Pediatric Oncology research group at the Department of Women's and Children's Health, Uppsala University, Gustaf Ljungman takes part in, and shares leadership of, the research group Psychosocial Oncology headed by Professor Louise von Essen. The title of the main projects are: 1 Cancer during adolescence. Psychosocial and health economic consequences and 2 Occurrence, development, and treatment of posttraumatic stress disorder among parents of children with cancer.

Funding: Lions 100.000 SEK

Functional and genetic aspects of neuroblastoma (F. Hedborg)

1. Our main line of investigation deals with biological effects of hypoxia on neuroblastoma cells. By use of expression array analyses, xenograft models, hypoxic cell culture and verifying experiments on clinical tumors we have gained qualitatively new knowledge on neuroblastoma biology. Publications are under way and some of the data were presented at the biannual international conference on Neuroblastoma held in Chiba, Japan in May, 2008.
2. In a collaborative work with Teresita Diaz de Ståhl and Jan Dumanski at the Dept of Genetics and Pathology, Rudbecklaboratoriet the genetics of neuroblastoma is studied by whole genome CGH array technology. Data is still in the making. Preliminary results suggest a novel model for age-dependent differences in tumor genetics.
3. Two cases of neuroblastoma, with highly unusual tumor biology of principal interest, were presented at the international neuroblastoma meeting in Japan 2008.
4. Animal experiments have been performed to test the hypoxia-dependence of targeting neuroblastoma with meta-Iodo-benzoguanidin (mIBG)

Collaborators: Krister Karlsson, Cihan Cetikaya, PhD, Teresita Diaz de Ståhl.

Funding: 300.000:- from the Swedish Children's Cancer Foundation

Molecular characterization of pediatric brain tumors and their stem cells (Susan Pfeifer)

Pediatric CNS tumors are the leading cause of death due to disease in children 1-15 years. A prerequisite for the development of targeting therapies and improved survival is knowledge of the biology of pediatric tumors, still poorly understood. Tumor specific genetic changes and changes in gene regulation in pediatric CNS tumors are studied in collaboration with Dept of Genetics and Pathology, Uppsala University. Using a clone-based array covering about 99% of the human genome, we have identified tumor

specific chromosomal alterations, few of them novel and others previously known, that may be related to tumor initiation/progression. We are further characterizing gene regulation in tumorigenesis, by applying innovative assays that utilize massively parallel ultrahigh-throughput DNA sequencing. In a collaborative effort between the Karolinska Institute, and the Universities of Uppsala and Lund, we have recently started a project aiming at increasing our knowledge of pediatric brain tumor stem cells and their role in uncontrolled cell growth. Our ultimate goal is to use this knowledge to design new experimental treatments.

Collaborators: Teresita Diaz de Ståhl, Jan Dumanski, Pelle Nilsson, Karin Forsberg-Nilsson, Uppsala University; Monica Nister, Urban Lendahl, Jonas Muhr, Johan Holmberg, Mikael Lindström, Stefan Holm, Bengt Gustafsson, Karolinska Institute; Peter Siesjö, Xialong Fan, Lunds University.

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Paediatric Neurology

Gunnar Ahlsten

The research of the Paediatric Neurology research group deals with clinical neurological diseases and neurological dysfunctions. The researchers come from many different professions and their research comprise a wide range of scientific questions.

Epilepsy

There are several ongoing studies. One study deals with a specific form of childhood epilepsy “Rolandic epilepsy” where especially the metabolism of the hippocampus of the brain is studied with Magnetic resonance. The hippocampus and anatomical variations in its anatomy and how this has any importance for the development of epilepsy is the subject of another study.

Other studies (in collaboration with international centers) deals with the genetic background of Rolandic epilepsy and childhood absence epilepsy, There is also an ongoing follow-up study of children previously treated for epilepsy.

Spina bifida

Research on this group of children has been carried out for at least 15 years. Different medical factors especially the Chiari II-malformation has been in focus in follow-up studies.

The global function of these children and adults is studied and its implications for what type and extent of support these individuals need at different ages has generated valuable new knowledge. A new study deals with children with spinal malformations who have an intact skin above the lesion.

Follow-up studies of prematurely born infants

Together with the Departments of Psychology, Ophtalmology, Neuroscience and Neonatology a longitudinal study of the development of visual perception in infants born before 32 weeks of gestation and its relation to periventricular leucomalacia or other perinatal brain damage has been going on for 3 years. 100 children is included so far. The study will provide much new information in this field.

Another study is a national prospective study on neurological, ophtalmological and psychological development of infants born after less than 27 weeks of gestation. The children will be examined at the age of 2 ½ years. The results of the study may have great importance for future perinatal care.

