# SIGNE LÖFGREN -PALKINTOAPURAHAT SUOMESSA JULKAISTUISTA SILMÄTAUTIEN ALAN VÄITÖSKIRJOISTA 1987 – 2007

Palkittujen väitöskirjojen lyhennelmät

**toim. Leila Laatikainen ja Tero Kivelä**

# SIGNE LÖFGREN AWARD GRANTS FOR OPHTHALMOLOGICAL THESES PUBLISHED IN FINLAND 1987 – 2007

Summaries of the Awarded Theses

**Leila Laatikainen and Tero Kivelä, editors**

Yliopistopaino
Helsinki University Press
Helsinki 2008

ISSN 0783-6295

## SILMÄSÄÄTIÖ

Silmäsäätiö on perustettu vuonna 1960. Sen tarkoituksena on silmätauteja, -vammoja ja -vikoja koskevan tieteellisen tutkimuksen edistäminen Suomessa.

Perustamisestaan lähtien vuoteen 2008 saakka säätiö on tukenut 779 tutkijaa ja tutkimuskohdetta nykyarvoltaan yhteensä 4.6 miljoonalla eurolla. Nykyisin säätiö jakaa vuosittain apurahoja tutkimushankkeisiin 200.000–250.000 euroa. Lisäksi säätiö palkitsee kaikki Suomessa hyväksytyt silmälääketieteen väitöskirjat prof. Signe Löfgrenin nimeä kantavalla erityisellä 2.500 euron palkintoapurahalla.

Silmäsäätiöllä on oma julkaisusarja alaa ja säätiötä koskevan kehityksen saattamiseksi laajempaan tietoisuuteen.

Säätiön hallituksessa on sekä silmälääketieteen että talouselämän edustus. Säätiön hallituksen puheenjohtajana toimii silmätautiopin professori emerita Leila Laatikainen.

SILMÄSÄÄTIÖ
Mannerheimintie 136 A 28, 00270 Helsinki
puh. 09 2412 041
sähköposti: silmasaatio@silmasaatio.fi
internet: www.silmasaatio.fi

---

## THE EYE FOUNDATION

The Eye Foundation was founded in 1960. Its goal is to promote research in eye diseases, injuries and abnormalities in Finland.

Since its birth, the Foundation has supported 779 scholars and research projects with 4.6 million euros in current value terms by 2008. Today, the Eye Foundation grants annually from 200,000 to 250,000 euros to research projects. In addition, it awards a special grant of 2,500 euros named after prof. Signe Löfgren to all those who have successfully defended a doctoral thesis in the field of ophthalmology.

The Eye Foundation publishes its own journal to further knowledge about progress in ophthalmology and in the activities of the Foundation.

The Board of Directors has representatives from ophthalmology and economy. Its current Chair is prof. Leila Laatikainen.

THE EYE FOUNDATION
Mannerheimintie 136 A 28, FI-00270 Helsinki
tel. +358 0 2412 041
e-mail: silmasaatio@silmasaatio.fi
internet: www.silmasaatio.fi

# Esipuhe

## SIGNE LÖFGREN -PALKINTOAPURAHAT SUOMESSA JULKAISTUISTA SILMÄTAUTIEN ALAN VÄITÖSKIRJOISTA 1987 – 2007

Silmäsäätiö on jakanut apurahoja silmätautien ja -vammojen tutkimukseen jo vuodesta 1964 lähtien. Yksi säätiön lahjoittajista ja perustajajäsenistä oli prof. Signe Löfgren (1897–1969). Hän testamenttasi lähes koko omaisuutensa Silmäsäätiölle. Evästyksenä hän totesi säätiön silloiselle puheenjohtajalle, prof. Salme Vannakselle: ”Jakakaa sitten apurahoja nuorille väitöskirjatyön tekijöille – itselläni ei ollut siihen aikanaan varaa.”

Prof. Löfgren oli arvostettu käytännön silmälääkäri. Hän toimi Viipurin, sittemmin Lahden Diakonissalaitoksen silmäsairaalan ylilääkärinä 70-vuotiaaksi vuoden 1967 loppuun asti. Hän oli ensimmäinen silmäosaston naisylilääkäri Suomessa ja Pohjoismaissa. Tunnustuksena ansioistaan hän sai professorin arvonimen vuonna 1955. Prof. Löfgrenin tutkimustyön kohteena hänen nuoruusvuosinaan oli trakooma ja glaukooman kirurginen hoito. Hänen elämästään ja työstään on kirjoitettu tarkemmin Silmäsäätiön julkaisusarjassa (no. 2, 1987).

