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## Content

Editorial Office.....	4
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### Abstract section

#### *Physiotherapy Programme*

<b>Hultgren E, Suchomel A</b> An Evaluation of Aerobic Capacity, Pain and Function in Patients Who Recently Diagnosed with Rheumatoid Arthritis.....	5
<b>Andersson J, Nilsson I</b> Low Back Pain in Women with Previous Back Pain during Pregnancy.....	6
<b>Lövgren A, Mohamud B</b> Patients Conceptions About the Causes of their Back/Neck Pain and What They Believe Can Ease Their Pain - An inquiry investigation among patients seeking physiotherapy in primary care.....	7
<b>Evers M, Hallengren S</b> Reference Values for Static, Clinical Balance Tests in Standing Position Among Healthy People, 65-85 Years of Age - A pilot study .....	8
<b>Axgren C, Maunsbach A</b> Intra- and Intertester Reliability of a Handheld Myometry for Measurement of Wrist Extension Strength.....	9

#### *Occupational Therapy Programme*

<b>Hellberg M, Åberg S</b> Content Validity of the Quality of Life Scale - Quality of life for persons with fibromyalgia .....	10
<b>Johansson I, Petersson I</b> Perception of Worker Role - A study of people with unipolar and bipolar disorders.....	11

#### *Social Care Programme*

<b>Tenghed S</b> Co-operation and Collaboration - How professionals experience cases of child abuse.....	12
<b>Andersson A-K, Granberg A</b> Children and Eating Disorders - A qualitative study about prevention and professional staff experience with eating disorders .....	13
<b>Hedbäck J, Lindström R</b> “Separate Worlds?” - Focus group interviews about school with girls in the 9 <sup>th</sup> form ...	14
<b>Gridiouchko N, Rundqvist M</b> Struggle on Behalf of a Different Child - A qualitative interview study of parents of children with Tourette’s syndrome.....	15
<b>Elofsson E, Renström H</b> Bullied as Children - A qualitative study of adults’ experiences of having been bullied as children .....	16

*Medical Biology Programme*

**Gunnerås M**

Expression and Modulation of CD28 on CD4-positive Peripheral Blood T-lymphocytes  
in Malignant Melanoma Cancer Patients and Normal Individuals ..... **17**

*Graduate School in Biomedicin*

**Thorn H**

Localisation of the Insulin Receptor to Caveolae of Adipocyte Plasma Membranes  
by Immunogold Labeling and Electron Microscopy..... **18**

*Medical Programme*

**Enebog J**

Chronic Pain and Discomfort Following the Mesh Plug Hernioplasty. - Results  
of a two year follow-up of a swedish material. .... **19**

**Serednitskaia G**

Effect of Oxidative Stress in Fanconi anemia Fibroblasts and Normal Fibroblasts ..... **20**

*PhD Thesis*

**Jenmalm M**

Development of IgG Subclass Antibodies to Allergens in Early Childhood ..... **21**

**Crafoord S**

Experimental Transplantation of Retinal and Iris Pigment Epithelial Cells into the  
Subretinal Space ..... **22**

**Shi-Mei Zhuang**

Molecular Genetic Alterations in Chemically-induced Lymphomas..... **23**

# Student Journal of Health Sciences

## Editorial office:

Correspondence concerning manuscripts and all editorial matters should be addressed to:

Student Journal of Health Sciences  
Faculty of Health Sciences  
Linköping University  
S-581 83 Linköping  
SWEDEN

e-post: shs@hul.liu.se  
telephone: +46 13 22 20 00

## Editorial Board:

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## **An Evaluation of Aerobic Capacity, Pain and Function in Patients Who Recently Diagnosed with Rheumatoid Arthritis**

Authors: **Hultgren E, Suchomel A**, Physiotherapy Programme, Faculty of Health Sciences, Linköpings Universitet, Sweden.

Tutor: Johansson K, RPT, PhD-student, Dept. of Medicine and Care, Faculty of Health Sciences, Linköpings Universitet, Sweden.

Physical inactivity due to pain means a risk for patients with rheumatoid arthritis (RA) even in the early course of the disease. Over time this can result in an impairment of aerobic capacity. The aim of the study was to increase the knowledge about aerobic capacity among patients recently diagnosed with RA and to see if there were any correlations between aerobic capacity, pain and function.

Thirty-seven patients (26 women and eleven men) from the clinic of Rheumatology at the University Hospital in Linköping were included in the study. Measurements were accomplished at one occasion during the period between January and August 1999. The following instruments and variables were used: Minor's submaximal treadmill test, visual analogue scale (VAS) for pain assessment, timed-stands test (TST), Health Assessment Questionnaire (HAQ), sex, age, disease duration, presence of rheumatoid factor (RF) and medication.