Mechanisms for brain injury in high-risk newborn infants and methods for early prediction of outcome

Newborn infants needing intensive care treatment constitute a high-risk group for perinatal brain injury and later handicaps. The mechanisms are only partly understood; major factors include hypoxia-ischemia, infection/inflammation, suboptimal nutrition and pain/distress. The acute symptoms are often vague; a majority of neonatal seizures are entirely subclinical.

This project investigates mechanisms for brain injury, and methods for early prediction of outcome in high-risk newborns. The overall aim is to identify infants who could benefit from early interventions in order to limit or reduce brain injury. The used

methods are mainly neurophysiological (EEG and continuous EEG-monitoring with amplitude-integrated EEG, aEEG), an epidemiological.

Evaluation of motor function

Different studies with different techniques are used to study children with cerebral palsy and spina bifida regarding balance, posture and muscle tone. Other research deals with energy consumption in different movement disorders.

The development of the motion analysis laboratory of the University Hospital is an important resource for some of these studies.

Arthrogyphosis multiplex congenita

An ongoing doctoral thesis project deals with this diagnose. In this condition the newborn child have multiple congenital joint contractures. After a national collection of cases the aim is to study underlying causative factors, describe the development of the children and evaluate the treatment that has been used.

Members of the group

Alhsten Gunnar	Associate professor
Bratteby-Tollerz, Linda	Magister
Dahl, Margareta	Associate professor
Eeg-Olofsson Orvar	Associate professor
Ehrstedt Christoffer	Research student
Hellström-Westas Lena	Associate professor
Höglund Anette	Magister
Jämtå Lena	Postgraduate student
Khalifa Najah	Ph.D
Kimber Eva	Postgraduate student
Kristiansen Ingela	Research student
Larsson Katrin	Research student
Laurell Katarina	Ph.D
Lidström Helene	Postgraduate student
Lidström Åsa	Magister
Lundberg Staffan	Ph.D
Norrlin Simone	Ph.D
Strömberg Bo	Associate professor
Tjäder Cecilia	Medical doctor
Wester Ulrika	Medical doctor
Ölund A-C	Medical doctor

Agencies that support the work:

ALF, Regional research council, Norrbacka-Eugenia foundation and other funds.

List of publications 2006-2008

Original papers

1/ [Chioza B](#), [Everett K](#), [Aschauer H](#), [Brouwer O](#), [Callenbach P](#), [Covanis A](#), [Dulac O](#), [Durner M](#), [Eeg-Olofsson O](#), [Feucht M](#), [Friis M](#), [Heils A](#), [Kjeldsen M](#), [Larsson K](#), [Lehesjoki AE](#), [Nabbout R](#), [Olsson I](#), [Sander T](#), [Siren A](#), [Robinson R](#), [Rees M](#), [Gardiner RM](#). Evaluation of *CACNA 1 H* in European patients with childhood absence epilepsy. *Epilepsy Res* 2006; 69:177-81.

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2/ Eeg-Olofsson O, Edebol Eeg-Olofsson K. The Electroencephalogram in Normal Neonates and Children. In: *Paediatric Clinical Neurophysiology*, K Edebol Eeg-Olofsson, ed. Mac Keith Press, London, 2006, pp 150-74.

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11/ Lidström H, Borgestig M. Assistive technology devices in computer activities. In: *Eliasson A, Burtner P eds. Improving hand function in cerebral palsy*. London: Mac Keith Press, 2008.

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Perinatal, Neonatal and Paediatric Cardiology

Anders Jonzon

Projects

1. Clinical studies concerning inflammatory substances and their migration in neonatal lung tissue.

Inflammatory reactions are involved in the development of bronchopulmonary disease in prematurely born infants. The studies hope to clarify what kind of white cells that are involved and which substances they respond to. The results might give possibilities to limit the harmful effects on lung tissue.

Researchers:

Richard Sindelar, MD PhD, Uppsala,
Maria Stålhammar PhD, Uppsala,
Lena Douhan Håkansson, MD, PhD, Uppsala
Cecilia Ewald, specialist nurse
Anders Jonzon, MD PhD, Uppsala

2. Studies of ventilatory support in small children

Ventilatory support in prematurely born children is a cornerstone in neonatal care. Barotaruma is thought to be a major contributor to lung damage. Intermittent ventilation, various patient-triggered modes and resistive and elastic unloading are investigated. The effects on airway pressure, patient response in various aspects are measured. In addition measurements are made concerning pulmonary vascular flow and water content.

Researchers:

Linda Wallström, MD, Uppsala
Josanne Munsters, MD, Nijmegen
Karl Wilhelm Olsson, MK, Uppsala
Richard Sindelar, MD PhD, Uppsala
Anders Jonzon, MD PhD, Uppsala
Johan Ågren, MD PhD,
Torgny Norsted, MD PhD,
Onnen Mörer, MD, Göttingen
Göran Hedenstierna, prof, Uppsala

3. Exchange of heat between child and mother during skin-to skin care.

Prematurely born children lose great amount of water and heat from the skin. Investigations are made to measure the losses during skin-to-skin treatment and consequent needs to compensate fluid losses. Better understanding of this form of care may diminish the need for incubator care and further enhance parental involvement.