Prof. Löfgrenin syntymän 90-vuotispäivän yhteydessä säätiö perusti vuonna 1987 erityisen palkintoapurahan kunnioittaakseen hänen muistoaan. Palkintoapuraha jaetaan vuosittain marraskuussa kaikille edeltäneen vuoden aikana silmätautien alalta tohtoriksi väitelleille.

Signe Löfgren -palkintoapurahoja on vuosina 1987–2007 myönnetty 73 tutkijalle. Näistä 47 on väitellyt Helsingin, 10 Kuopion, 9 Turun ja 6 Oulun yliopistossa sekä yksi Tukholman Karoliinisessa instituutissa.

Alkuun palkittuja pyydettiin pitämään luento ja luovuttamaan väitöskirjasta yhteenveto Silmäsäätiön julkaisuja varten. Näistä vaatimuksista on sittemmin luovuttu. Palkintoapurahan täytettyä 20 vuotta Silmäsäätiön hallitus päätti kerätä nämä yhteenvedot vuosilta 1987 – 2007 ja julkaista ne yhtenäisenä kirjana. Nyt julkaistavat yhteenvedot ovat väitelleiden laatimia. Kirjoittajilla oli myös tilaisuus lyhyesti kommentoida väitöstään nykytietämyksen valossa. Toimittajina olemme joutuneet joitakin yhteenvetoja hieman lyhentämään ja jonkin verran yhdenmukaistamaan muotoseikkoja kuten numeroiden esitystapaa ja lyhenteitä lukijan tehtävää helpottamaan. Yhteenvedot julkaistaan väitöskirjan alkuperäiskielellä.

Kiitämme kaikkia yhteenvedon lähettäneitä kollegoja yhteistyöstä tämän tärkeän julkaisun aikaan saamiseksi. Se tarjoaa ainutlaatuisen näköalan suomalaiseen silmätutkimukseen viimeisten kahdenkymmenen vuoden ajalta.

Helsingissä lokakuun 20. päivänä 2008

Prof. Leila Laatikainen
Hallituksen puheenjohtaja

Prof. Tero Kivelä
Hallituksen jäsen

# Preface

## SIGNE LÖFGREN AWARD GRANTS FOR OPHTHALMOLOGICAL THESES PUBLISHED IN FINLAND 1987 – 2007

The Eye Foundation has given grants for research of eye diseases and injuries since 1964. One donor and a founding member of the Foundation was prof. Signe Löfgren (1897–1969). In her last will, she gave almost her entire estate to the Eye Foundation. She provided prof. Salme Vannas, the chairman of the Board of Directors at that time, with the following advice: "Please be sure to give grants to young scholars who aspire to write a thesis – I had no funds for that in my time."

Prof. Löfgren was a widely respected practising ophthalmologist and the head of the Deaconess Eye Hospital in Wiborg, Finland and, later, Lahti, Finland, when the hospital was relocated in the aftermath of the II World War. She held this position until the end of 1967 when she was 70 years old. Prof. Löfgren was the first female head of an eye department in the Nordic Countries. To honour her achievements, she was nominated professor in 1955. Her research as a young ophthalmologist centred on trachoma and surgery for glaucoma. Her life and deeds have been detailed in an issue of the Survey of the Eye Foundation (no. 2, 1987).

In 1987, the Eye Foundation founded an Award Grant to commemorate the 90th birthday of prof. Löfgren. The Award is donated annually in November to physicians promoted to doctoral degree based on ophthalmic research.

From 1987 to 2007, the Signe Löfgren Award Grant has been donated to 73 scholars, 47 of whom come from the University of Helsinki, 10 from the University of Kuopio, 9 from the University of Turku, and 6 from the University of Oulu, Finland, and one from the Karolinska Institutet, Stockholm, Sweden.

Initially, the awardees were required to deliver a paper and to abridge their thesis for the Survey, but this practice was later discontinued. In connection with the 20th Anniversary of the Award, the Foundation decided to collect summaries of all theses that were awarded until 2007 and to publish them in one volume. The summaries are written by the awardees who had an opportunity to comment on their work in recent light. The editors shortened summaries to fit one page and, in the interest of the reader, standardised presentation as regards e.g. abbreviations and statistics. The summaries are published in the original language of the thesis, either in English or in Finnish.

We gratefully acknowledge the co-operation of our colleagues who contributed to this truly noteworthy compendium, which will provide a unique overview of the ophthalmic research in Finland during the last two decades.