Ninety-five percent of all patients were found in the three lowest groups concerning aerobic capacity, totally seven groups. Those who had the lowest values of aerobic capacity were significantly younger. Women had lower aerobic capacity than men ( $p < 0.01$ ) and those with positive RF had lower aerobic capacity compared to those with negative RF ( $p < 0.05$ ). A significant correlation was found between VAS and HAQ ( $r = 0.68$   $p < 0.01$ ). Patients who estimated lower pain had better function according to HAQ.

The patients' low aerobic capacity may increase the risk for diseases caused by physical inactivity. Future recommendations need to emphasise the importance of increased physical activity.

Key words: treadmill test, visual analogue scale, timed-stands test, Health Assessment Questionnaire, joint disease

## **Low Back Pain in Women with Previous Back Pain during Pregnancy**

Authors: **Andersson J, Nilsson I**, Physiotherapy Programme, Faculty of Health Sciences, Linköpings Universitet Sweden.

Tutors: Kvist J RPT, PhD-student, Dept. of Neuroscience and Locomotion, Brynhildsen J MD, PhD, Hammar M MD, prof, Dept. of Health and Environment, Faculty of Health Sciences, Linköpings Universitet, Sweden.

A 12-year follow up of 52 women with severe low back pain during pregnancy (index group) and 25 women without low back pain showed that the index group still suffered more from low back pain at the 12-year follow up.

The aim of this study was to evaluate whether the index group still, 14 years later suffers from low back pain. We also wanted to investigate if the answers from pain provocation tests differed between the two groups and to see whether low back pain varies in the different phases during the menstrual cycle.

The women were asked about occupational conditions, current low back pain and went through an examination of the back consisting of pain provocation tests for the low back and sacroiliac joints. The women were also asked to register menstruation periods and the degree of low back pain in a diary during three months.

The result showed that the index group estimated their current low back pain significantly higher than the control group on VAS ( $p < 0,01$ ). No difference was found concerning the pain provocation tests. Furthermore, no difference in severity of low back pain was seen between the different phases of the menstrual cycle

Keywords: low back pain, pain provocation tests, menstrual cycle, sacro-iliac joint

## **Patients Conceptions About the Causes of their Back/Neck Pain and What They Believe Can Ease Their Pain - An inquiry investigation among patients seeking physiotherapy in primary care**

Authors: **Lövgren A, Mohamud B**, Physiotherapy Programme, Faculty of Health Sciences, Linköpings Universitet, Sweden.

Tutor: Skargren E RPT, PhD, Dept. of Neuroscience and Locomotion, Faculty of Health Sciences, Linköpings universitet, Sweden.

The aims of this study were to describe patient's beliefs about the causes of their back/neck pain and what they thought could ease their pain. The aim was further to investigate whether earlier experience of pain, duration of pain or location of pain could influence such beliefs.

Eighty patients who received physiotherapy treatment for the first or second time during the current episode answered a questionnaire. In the questionnaire, the patients' answered questions on background data, described the causes of their pain and the measures they would have taken.

Five different categories of causes and five different categories of measures were identified. The most common categories for the causes were work/ergonomics and biological factors followed by trauma, psychosocial factors and life style. The most common categories for the measures were physiotherapy and life style: own physical activity, followed by other life styles changes, changes in work/ergonomics and treatment by other professions than physiotherapists. Earlier experience seemed to influence patient's beliefs while there is an indication that the duration of pain does not influence these beliefs.

The results showed a wide spectra of different patient beliefs about the causes of and measures they would have taken to ease their back/neck pain which is worth taking into consideration when physiotherapists meets these patients.

Key words: patients beliefs, aetiology; measures, back pain, neck pain, physiotherapy

## **Reference Values for Static, Clinical Balance Tests in Standing Position Among Healthy People, 65-85 Years of Age - A pilot study**

Authors: **Evers M, Hallengren S**, Physiotherapy Programme, Faculty of Health Sciences, Linköpings Universitet, Sweden.

Tutor: Gustavsson A, PhD-student Dept. of Neuroscience and Locomotion, Faculty of Health Sciences, Linköpings universitet, Sweden.

The aim with this pilot-project was to develop reference values for static, clinical balance tests in standing position among healthy elderly people, 65-90 years of age.

The balance tests studied were Rombergs test, sharpened Rombergs test and the one-legged stance test on the dominant and the nondominant leg. All the tests were performed both with open and closed eyes. The maximum time for the test was set to 30 seconds. 30 people, 9 men and 21 women were divided into intervals of five-years, from 65-85 years.

All the participants were able to stand in Rombergs position with open as well as closed eyes for 30 seconds, which indicates that Rombergs test isn't a sensitive test of balance among healthy elderly people. One-legged stance test was found to be the best test to assess balance. A significant decrease in balance time was found among the age groups in the one-legged stance tests both with closed and opened eyes. No significant difference among groups was seen concerning Rombergs- and sharpened Rombergs tests. A trend of decrease in balance time was seen in the age groups, 70-85 with increasing age in sharpened Rombergs test with eyes closed.

In future studies, that develop standard values for static, clinical balance tests in standing position, it is important to include more participants and to include equal amount of men and women in the different five-year-intervals.