Researchers:

Johan Ågren, MD PhD,
Ann-Britt Heinemann, specialist nurse
Jenny Puranen, MK
Kerstin Hedberg Nyqvist, specialist nurse, PhD

4. Fluid balance at different infusion rates in extremely premature infants.

There is little knowledge concerning amounts of fluids needed to best support the smallest population of prematurely born infants. Studies are made both retrospectively and prospectively.

Researchers:

Johan Ågren, MD PhD,
Dimitrios Kritikos, MD

5. Markers for development of lungdisease and pulmonary hypertension in extremely prematurely born infants.

In order to prevent pulmonary hypertension, a potentially serious condition, we are investigating possible preventive measures to preclude increases in pulmonary vascular resistance.

Researchers:

Erik Norman, MD, PhD
Johan Ågren, MD, PhD
Uwe Ewald, MD, PhD professor,
Anders Jonzon, MD, PhD
Dimitrios Kritikos, MD

6. Investigations on cardiac rhythm in small children

a. Congenital heart block is a disease mostly connected to maternal rheumatic disease. We are collecting blood specimens from all patients in Sweden, their parents and siblings in order to find markers where the risk for a fetus to establish heart block is high. We are also trying to find if there are specific genotypes that are more sensitive to an attack of maternal antibodies.

Researchers:

Marie Wahren-Herlenius, MD, PhD, professor, Stockholm
Stina Salomonsson, PhD, Stockholm
Sven-Erik Sonesson, MD, PhD, Stockholm
Håkan Eliasson, MD, Stockholm
Annika Öhman, MD, Uppsala
Anders Jonzon, MD, PhD, Uppsala

b. Clinical application of mobile-phone transmission of EKG in diagnosing heart rhythm disturbances in children. Effects of antiarrhythmic drugs on heart rhythm variability in small children.

Elinor Bärnevåg, bio-med.tech, Uppsala
Annika Öhman, MD, Uppsala
Anders Jonzon, MD PhD, Uppsala

7. Quality of life in children and young adults in need of ventilatory support. We are particularly interested in the use of phrenic nerve stimulation as a way to mimic spontaneous respiration.

Researchers:

Richard Sindelar, MD PhD, Uppsala

Anders Jonzon, MD PhD, Uppsala

Gunnar Sedin, MD, PhD, prof.

8. Follow up studies concerning motor development, speech development in infants born to early.

Researchers:

Kristina Persson, physiother. PhD

Margareta Jennische, PhD

Gunnar Sedin, MD, PhD, prof.

Publications 2006-2008

2006

Full Papers

Sindelar R, Jonzon A, Schulze A and Sedin G. Surfactant replacement partially restores the activity of pulmonary stretch receptors in surfactant-depleted cats. J Appl Physiol 100:594-601, 2006.

Sindelar R, Rieger-Fackeldey E, Jonzon A, Schaller P, Schulze A and Sedin G. Maintained inspiratory activity during proportional assist ventilation in surfactant-depleted cats early after surfactant instillation: phrenic nerve and pulmonary stretch receptor activity. Respir Res 7:38, 2006.

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Farooqi A, Hägglöf B, Sedin G, Gothefors L and Serenius F. Growth in 10- to 12- year-old children born at 23-25 weeks of gestation in the 1990s: A Swedish national prospective follow-up study. Pediatr 118(5),1452-1465. 2006.

Farooqi A, Hägglöf B, Sedin G, Gothefors L and Serenius F. Chronic conditions, functional limitations and special health care needs in 10- to 12-year-old children born at 23-25 weeks of gestation in the 1990s: A Swedish national prospective follow-up study. Pediatr 118(5),1466-1477, 2006.

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Jonzon A. Arytmier hos barn. Barnbladet nr 3, 2006.

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Sedin G. Physical Environment: The thermal environment. In Neonatal-Perinatal Medicine, 8th Edition. Chapter 29, part 1, p 585-597. Eds AA Fanaroff, RJ Martin. Mosby Inc, Philadelphia, 2006.

2007

Full Papers

Farooqi A, Hägglöf B, Sedin G, Gothefors L and Serenius S. Mental Health and social competencies in 10- to 12-year-old children born at 23-25 weeks' gestation in the 1990s: A Swedish national prospective follow-up study. Pediatr 120(1),118-133, 2007.

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Hemgren E and Persson K. Associations of motor co-ordination and attention with motor-perceptual development in 3-year-old preterm and full-term children who needed neonatal intensive care. Child Care Health Dev 33(1):11-21, 2007.

2008

Full Papers

Rieger-Fackeldey, E., Sindelar, R., Sedin,G., Jonzon, A. Bronchopulmonary C-fibers modulate the breathing pattern in surfactant-depleted juvenile cats. Respir Physiol Neurobiol 160, 341-349, 2008.