Helsinki, October 20th 2008

Prof. Leila Laatikainen
Chairman of the Board of Directors

Prof. Tero Kivelä
Member of the Board of Directors

Professori – Professor Signe Löfgren
(1897–1969)

# Palkittujen väitöskirjojen lyhennelmät

# Summaries of the Awarded Theses

# 1987

## ANTIGENIC PROPERTIES OF RETINOBLASTOMA TISSUE IN RELATION TO NEURONAL AND GLIAL CELLS OF THE HUMAN RETINA

**Tero Kivelä, Helsingin yliopisto – University of Helsinki**

Antigens associated with neurons and glial cells in the central and peripheral nervous system were studied in 55 formalin-fixed, paraffin-embedded surgical retinoblastoma (RB) specimens and identically processed human retina by immunohistochemistry.

Neuron-specific enolase (NSE) was found in all neuronal cell types of the retina and in most RB cells. Small, differentiated and bilateral tumours were more uniformly positive for NSE. Neurofilaments (NF) were detected in cell processes in the nerve fibre and inner plexiform layers, but not in neuronal cell bodies or RB cells. The scarcity of NF may have been in part related to the specificity of the monoclonal antibody, because it detected only the high molecular weight NF protein.

Vimentin, glial fibrillary acidic protein (GFAP) and S-100 protein were found in astrocytes of the nerve fibre and ganglion cell layers. All Müller's cells were positive for vimentin, whereas GFAP and S-100 protein were found in this cell type preferentially close to the ora serrata and appeared to be expressed only as a reactive phenomenon. In RB, these antigens mostly were found in astrocyte-like cells with cytoplasmic processes, which originated from infiltrated retina and secondarily proliferated within RB, and not in RB cells. The HNK-1 carbohydrate epitope, which is associated with neural cell adhesion molecules and myelin, was expressed on membranes of Müller's cells and in both plexiform layers of the retina. It was observed in stromal elements of RB only.

Of 11 lectins tested, concanavalin A (ConA) and the Lens culinaris (LCA), wheat germ (WGA), Ricinus communis I (RCAI) and peanut agglutinins (PNA) labelled photoreceptor cells. PNA reacted specifically with cones. All these lectins except PNA also labelled other neuronal cells of the retina. Undifferentiated and differentiated RB cells bound ConA and LCA. In many tumours, WGA, RCAI, and PNA reacted also with Flexner-Wintersteiner rosettes and some undifferentiated RB cells. The binding pattern most closely resembled that of photoreceptors.

**Author's Comment:**

The results were compatible with a primarily neuronal nature of RB and they did not support the then common view that RB would differentiate also in glial direction and would thus originate from a pluripotential retinal stem cell. The neuronal nature of RB has later been confirmed and holds true today.

*Tero Kivelä, MD, is currently professor in ophthalmology and chief physician at the Helsinki University Eye Hospital*

# 1987

## SILMÄLASIEN KÄYTTÖ, SILMÄSAIRAUKSIEN JA -TAPATURMIEN ESIINTYVYYS SEKÄ NIIDEN TALOUDELLINEN MERKITYS KOTITALOUKSILLE

**Pentti Mikkonen, Kuopion yliopisto – University of Kuopio**

Tutkimus koostui postikyselystä ja kliinisestä silmätutkimuksesta. Postikyselyssä vuodenvaihteessa 1978–1979 lähetettiin 11467 henkilölle 77 moniosaista kysymystä sisältävä lomake. Lopullinen tulostettavien määrä oli 69 % lähtöaineistosta. Kliininen tutkimus suoritettiin vuonna 1979 kolmella paikkakunnalla, joista kullakin siihen kutsuttiin satunnaisotannan perusteella 500 tutkittavaa eli yhteensä 1500 henkilöä. Tutkimukseen osallistui 66 % kutsutuista.

Postikyselyyn vastanneista 50 % käytti silmälaseja, naiset (58 %) huomattavasti useammin kuin miehet (41 %). Yliopistotasoisen koulutuksen saaneet käyttivät keskimääräistä enemmän silmälaseja. Pelkästään lähilasien käyttäjiä oli 36 % silmälasien käyttäjistä. Miehet (19 %) käyttivät kaksiteholaseja vähemmän kuin naiset (26 %).

Kliiniseen tutkimukseen osallistuneista silmälaseja käytti 48 %. Tutkituista 30 %:lle oli joko tarpeen määrätä ensimmäiset silmälasit (11 %) tai uusia entiset silmälasit (18 %). Keskimääräinen silmälasien vaihtoväli oli 2 vuotta 4 kuukautta.

Postikyselyn mukaan 0.6 % väestöstä sairasti glaukoomaa. Kliiniseen silmätutkimukseen osallistuneista 1.7 %:lla silmänpaine oli yli 21 mmHg. Kaihia oli ilmoituksensa mukaan 1.3 %:lla vastaajista. Hoitamattomia silmätauteja ilmeni postikyselyssä harvoin eivätkä ne olleet vakavia. Naiset (65 %) olivat olleet useammin hoidossa silmätautien vuoksi kuin miehet (56 %). Vajaa 25 % oli hoidettu yksityisvastaanotolla.