Keywords: aged, balance test, equilibrium, physical therapy, reference values



## **Intra- and Intertester Reliability of a Handheld Myometry for Measurement of Wrist Extension Strength**

Authors: **Axgren C, Maunsbach A**, Physiotherapy Programme, Faculty of Health Sciences, Linköpings Universitet, Sweden.

Tutor: Ertzgaard S, RPT, MSc, Dept. of Neuroscience and Locomotion, Faculty of Health Sciences, Linköpings Universitet, Sweden.

Epicondylitis is a common cause for pain in the forearm. One of the symptoms is weakness in the wrist extensors. It is therefore important in clinical settings to be able to estimate strength within this muscle group, in order to compare the patients' strength versus the normal population and to evaluate the effectiveness of physiotherapy treatment. Finding a reliable measurement for this object is therefore very important.

The purpose of this study was to determine the intra- and intertest reliability of the myometry Chatillon DFM 100, measuring wrist extension strength in persons without known disorders affecting their upper extremity. 30 students at the physiotherapy programme in Linköping ranging in age from 22 to 45 years (mean 28,0 SD 6,4) participated in the study.

The result of this study showed a very good intra- and intertest reliability. ICC (Intra Class Correlation) value concerning intratester reliability was for observer A 0,94 and for observer B 0,93.

ICC value concerning intertest reliability was 0,90 in test and 0,89 in retest. Therefore, the Chatillon DFM 100 seems to be a suitable measurement to use in clinical settings when assessing wrist extensor strength.

Keywords: lateral epicondylitis, muscle strength, myometry, physiotherapy, reliability, wrist extensor

## **Content Validity of the Quality of Life Scale - Quality of life for persons with fibromyalgia**

Authors: **Hellberg M, Åberg S**, Occupational Therapy Programme, Faculty of Health Sciences, Linköpings Universitet, Sweden.

Tutors: Henriksson C, OT, PhD, Liedberg G, OT, MSc, Dept. of Neuroscience and Locomotion, Faculty of Health Sciences, Linköpings Universitet, Sweden.

During recent years the health care sector has begun to pay attention not only to the results of medical treatment, but also to the patients' quality of life. Consequently there are many instruments for measuring patients' quality of life. For the results to be reliable, it is essential that the measurements have reliability and validity. The Quality of Life Scale (Swedish version, QOLS-S) is an instrument used to measure the quality of life of people with chronic pain. In occupational therapy an important aim is to enhance or maintain the patients' quality of life. Consequently, a reliable instrument for evaluation of this treatment is necessary.

The purpose of this study is to assess the content validity of the QOLS-S in order to measure the quality of life of patients with fibromyalgia.

The perception of what is important for quality of life for ten patients with fibromyalgia have been investigated by means of interviews in three focus groups. Data from the interviews have been analysed with the support of a phenomenographic approach. The results are presented in ten categories. The contents of four categories are not represented in the QOLS-S. The lack of these categories shows a weakness in the instruments validity in measuring quality of life for patients with fibromyalgia. The other six categories, however, are well represented by the items in the instrument.

Keywords: quality of life, measurements for quality of life, content validity, fibromyalgia, occupational therapy

## **Perception of Worker Role - A study of people with unipolar and bipolar disorders**

Authors: **Johansson I, Petersson I**, Occupational Therapy Programme, Faculty of Health Sciences, Linköpings Universitet, Sweden.

Tutors: Eklund E, OT, MSc, Haglund L, OT, PhD, Dept. of Neuroscience and Locomotion, Faculty of Health Sciences, Linköpings Universitet, Sweden.

The purpose of this study was to investigate whether there are any differences in the perception of the worker role between people with unipolar and those with bipolar disorders.

The instrument used for this purpose was the Swedish Worker Role Interview (SWRI), version 1. The SWRI is a semistructured interview instrument based on A Model of Human Occupation. The SWRI is designed to identify the psychosocial and environmental variables that may influence the ability of the injured worker to return to work. Persons with unipolar (n=9) and bipolar (n=7) disorders were interviewed and rated in the SWRI 17 items. The rating scale is a 4-point scale. A rating of "1" indicates that the item strongly interferes with the return to work, whereas a rating of "4" indicates that the item strongly supports it. Means and standard deviations of each of the items were calculated for each group of people. Group ratings were compared using the Mann-Whitney U-test, with a rejection limit of  $p=0.05$ .

Differences were found between the group rating means. People with bipolar disorder were rated lower on 10 of 17 items. The greatest difference was identified on the item "perception of physical work environment". Other items where people with bipolar disorders were rated lower were "habits" and "social environment". Thus, the study identified no significant differences between the groups.

The study indicates that people with bipolar disorder have more items that interfere with their worker role, and may therefore have more difficulties with the return to work than people with unipolar disorder.

Keywords: unipolar disorder, bipolar disorder, occupational therapy, work capacity, work evaluation.