Matsson, H., Eason, J., Bookwalter, CS., Klar, J., Gustavsson, P.,Sunnegardh. J., Enell, H., Jonzon, A., Vikkula, M., Gutierrez, I., Granados Riveron, J., Pope, M., Bu'Lock, F., Cox, J., Robinson, TE., Song, F., David Brook, J., Marston, S., Trybus, KM., Dahl, N. Alpha-cardiac actin mutations produce atrial septal defects. Hum Mol Genet 17, 256-265, 2008.

Hemgren, E and Persson K. Deficits in motor co-ordination and attention at 3 years of age predict motor deviations in 6.5-year-old children who needed neonatal intensive care. Child Care Health Dev 35(1):120-129, 2008.

Book Chapters

Sedin G and Ågren J. Kuvösvård. Nyföddhetsboken, Studentlitteratur, eds H Lagercrantz, Lena Hellström-Westas, M Norman, 2008.

Ågren J and Sedin G. Vätskebalans. Nyföddhetsboken, Studentlitteratur, eds H Lagercrantz, Lena Hellström-Westas, M Norman, 2008.

Agencies that support the work

Anders Jonzon	Hjärt- Lungfonden	400.000 SEK
Anders Jonzon	Stiftelsen Samariten	100.000 SEK
Richard Sindelar	Externa Medel	185.000 SEK
Richard Sindelar	Externa Medel	100.000 SEK

General Paediatric

Lennart Nordvall

The "General Paediatric Research Group" is a heterogeneous group made up of one entity with focus on Paediatric inflammatory diseases and in addition to that other general paediatric research areas i.e Paediatric pulmonary diseases with focus on cystic fibrosis and other pulmonary diseases, Paediatric nephrology and Neonatal infectious diseases. Another very research active entity within the group is the Child Public Health Unit with focus on child health care and preventive medicine.

Centre for Paediatric inflammation research

A "Centre for Paediatric Inflammation Research" has been established within the research group. Research focus is put on improved clinical phenotyping of childhood inflammatory diseases and improved characterization of inflammatory characteristics of diseases in collaboration between clinical and preclinical scientists. The purpose of these efforts is to be able to improve diagnosis and to tailor and optimize anti-inflammatory treatment in patients. Minimally-invasive sampling methods suitable for use in paediatric patients are being developed. A large Vinnova grant has been received for the purpose. Participants in the center are Professor Kjell Alving, PhD, Professor Lennart Nordvall, MD, PhD, Dr Tony Hansson, PhD, Dr Lillemor Berntson, MD, PhD, Dr Ingrid Dahlbom, PhD, Dr Andrei Malinovschi, MD, PhD, Ms Britt-Inger Nyberg, BSc, Ms Pia Kalm-Stephens, BSc

Airway inflammation

In asthma focus is put on airway inflammation by measuring exhaled nitric oxide, a surrogate marker of allergic inflammation. A research prototype NIOX Flex is being evaluated and enables monitoring of nitric oxide (NO) in various compartments of the airways (bronchi, alveoli) of which the therapeutic implication is to be able to tailor treatment. In patients with very low levels of NO emphasis is put on differential diagnosis in childhood asthma. Here focus is on differential diagnosis versus ciliary dysfunction and chronic infection. Further, studies of the importance of food allergy in asthma are under way.

Gastrointestinal inflammation

We are developing concepts for characterising individual patients with gastrointestinal inflammations based on disease specific antibodies and panels of inflammatory molecules. Our research main focus is on the possibilities to improve the use of disease related antibodies and inflammatory molecules for early diagnosis and non-invasive follow up of celiac disease and other symptom-sharing gastrointestinal diseases. Furthermore, we are investigating the association between celiac disease and other chronic inflammatory diseases, and whether undiagnosed inflammation that disturbs the intestinal barrier may lead to the development of other diseases e.g. type 1 diabetes. Another area of interest is gastrointestinal inflammation in IgE and non-IgE mediated food allergies.

The research and development projects at the clinical section for gastroenterology and nutrition have focused on IBD, celiac disease and clinical nutrition.

A new collaborative project between the Dpt of Clin Genetics and Pathology (Prof. U Gyllensten, Assoc Prof. Alkwin Wanders) and the Dept of Woman and Child Health (Assoc Prof. Gun Frisk, Assoc Prof. Yigael Finkel) and CMM Karolinska Institutet, Assoc Prof. Jonas Fuxe aims to study the effects of enterotopic virus on tight junction proteins in the stomach and small and large intestine. This presumed effect could be a starting point for the inflammatory response in IBD. This project is timely in the context of present research frontiers in IBD.

A nationwide inventory of endoscopy resources for paediatric clinical and scientific purposes was carried out to be published in collaboration with colleagues from Great Britain.