## **Co-operation and Collaboration - How professionals experience cases of child abuse**

Author: **Tenghed S**, Social Care Programme, Faculty of Health Sciences, Linköpings Universitet, Sweden.  
Tutor: Cedersund E, PhD, Dept. of Health and Environment, Faculty of Health Sciences, Linköpings Universitet, Sweden.

The aim of this study is to examine how professionals experience co-operation and collaboration when dealing with cases of abused children from birth to 6 years of age.

The results are based on 15 questionnaires with a critical incident design that were sent to eleven agencies and organisations involved with this type of problem. The difficulty in defining the concept of child abuse and the effects this has on the issue of co-operation are discussed. The respondents' use of the concept of co-operation is primarily process-oriented, and is associated with the different organisations' need to maintain their own legitimacy.

The different organisations are divided into a reporting group and a managing group, depending on their role in investigating cases of child abuse. Criticism concerning co-operation was levelled by the former against the latter group. Social services is the agency most frequently mentioned in this material. Unfortunately, this agency did not participate in the study. The conflict between the reporting group and the managing group is illustrated with a discussion about how resources are unequally distributed between them, and about the need different organisations have to collaborate with more prestigious authorities.

Keywords: co-operation. collaboration, child abuse, the critical incident technique, organisation

## **Children and Eating Disorders - A qualitative study about prevention and professional staff experience with eating disorders**

Author: **Andersson A-K, Granberg A**, Social Care Programme, Faculty of Health Sciences, Linköpings Universitet, Sweden.

Tutor: Söderlind I, PhD, Dept. of Health and Environment, Linköpings Universitet, Sweden.

The main purpose of this study is to examine preventive measures related to eating disorders in children 0-10 years of age.

The study is based on six qualitative interviews with staff working in a child welfare clinic, an open kindergarten, a kindergarten, an elementary school and the school health services.

Eating disorders often begin with the person eating less food and eating less frequently. The causes of eating disorders are many, and can be both on a personal level and a societal level. In the study, we define the concept of eating disorders. The number of children and adolescents with eating disorders seems to be increasing concurrently with the thinner and thinner ideal of beauty. The importance of the family is emphasised both in earlier research as well as in our interviews.

In this study it was found that preventive work is being done, although it is not always labelled as such. For example, it can involve informing parents about set routines when the child is three months of age, and the importance of parents joining their children at mealtimes and trying to make eating a positive experience.

According to the interviews, a child notices when a person is overweight more easily than when a person is too thin. Those interviewed seemed, however, to interpret eating disorders against a thinner ideal.

Keywords: eating disorders, preventive, child, self-confidence, social pedagogy

## **“Separate Worlds?” - Focus group interviews about school with girls in the 9<sup>th</sup> form**

Author: **Hedbäck J, Lindström R**, Social Care Programme, Faculty of Health Sciences, Linköpings Universitet, Sweden.

Tutor: Fried K, lecturer, Dept. of Health and Environment, Faculty of Health Sciences, Linköpings Universitet, Sweden.

The aim of this study is to examine the opinions of girls in the ninth form about their school. The schools were located in two different suburbs, one classified as extremely low income and one as extremely high income. Using the focus group method, we met with a group of six to seven girls from each area to see if there were similarities or differences in how they viewed their respective schools, and how they felt others viewed their school and the effect this had on them. We met twice with each of the groups, for one hour each time.

Through focus group discussions we found both differences and similarities in how the girls perceived their schools. All of them said that they liked school and felt secure there, but the pupils from the low-income area in particular also felt that they were branded in a negative way by those from the outside.

Previous research also shows that many pupils today like school, and the differences in well being in schools located in different areas are not large. The background to the study consists of previous research on the school situation, and definitions of the concepts of suburbs and segregation and how these have been linked together. As a theoretical basis we described how the individual interacts with his/her environment by using symbolic interactionism and the stamping theory.

Keywords: social pedagogic, school environment, focus groups, suburbs, girls

## **Struggle on Behalf of a Different Child - A qualitative interview study of parents of children with Tourette's syndrome**

Author: **Gridiouchko N, Rundqvist M**, Social Care Programme, Faculty of Health Sciences, Linköpings Universitet, Sweden.

Tutor: Samuelsson L, lecturer, Dept. of Health and Environment, Linköpings Universitet, Sweden.

This is a qualitative interview study focusing on parents of children with Tourette's syndrome, which is a functional disorder causing problems in various areas. We examined the social interaction between the parents, the children, and those around them.

The aim of the study was to allow these parents to speak out and talk about how they experience and handle their life situation. Different concepts from symbolic interactionist theory comprise the basis of our work.

The results show that the parents of these children feel stigmatised by those around them as a result of their child's disorder, and that their existence is characterised by a struggle on behalf of their children. This indicates that there is accord between how the parents experience their life situation and the theoretical bases of our study. It is also seen that in the long term the diagnosis had a positive affect on the parents and the school due to a change that took place in the attitudes toward them and the children. The change in attitude led to the parents being able to develop new solutions to problems that improved the family's life situation.

Keywords: Tourette's syndrome, symbolic interactionism, parenthood, stigma, life strategy

## **Bullied as Children - A qualitative study of adults' experiences of having been bullied as children**

Authors: **Elofsson E, Renström H**, Social Care Programme, Faculty of Health Sciences, Linköpings Universitet, Sweden.

Tutor: Lindgren C, PhD-student, The Tema Institute, Linköpings Universitet, Sweden.

The purpose of this study is to investigate by means of interviews the thoughts and reasoning of adults who were bullied as children concerning how they handled and were affected by their experiences. The study is based on a qualitative survey consisting of five interviews. Our aim is to look at the bullying of children from an adult perspective.

The stories of those interviewed are reported in the framework of the three components of Aaron Antonovsky's Sense of Coherence theory, i.e. intelligibility, manageability and meaningfulness. Using intelligibility, it is seen that some persons blamed themselves, while others blamed those around them. Using manageability, it is seen that those interviewed had a number of different resources for support in handling their situation such as family, friends, God, and inner qualities such as a sense of humour. There was great variation in the sense of meaningfulness felt by those interviewed, from not feeling life had any meaning at all to feeling highly hopeful that the bullying would eventually stop. The most important conclusion was that bullying leaves its mark, and in adulthood one is affected in one way or another.

We think the aim of this study is highly relevant to our future work in the field of social pedagogy, as bullying is an all too common problem in our society, and we will most certainly meet its victims.

Keywords: bullying, intelligibility, manageability, meaningfulness, experiences



## **Expression and Modulation of CD28 on CD4-positive Peripheral Blood T-lymphocytes in Malignant Melanoma Cancer Patients and Normal Individuals**

Author: **Gunnerås M**, Medical Biology Programme, Faculty of Health Sciences, Linköpings Universitet, Sweden.

Tutor: Clinchy B, PhD, Clinical Tumor Immunology, Dept. of Oncology, University Hospital, Linköping, Sweden.

CD28 is a cell surface receptor expressed by most CD4+ T cells and regarded as a major co-stimulatory molecule in T cell activation. In malignant melanoma cancer patients, tumor-infiltrating lymphocytes have previously been found to have a reduced expression of CD28, thus making them unable to contribute to antitumor immunity. The regulation of CD28 surface expression is also still poorly understood.

The first aim of this study was to investigate the occurrence of CD28 on peripheral blood CD4+ T cells in malignant melanoma cancer patients. Since the influence of cytokines on CD28 expression has not been very well studied, a second objective was to investigate the effects of the cytokines IL-4, IL-10, IFN- $\gamma$  and IFN- $\beta$  on this molecule on peripheral CD4+ T cells from normal individuals.

Mononuclear cells were separated from fresh peripheral blood, double stained for CD4 and CD28 and evaluated by flow cytometry. In some experiments, mononuclear cells from healthy individuals were incubated with different cytokines at different concentrations for 20h before staining. A total of 10 malignant melanoma patients were studied. 8 normal, healthy individuals were used as controls.

The results did not show a significant difference in percent CD28-CD4+ T cells between patients and normal controls. After exposure to different cytokines, no major changes were observed in CD28 expression on the CD4+ T cells from normal controls.

This study did not indicate that a systemic down-regulation of the immune response due to melanoma down-regulates CD28 expression on CD4+ peripheral blood lymphocytes. Nor did the results show that the cytokines tested are involved in the modulation of CD28, with the exception of IL-4, where a slight reduction in CD28 mean fluorescence intensity was observed in all experiments. IL-4 may therefore influence the CD28 expression on melanoma tumor-infiltrating lymphocytes, thereby contributing to an impaired immunosurveillance against the tumor.

Keywords: CD28, CD4, malignant melanoma, cytokines, modulation.

## **Localisation of the Insulin Receptor to Caveolae of Adipocyte Plasma Membranes by Immunogold Labeling and Electron Microscopy**

Author: **Thorn H**, Graduate School in Biomedicine, Faculty of Health Sciences, Linköpings Universitet, Sweden.

Tutor: Gustavsson J, PhD, Dept. of Biomedicine and Surgery, Faculty of Health Sciences, Linköpings Universitet, Sweden.

Binding of insulin to its receptor results in enhanced transport of glucose into muscle and fat tissue thereby lowering blood glucose levels. Glucose is transported into the cell by specific glucose transporters (GLUT 1-5, 7). Some years ago, it was shown that a phosphorylated oligosaccharid (POS) mimicked the metabolic effects of insulin in adipocytes. The precursor for POS, a phosphatidylinositol glycan (PIG), has been shown to be enriched in caveolae. Hydrolysis of PIG also gives rise to the second messenger 1,2-diacylglycerol (DAG). Exogenous DAG has been shown to stimulate glucose transport and translocation of glucose transporters from intracellular compartments to the plasma membrane in adipocytes. Both PIG and GLUT4, the major glucose transporter in adipocytes, has been shown to be localized to caveolae microdomains, which suggest that the control of glucose transport by insulin and cell metabolism are localized to caveolae.