Rheumatic inflammation

The pediatric rheumatology research during 2008 has involved four projects: The study of JIA (juvenile idiopathic arthritis) in the Nordic countries has continued. Different variables for disease activity has been part of the project. One important result is the paper on HLA-B27 and its influence on the clinical signs and symptoms in boys with JIA. Anders Öman has been introduced into the project during 2008 and data has been prepared for coming publications.

Anders Öman and Lillemor Berntson have continued a project with Sandra Kleinau (BMC) in which complement receptors in juvenile idiopathic arthritis are studied. Preliminary results are available but some more samples are needed to complete the study.

Collection of data in the regional, prospective, population based study in children with JIA and celiac disease has continued. The project is part of the regional collaboration in children with JIA and gives possibility for future research within the field.

The national registry for children with JIA, receiving biological drugs, is now prepared to be implemented.

Agencies that support the work

The Centre for paediatric inflammation research in collaboration with other groups at Uppsala University and three industrial partners recently received a SEK 20 milj.grant over four years from The Swedish Governmental Agency for Innovation Systems (VINNOVA Sambio 2007-00084) in collaboration with Phadia AB, Aerocrine AB and Alimenta Medical AB. One of the purposes of this grant is to strengthen collaboration between academic researchers and industry. Funding has also been received from the Gillbergska Foundation, Samverkansfonden, the Swedish Heart-Lung foundation 200 000 and Stiftelsen Astma- och Allergiförbundets forskningsfond. 300 0000.

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27. Fläring U, Finkel Y Nutrition in the Paediatric Intensive Care Unit Invited review for Paediatric Anesthesia accepted Dec 2008

Dissertations

- Ingrid Dahlbom. The significance of IgG antibodies against tissue transglutaminase in coeliac disease.
- Andrei Malinowski. Nitric oxide exchange in central and peripheral airways. Determinants in health and respiratory disease.

Paediatric neonatal infections

Two projects were finished by Erik Normann during a second and last year as a post-doc working at the University of Alberta, Edmonton, Canada. One project was about the importance of intra-uterine infections on the foetal lung and brain development. For this project a mouse model was developed. Also, the combined effect of antenatal inflammation and postnatal exposure to high levels of oxygen was studied. The second project was to develop a simple method for monocyte isolation from umbilical cord blood.

Normann E, Gnarpe J, Wettergren B, Janson C, Wickman M, Nordvall L. The association between Chlamydia pneumoniae antibodies and wheezing in young children and the influence of sex. *Thorax* 2006;61:1054-8.

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Pediatric Nephrology

During 2008 the nephrological research has been focussed on the paediatric urinary tract. Dr Nevés is Secretary General of the International Children's Continence Society (ICCS), the relevant global research organisation. In this position he has had a central role in organising the ICCS biennial conference in Boston, October 2008. He has also lectured in several locations nationally and internationally.

There are several ongoing research projects regarding therapy-resistant enuresis. Specific therapies that are under investigation are reboxetin and sleep modification via orthodontic procedures.

Dr Nevés is principal local investigator in the National Reflux Study – a randomised trial of antibiotic prophylaxis, endoscopic treatment and watchful waiting in children with dilated vesicoureteral reflux. Data collection has been concluded december 2008 and will be presented at an international conference in Gothenburg in 2009. Uppsala will participate in the evaluation of outcome vis-a-vis renal damage, urinary tract infections and the reflux *per se*.

Publications 2006-2008

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von Gontard A, Nevéus T (2006). Management of disorders of bladder and bowel control in childhood. 355 pages. London, Mac Keith Press.

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Nevéus T. Enuretic sleep: deep, disturbed or just wet? *Pediatr Nephrol*. 2008;23(8):1201-2.

Nevéus T. (Editorial) *J Urol*. 2008;180(3):1090.

Agencies that supported the work

2006 and 2007; approximately 200 000 SEK from Pfizer 2008; approximately 110 000 SEK from Ferring Pharmaceuticals.

Smaller funds and contributions.

Studies ongoing at the Uppsala CF center

Treatment study of Azitromax in patients with cystic fibrosis in the Nordic countries

Monitoring of energy and body composition in patients with cystic fibrosis through different methods

Monitoring of different factors in the immune system in patients with cystic fibrosis

Examining blood and mucosa samples from patients with cystic fibrosis and trying to find proteins to explain differences in disease severity, an EU study

Genotypes, phenotypes and colonization of *Pseudomonas aeruginosa* in patients with cystic fibrosis in all Nordic countries

Scandinavian nutritional multicenter study of cystic fibrosis patients in the Nordic countries

Screening of depression and life quality in patients with cystic fibrosis, a combined study in Europe and the US

Treatment study with specific immunoglobulin Y in patients with cystic fibrosis to try inhibiting growth of mucoid *Pseudomonas aeruginosa*