Caveolae are 50-100 nm sack-like structures in the plasma membrane of several cell types. There are implications that the insulin receptor is localized to caveolae microdomains and that caveolae appear to be involved in the development of insulin resistance of non-insulin dependent diabetes mellitus.

The aim was to visualize caveolae by electron microscopy techniques and describe the distribution of caveola microdomains in the plasma membrane. Is the insulin receptor localized to caveolae microdomains in plasmamembranes of 3T3-L1 adipocytes?

Embryonic 3T3.L1 mouse fibroblasts were cultured on glass coverslips or formvar coated nickel grids (300 Mesh) at 37°C in a humidified incubator with 10% CO<sub>2</sub>. Two days after confluence, cells were differentiated into adipocytes. Cells on coverslips with nickel grids were probe sonicated and remaining plasmamembranes were pre-fixed with paraformaldehyde and glutaraldehyde. Post-fixation was done with glutaraldehyde and OsO<sub>4</sub>. The localization of caveolin, the major caveolae building protein, and the insulin receptor was determined by double immunogold labeling and examined with transmission electron microscopy.

Anti-insulin antibodies labeled with secondary goat, anti-mouse immuno gold antibodies (15 nm) were often, but not exclusively, bound to structures that were labeled with anti-caveolin antibodies, defining the structures as caveolae. It is also obvious that labeled caveolin form a scaffold around caveolae, and that labeled insulin receptors are often localized to the center of caveolae.

The results from this study show that the insulin receptor is localized to caveolae microdomains in 3T3-L1 adipocytes. Caveolae microdomains are distributed as clusters in the plasma membrane. It is possible to prepare 3T3-L1 adipocyte plasma membranes for examination with electron microscopy techniques.

## **Chronic Pain and Discomfort Following the Mesh Plug Hernioplasty - Results of a two year follow-up of a swedish material.**

Author: **Enebog J**, Medical Programme, Faculty of Health Sciences, Linköpings Universitet, Sweden.

Tutor: Zdolsek J, MD, PhD, Gastrenterology clinic, University Hospital, Linköping, Sweden.

Neuralgia following hernia surgery is a well-known complication. The aim of this study is to study the prevalence of not just chronic pain but also discomfort after mesh plug hernioplasty. The study is designed as a prospective follow-up study.

A total of 385 inguinal and femoral hemias in 372 consecutive patients were operated on as described by Rutkow and Robbins. 362 patients (97.3 %) completed a questionnaire in which they were asked whether they experienced pain or discomfort in their operated groin or not (median follow-up 12.8 months). Patients experiencing pain or discomfort were then asked to complete another questionnaire in order to characterize their symptoms and were also offered clinical examination.

85 (23.5%) patients reported chronic pain or discomfort. By the time the questionnaire regarding the character of their symptoms had been completed 32 patients of these still had pain or discomfort (median follow-up 25.0 months). Three patients (0.8%) had severe pain (classified by the patients themselves as "not acceptable"). Six patients reported "sexual complications", pain during intercourse (one patient), painful erection (three) and painful ejaculation (two).

In conclusion, approximately two years after surgery about 10% of the patients experienced some degree of pain or local discomfort in their operated groin.

Key words: hernia repair, complications. chronic pain, polypropylene mesh

## Effect of Oxidative Stress in Fanconi anemia Fibroblasts and Normal Fibroblasts

Author: **Serednitskaia G**, Medical Programme, Faculty of Health Sciences, Linköpings Universitet, Sweden.

Tutor: Öllinger K, PhD, Dept. of Neuroscience and Locomotion., Linköpings Universitet, Sweden.

Fanconi anemia (FA) belongs to a group of human genetic diseases characterised by chromosomal instability, cell cycle anomalies, cancer predisposition and high sensitivity to genotoxic agents associated to DNA lesions. The basic cellular malfunction primary associated with FA is not yet known. Since FA cells show high oxygen sensitivity, we decided to compare fibroblasts from patients suffering from FA (GNM, FON, STT) with normal fibroblast concerning the enzymatic antioxidant status, the ability to produce reactive oxygen species upon addition of a redoxcycling quinone, and the ability to detoxify ROS.

We found higher amounts of SOD in STT compared to normal fibroblast strain (AG-1518); the difference between GNM, FON and AG-1518 was not significant. The catalase activity in FA fibroblasts were lower than in normal fibroblasts, while all FA cells showed increased activity of glutathione peroxidase. No significant difference in total glutathione contents in untreated cells was found. We saw a tendency that the cells with higher level of total glutathione also had higher glutathione peroxidase activity. Moreover glutathione reductase activity was higher in GNM and FON than in normal fibroblasts. The studied cells' ability to metabolise naphthazarin was also proven by the direct measurement of oxygen consumption and by detection of superoxide radical production by nitroblue tetrasolium. AG-1518, GNM and FON showed increase of oxygen consumption with 258%, 90% and 79%, respectively. Those values are in agreement with results from NBT as cells with high oxygen consumption produced more superoxide. At the same time, AG-1518 showed better capacity to restore GSH and ATP levels after exposure for naphthazarin compared to FA cells.