Published articles and book chapters from Uppsala CF center 2006 through 2008

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4. Nilsson E, Kollberg H, Johannesson M, Wejåker PE, Carlander D, Larsson A. More than 10 years' continuous oral treatment with specific immunoglobulin Y for the prevention of *Pseudomonas aeruginosa* infections: a case report. *J Med Food.* 2007 Jun;10(2):375-8
5. Vanthanouvong V, Kozlova I, Johannesson M, Nääs E, Nordvall SL, Dragomir A, Roomans GM. Composition of nasal airway surface liquid in cystic fibrosis and other airway diseases determined by X-ray microanalysis *Microsc Res Tech.* 2006 Apr;69(4):271-6
6. Roomans GM, Ivanovs A, Shebani EB, Johannesson M. Transmission electron microscopy in the diagnosis of primary ciliary dyskinesia. *Ups J Med Sci.* 2006;111(1):155-68.
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General Paediatrics - Child Public Health Unit

The Child Health Unit in Uppsala carries a strong tradition of preventive research and of developing methods for the child health surveillance services. Due to a major research grant the focus for 2008 has been parenting support. Comprising 14 studies the project aimed to survey available parenting supports as well as the needs of parents with children 0-18 years of age. The main results were that services for children 0-1,5 years are congruent with parents' needs, although there is a gender-bias in service provision and a need for more evidence-based methods and home-visits. Services during maternity need to fulfil the psychosocial needs of parents with more appointments and better parents' groups with room for interaction. Preschools and schools could be used as a platform for parenting support to a much greater extent than is done today, especially through providing discussion forums and expert advice for parents. Parents of teenagers need easily accessible and non-stigmatising support both for themselves and their teenagers. A trial of an evidence-based parenting programme – Triple P – has resulted in yet another major grant for 2009 for a randomised controlled study of the programme.

During 2002-2008, a controlled quasi-experimental intervention trial was performed in 36 child health centres within primary care in Uppsala county (experiment) and 36 centres in five other Swedish counties (control). The aim was to improve the psychosocial effectiveness of the preventive health services for preschool children aged 0-18 months. The intervention was expected to lead to better handling of postpartum depression, improved parent-child interaction and language development, closer social networks, and decreased stress in parents. Mothers of 1963 children participated in baseline and follow-up measurements. Apart from more parents being invited to parent groups and higher parental participation in parent groups, there were no obvious effects attributable to the intervention. However, important experiences were gained as to difficulties associated with implementing an intervention trial under routine conditions. The study was supported by the Swedish Council for Working Life and Social Research, the County Council of Uppsala, and Allmänna Barnhuset.

Publications 2006-2008

International peer-reviewed publications

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4. Stenhammar C., **Sarkadi A.**, Edlund B. The role of parents' educational background in lifestyle attitudes and practices for their 6-year-olds. *Public Health Nutrition* 2007; **2**:1-9
5. **Sarkadi A.**, Kristiansson R., Oberklaid F., and Bremberg, S. Fathers' involvement and children's developmental outcomes. A systematic review of longitudinal studies. *Acta Paediatrica Scandinavica* 2008; **97**(2):153-8.

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8. **Westerlund M, Lagerberg D.** Expressive vocabulary in 18-month-old children in relation to demographic factors, mother and child characteristics, communication style and shared reading. *Child Care Health Dev* 2008;34:257-266.
9. **Westerlund M, Berglund & Eriksson:** Can Severe Language Delayed 3-Year-Olds be identified at 18 Months? *Journal of Speech, Language and Hearing Research*, 2006; 49: 237-247.
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Reports

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National peer-reviewed publications

1. Runestam K, Sarkadi, A. Inget informerat samtycke inför rutinmässigt ultraljud heller. Debattinlägg. (No informed consent before routine ultrasound [in pregnancy] either. Debate article). *Läkartidningen* 2007; 104(39): 2823
2. **Westerlund M.** Språkscreening av 2,5-3-åringar identifierar även andra avvikelser. *Läkartidningen*, 2008: 105 (3); 132-134.

Agencies that supported the work

- 2008 National Institute of Public Health. 3.1 million SEK for preparing a background report to the Swedish government's special investigator on parenting support. *Parenting support in Sweden today: When, what, and how?*