The present results demonstrate that FA fibroblasts are not deficient in their antioxidant defence but, compared to normal fibroblast strain, FA cells are more sensitive to oxidative stress.

## Development of IgG Subclass Antibodies to Allergens in Early Childhood

Author: **Jenmalm M**, MD, Dept. of Health and Environment, Faculty of Health Sciences, Linköpings Universitet, Sweden.

Supervisor: Björkstén B, prof, Dept. of Health and Environment Linköpings Universitet, Sweden.

Immune responses to allergens in young children include both Th1 and Th2 like immunity, which may regulate the secretion of IgG subclass antibodies differently. The time, route and level of exposure to an allergen, as well as maternally transferred immunity, may be decisive whether sensitisation or tolerance will ensue. To study this, we established sensitive methods and investigated the development of IgG subclass antibodies to food and inhalant allergens during childhood.

The study group comprised a cohort of 96 children participating in a prospective study. IgG subclass antibodies to  $\beta$ -lactoglobulin, ovalbumin, Bet v 1 and cat dander were analysed at birth, 6 and 18 months and 8 years by ELISA. At 8 years of age, PBMC from 55 of the children were stimulated with birch and  $\beta$ -lactoglobulin. Production of IL-5, IL-6, IL-10, IL-13 and IFN- $\gamma$  was analysed by ELISA and expression of IL-4 and IL-9 mRNA by semiquantitative RT-PCR.

High cord blood levels of IgG antibodies to inhalant, but not to food, allergens were associated with less development of atopy in the children during the first eight years of life. IgG subclass antibody responses to allergens were commonly detected during childhood and were largely restricted to the IgG<sub>1</sub> subclass. The production of this opsonising and complement activating subclass was associated with Th1 like immunity at 8 years of age. IgG subclass antibodies to food allergens peaked in infancy, whereas antibodies to the inhalant perennial allergen cat, but not the inhalant seasonal allergen birch, increased with age. Exposure to cow's milk during the first three months of life was associated with high IgG subclass antibodies to  $\beta$ -lactoglobulin, up to eight years. Exposure to cat and birch tended to be associated with high antibody levels to those allergens, whereas antibody levels to ovalbumin were not related to the introduction of egg in the diet. Atopic symptoms and the presence of positive skin prick tests and circulating IgE antibodies to allergens were associated with high levels of IgG subclass, especially Th2 associated IgG<sub>4</sub>, antibody responses to allergens. For the food allergens, the differences were mostly marked early in life. Birch induced IL-4 expression may be the major factor determining IgE antibody formation to that allergen, while allergen induced IL-5, IL-6 and IL-10 secretion in PBMC was associated with atopic symptoms.

Maternally derived antibodies may modulate immune responses. The tolerance-inducing mechanisms in the intestinal mucosa may be less effective during the first months of life. Responses to food and inhalant allergens show different kinetics. Th1 like associated IgG<sub>1</sub> antibodies to allergens are commonly observed in both atopic and non-atopic children, whereas Th2 like associated IgG<sub>4</sub> responses are more atopy dependent.

## Experimental Transplantation of Retinal and Iris Pigment Epithelial Cells into the Subretinal Space

Author: **Crafoord S, MD**, Dept. of Neuroscience and Locomotion, Faculty of Health Sciences, Linköpings Universitet, Sweden.

Supervisor: **Algvere PV**, prof, Dept. of Neuroscience and Locomotion, Faculty of Health Sciences, Linköpings Universitet, Sweden.

A dysfunction of the retinal pigment epithelium (RPE) is the main cause for the development of age-related macular degeneration (ARMD) and visual loss in elderly people. Since about 10 years experimental and clinical attempts to transplant RPE cells have been performed. The aims of this study was to elucidate the long term results of RPE allografts, to develop an atraumatic transplantation technique and to explore the cellular response to RPE allografts, melanin granules and autologous IPE cells.

Surgery was performed on rabbits with a follow up period of up to six months. After a pars plan vitrectomy, a subretinal bleb was created into which a suspension of RPE / IPE donor cells or melanin granules was injected. Pigmented RPE donor cells or preparations of melanin granules were implanted subretinally in albino rabbits. Pigmented rabbits were used in IPE transplantation. The eyes were monitored with ophthalmoscopy, fundus photography, light microscopy, electron microscopy and immunohistochemistry.

Transplantation of suspensions of fresh pigment RPE cells to the subretinal space in rabbits is feasible and induces virtually no complications when an atraumatic surgical procedure is used. The allograft forms a monolayer in conjunction with the native RPE and persists almost intact up to three months. At six months after transplantation, there was a cellular response exhibiting multilayers of cells, such as RPE and macrophages. Damage to adjacent photoreceptors in combination with melanin granules in the subretinal space indicates graft failure. No infiltration of lymphocytes was seen. Whether the cellular response was due to immunological or non-immunological mechanisms could not be determined from this experiment.