Paediatric Surgery and Paediatric Urology

Rolf Christofferson

Docosahexaenoic acid oxidation in preterm infants

Angsten G

Abstract: Dietary supply of fatty acids in preterm infants has recently received considerable interest with focus on long chain polyunsaturated fatty acids (LCPUFA). Although LCPUFA can be endogenously synthesized from essential fatty acids, synthesis seems not to meet infantile requirements. Several studies have provided evidence that preterm infants without dietary supply of LCPUFA exhibit lower plasma concentrations of LCPUFA than infants receiving LCPUFA in amounts as contained in breast milk. Furthermore, improved visual and neurological development could be demonstrated in preterm infants receiving LCPUFA compared to infants not supplemented. To improve nutrition of preterm infants further it is important to obtain a more detailed – preferably quantitative – analysis of the LCPUFA metabolism. The project focuses on the n-3 LCPUFA docosahexaenoic acid (DHA), a metabolite of α -linolenic acid. Since DHA is an important component of the cell membrane, it is incorporated into the membranes of e.g. neural cells at high concentrations. Thus, the DHA requirement is assumed to be high during the period of rapid brain growth during the first months of life. In this project, breast fed preterm infants are given an oral dose of uniformly ^{13}C labelled DHA and the fractions of oxidized tracer are determined. The project will give new information on the LCPUFA metabolism and may contribute to development of formulas meeting preterm infantile requirements.

Long term outcome of renal and bladder function in children with myelomeningocele

Barker G, Läckgren G, Stenberg A

Abstract: Children with neural tube defects such as myelomeningocele (MMC), but also milder forms of craniospinal dysraphism, are at risk for neurogenic bladder dysfunction. Most of these children are born with normal renal function, but progression of bladder dysfunction without intervention will lead to upper tract deterioration due to obstruction or vesico-ureteral reflux and subsequent infections. Clean intermittent catheterization (CIC) every 3-4 hours was introduced in 1970-80 to provide low-pressure emptying of the bladder, thereby protecting the upper tracts. Today, CIC is usually introduced in newborns with MMC. The aim of this study is to retrospectively compare three groups of patients with MMC treated at our Department in terms of renal function, bladder function, presence of urinary tract calculi, frequency of follow-up, incidence of urinary tract infections, and the need for major reconstructive surgery. Also, the impact of MMC complications such as tethered cord will be audited.

The first group is children born 1970-1986. These children have been followed-up carefully, but will not have started CIC as babies. Their upper urinary tracts will have been monitored closely, and many of them have undergone major reconstructive surgery due to high-pressure, unstable bladders.

The second group is children born 1987-2000. These children will have started CIC at a much younger age, but will not have been followed-up at as regular intervals as group one, since CIC usually reduces upper tract deterioration. The older patients in this cohort may also have undergone major reconstructive surgery. The children in both

groups that have undergone major reconstructive surgery such as bladder augmentation, continent urinary diversion, and bladder neck plasty or artificial sphincters will be assessed for continence, condition of the upper urinary tracts and renal function.

The third group, children with MMC born since 2000, is looked at prospectively, since they have all undergone urodynamic assessment and started CIC as newborns. Many of these children will also have continuous night-time catheterization of the bladder, which might reduce bladder instability and reduce the need for major reconstructive surgery. With a longer follow-up, the outcome in terms of renal and bladder function, urinary tract calculi, upper tract condition and incidence of urinary tract infections can be compared to the other two cohorts.

Short bowel syndrome and bacterial translocation

Högberg N, Meurling S, Stenbäck A

Abstract: Short bowel syndrome (SBS) is a malignant condition with a high morbidity and mortality in infants and children. SBS is caused by congenital intestinal atresias or impaired intestinal circulation causing bowel gangrene such as necrotizing enterocolitis and volvulus, making extensive bowel resection necessary. In SBS, the absorption of fluid, salts, vitamins and minerals is impaired, the intestinal microbial flora is changed, and the intestinal immune system is compromised. The child is partly or totally dependent on parenteral nutrition, administered through an intravenous line. The composition of the parental nutrition in SBS is important to avoid malnutrition, impaired growth and development, secondary liver failure, and susceptibility to infections. Septicemia is a common, sometimes lethal, complication to SBS. Septicemia can be caused by bacterial translocation through the damaged bowel wall or through the intravenous line. In this project, we evaluate the outcome of children with SBS with regard to the length of remaining bowel, the fraction and composition of the parenteral nutrition, the incidence of septicemia and causative microbes, and its chemotherapeutic intervention. We are also investigating if microdialysis of ischemia markers in the premature intestine can indicate necrotizing enterocolitis before it is clinically evident and requires bowel resection. In order to dissect the processes of microbial overgrowth, subsequent translocation, and the host's response to it, we have developed an animal model for intestinal translocation. The project will give new information on the clinical management of SBS in infants and children.

Endoscopic treatment of vesicouretral reflux in children

Läckgren G, Sköldenberg E, Stenberg A

Abstract: Patients with vesicoureteral reflux (VUR) can be treated with antibiotic prophylaxis, open surgery, or by endoscopic treatment. Antibiotic prophylaxis is intended to avoid infections while waiting for VUR to resolve spontaneously. It involves daily medication, and breakthrough infections can occur with a risk for extended antibiotic resistance. Open surgery – i.e. ureteral reimplantation - offers a high cure rate (80-99%), but it is an extensive surgical procedure with a risk for complications such as obstruction of the ureterovesical junction. Also it entails a hospital stay, increasing the impact on the patient and associated costs.