Cyclosporine (CsA) could not prevent disintegration of the RPE transplant and graft failure. CsA was not capable of promoting graft survival as compared to the controls. The transplant seems to be disrupted either by immunological mechanisms that are not inhibited by CsA, or by nonimmunologic events.

Implantation of melanin granules to the subretinal space of albino rabbits induces a considerable phagocytic cellular response involving the host's RPE, macrophages and glial cells. The migration of pigment-laden cells into the neural retina was frequently associated with focal photoreceptor damage. The cellular response was identical to that ensuing RPE cell transplantation. These findings support the concept that non-immunological events have a considerable influence on the outcome.

In order to evaluate the impact of non-immunological mechanisms, a technique of transplanting fresh autologous IPE cells to the subretinal space of the same eye was developed. Grafted IPE cells were seen to survive for six months. There was a remodeling of the compound cellular layers in the subretinal space over time where grafted IPE cells joined the native RPE cells. The cellular response that developed exhibited macrophages, but no lymphocytes, and was in this respect similar to that observed following RPE transplantation.

In RPE allografts, the photoreceptors appeared normal on light microscopy at three months, but at six months, the photoreceptors overlying the transplants generally exhibited pathological changes. In autologous IPE grafts, on the other hand, the photoreceptors displayed normal outer segment length and outer nuclear layer on top of grafted IPE cells. Focally, multilayers of both grafted IPE and RPE cells, together with macrophages, induce damage to adjacent photoreceptors as observed at 6 months. Cellular multilayers in the subretinal space, irrespective of genesis, are likely to have adverse effects on photoreceptors. The experiments using autologous IPE grafts show that non-immunogenic mechanisms have a decisive impact on the outcome of the transplant in the subretinal space.

## Molecular Genetic Alterations in Chemically-induced Lymphomas

Author: **Shi-Mei Zhuang, PhD**, MD, Dept. of Biomedicine and Surgery, Faculty of Health Sciences, Linköping University, Sweden.

Supervisor: Söderkvist P prof, Dept. of Biomedicine and Surgery, Linköping University, Sweden.

Lymphoma is one of the most common malignancies in humans. Its incidence has increased rapidly in the past 30 years. However, the molecular mechanisms underlying the development of lymphomas are largely unknown.

Environmental carcinogens play an important role in tumorigenesis. 1,3-butadiene (BD) and 2',3-dideoxycytidine (ddC) are two carcinogens to which humans are exposed. Cancer bioassays in mice have revealed that both BD and ddC induce high frequencies of lymphomas. The present study provides a genetic dissection of these chemically-induced lymphomas, with a focus on identification of potential tumor suppressor loci and genetic alterations in genes involved in the pRb, p53 and Ras/Raf pathways. These pathways are important in the control of cell proliferation.

Approximately 87% of BD-induced and 75% of ddC-induced lymphomas show allelic losses or mutations in genes examined. Similar frequencies for inactivation of the p53 pathway were observed in BD- and ddC-induced tumors, whereas disruption of the pRb pathway is more common in ddC-induced lymphomas. On the other hand, BD-induced tumors display more frequent activation of the Ras/Raf pathway. These data indicate the genotoxicity of both ddC and BD, and also confirm the carcinogenicity of these chemicals at a molecular level.

This study also reveals that different genetic alterations occur in distinct stages of the development of BD-induced lymphomas. Ras mutations were detected in tumors derived from mice exposed to BD for only 26 weeks or at a rather low concentration (20 ppm), suggesting that ras mutations may occur early in tumor formation. In contrast, all six tumors with aberrations of p53 occurred in the high dose (625 ppm), continuous long-term exposure group, and these tumors appear to have a more aggressive phenotype, indicating that inactivation of p53 may be a late event, associated with progression of BD-induced lymphomas. Furthermore, two or more genetic alterations were found in 67% of tumors from the 625 ppm dose group and in only 46% of lymphomas derived from mice exposed to 312 ppm of BD. In addition, more than five genetic aberrations occurred only in the 625 ppm dose group. These results support the contention that there is a dose-dependent increase of genetic alterations in BD-induced tumors.

The mutational pattern resulting from carcinogen-exposure has been observed in both human and animal tumors. In the present study, the specific K-ras codon 13 CGC mutation and allelic loss of the Raf1 locus on chromosome 6 were detected only in BD-induced lymphomas, while frequent allelic loss of the telomeric region of chromosome 2 was observed only in ddC-induced tumors, suggesting an agent-specific effect.

The genome-wide screen of allelic losses revealed that multiple potential tumor suppressor genes contribute to the development of BD- and ddC-induced lymphomas. Moreover, most of the identified regions with frequent allelic losses carry unknown tumor suppressor genes, whose isolation and identification are of great interest for further investigation.