Endoscopic injection offers cure rates similar to those of open surgery, and has the advantage of being a minimally invasive procedure. If parents are given information on all three approaches, the majority chose endoscopic treatment for their children. The safety and efficacy of the procedure is dependent on the injectable material chosen. The

ideal material would be biocompatible, easy to inject, non-migratory, durable, and provide high VUR response rates. Deflux® consists of dextranomer spheres (80–250 µm in diameter) in a gel of stabilized, non-animal hyaluronic acid. The properties of Deflux are well suited as an injectable material for VUR. It is biocompatible and has excellent tolerability and safety. The material does not migrate from the injection site. Also, both components are biodegradable over time, preventing long-term accumulation. Despite a certain degradation, a long-term durability of Deflux has been demonstrated. Deflux is the only substance approved by the FDA for treating children with VUR in the USA. The first large, long-term study of Deflux was performed by us and involved 221 children with VUR. 22% of patients required repeat endoscopic treatment. In total, 68% of children demonstrated a positive response (VUR grade I or less) at their last voiding cystourethrogram. The initial positive response was sustained: 96% of ureters free from VUR at 3–12 months post-treatment remained free from VUR grade >II until 2–5 years after treatment. Endoscopic treatment with Deflux was well tolerated with adverse events occurring in only 2% of patients.

Among children predisposed to urinary tract infection (UTI), VUR increases the risk that the infection will reach the upper urinary tract and cause renal scarring and impaired kidney function. The ultimate aim of VUR treatment is to reduce the risk of renal scarring, so the post-treatment incidence of febrile UTIs is an important consideration when choosing VUR therapy. Studies indicate that antibiotic prophylaxis has a 5-year incidence of febrile UTIs of 21–22%, and open surgery a 5-year incidence of 8–10%. We performed a questionnaire-based study to investigate long-term outcomes and the experiences of patients and their parents associated with Deflux treatment. Endoscopic treatment showed a 10-year incidence of febrile UTIs of only 3.4%. However, there is no requirement to differentiate children with complications such as VUR associated with double ureters, small kidneys or bladder dysfunction as treatment with Deflux is similarly effective in these patients.

Angiogenesis in childhood cancers

Azarbayjani F, Christofferson R, Fuchs D, Georgantzi K, Schiller P, Sköldenberg E

Abstract: The survival in childhood cancer has improved considerably the last 30 years, but still 25-50% of children with solid tumors die of their disease. The ultimate cause of death is usually metastatic disease. In order to grow and form metastases, a cancer must acquire the ability to induce new blood vessel formation, angiogenesis, and also new lymph vessels, lymphangiogenesis. The aims of this project are to explore the mechanisms of metastasis, to identify targets for restricting metastasis, and to challenge new therapies in relevant and reproducible animal models for metastatic childhood cancer. Cancer cells must enter, survive in, and then exit from the vascular or lymphatic system in order to establish metastases. Angiogenesis and lymphangiogenesis are cross-talking, complex processes involving endogenous stimulators, inhibitors, and their receptors. The signals are modulated by cancer cells, endothelial cells, macrophages, and the extracellular matrix. Vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) are two of several growth factors involved in angio- and lymphangiogenesis. Their importance in clinical cancer is without doubt, since administration of a VEGF-antibody (bevacizumab) in combination with chemotherapy prolongs survival in patients with metastatic colorectal cancer and non-small cell lung cancer, and so does a VEGF-/PDGF-receptor inhibitor (SU11248) in metastatic renal cancer. We use cell cultures, in vitro-cytotoxicity assays, orthotopic and heterotopic xenotransplantation of human cancer cells, mainly neuroblastoma cells, to immunodeficient mice, ultrasound with contrast-tuned imaging to quantify tumor

perfusion, small animal PET/CT, immunohistochemistry, FACS, stereological quantification of angiogenesis, and microarrays. Our project will dissect the biology and therapeutic intervention of metastasis in childhood cancers. New targets for restricting metastasis can be identified. New drugs, and new combinations of drugs and chemotherapy, will be evaluated with respect to their ability to inhibit angiogenesis, lymphangiogenesis, and metastatic spread and growth. The translational design of the project permits direct clinical applications. Angiogenesis inhibition has already become a valuable adjunct in adult cancer. Angiogenesis inhibition is likely to reduce late effects of chemotherapy and improve survival and quality of life in children with cancer.

Members of the group

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Kajsa Gustafsson,	M.D., resident
Niclas Högberg,	M.D., resident
Göran Läckgren,	Professor, M.D., Ph.D.
Staffan Meurling,	Professor, M.D., Ph.D.
Erik Sköldenberg,	M.D., Ph.D., resident
Arne Stenberg,	Surgeon-in-Chief, associate professor, M.D., Ph.D.
Anders Stenbäck,	M.D., Ph.D., resident

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