Silmätapaturmien, etenkin vaikeasti vammauttavien, määrä oli vähäinen. Silmätapaturmapotilaista suurin osa (76 %) oli miehiä. Yleisin silmätapaturma, joita oli lähes puolet kaikista silmätapaturmista, oli vierasesineen aiheuttama. Vastaajista 2.5 % oli joutunut olemaan poissa työstään silmätapaturman takia.

Keskimääräiset sairauskulut olivat 2.8 % kotitalouden ansiotuloista, silmistä aiheutuneet kustannukset 1.1 %. Silmälasikustannukset olivat huomattavat muihin terveydenhoitomenoihin nähden, 12.8 % kotitalouden sairauskuluista.

*Pentti Mikkonen, MD, is currently in private practice*

# 1987

## REFRACTION CHANGES AND VISION DISORDERS IN FINNISH SCHOOL CHILDREN

**Maija Mäntyjärvi, Kuopion yliopisto – University of Kuopio**

In Kuopio, 12 500 school children were under the school health care in the years 1977 to 1984. Annually, 700-1500 children were sent from eye screening to an eye examination carried out by the Health Center ophthalmologist – the author.

Both in 1977 and 1984, in 100 consecutive examinations 60% of the children were girls and 58% had myopic refraction.

The comprehensive school health care gave the possibility to evaluate the incidence of myopia at school age. Myopia began mostly at the ages of 11 to 13 years, when 4 per 100 children became myopic annually. Cumulative calculations showed that 20% of children can be myopic by the age of 15 years.

Of those children whose myopia began at the ages of 7 to 10 years, 17.5% progressed to have -6.0 D of myopia or more. When myopia began at the ages of 11 to 14 years, it progressed to high numbers only in 1.1%.

The amplitude of accommodation was similar in hyperopic and myopic children; 14% of the children had decreased amplitude of accommodation of 7 D or less. Most of them were girls aged 13 to 14 years.

Psychogenic amblyopia occurred mostly in girls (92%) with the mean age of 10 years. The annual incidence of psychogenic amblyopia was 1.4/1000 children. Recovery occurred often in three months but could last up to four years.

Screening congenital red-green colour vision defects is important for career guidance. The Boström-Kugelberg test showed the best sensitivity but also false positives. The Ishihara test showed no false positives and could be a better choice for screening.

**Author's Comment:**
The etiology of myopia remains unknown. According to twin studies, heredity plays a role but the other underlying factors are unclear. At present, the main research interest is in the heredity of myopia while its epidemiology, prevalence and progression seem to remain at the background.

*Maija Mäntyjärvi, MD, is professor in ophthalmology*
*retired from the University of Kuopio*

# 1988

## LASER POWER IN ARGON LASER TRABECULOPLASTY

**Harri Rouhiainen, Kuopion yliopisto – University of Kuopio**

This study, which started in the middle of the 1980's, was based on the fact that the argon laser we used in those days was aging and losing its power. Since there was no financial base to renew the apparatus, it had to be used for everyday clinical work. The laser power level suggested in the original publication of argon laser trabeculoplasty by Wise & Witter in 1979 to reduce intraocular pressure (IOP) in ocular hypertensive and glaucoma patients was between 800 and 2200 mW, and the usual power setting in clinical work between 1000 and 1500 mW in most cases. With the aging apparatus, we had to treat patients with power levels as low as 100 mW, much less than suggested originally, but still we could get a beneficial effect on some patients. Thus, the study started with the idea of finding out the possible treatment and patient variables which would affect the outcome of laser trabeculoplasty with low power levels.

Later on, a new apparatus was delivered for the clinic and thus more laser power was available for the treatment. Because the study had started with low power levels, it seemed natural to continue it with the new machine to find out the laser power level best suitable for clinical use with reasonable results and minimal side effects.

The study was carried out with glaucoma patients introduced to the clinic by ophthalmologists in order to optimise glaucoma treatment. In some patients, trabeculoplasty was the only treatment modality, but most were also on topical glaucoma medication.

Many publications about the procedure came out during the decade which passed since the original work. None of them dealt with suitable power levels, and some discussed the complications. Mostly the papers were concentrated to prove the efficacy of the procedure. The main finding in my seven original publications was that with a laser power level considerably lower than originally suggested, one could get the same beneficial IOP effect with less postoperative complications. It turned out that in most cases the power setting between 500 and 700 mW would be enough.

**Author's Comment:**
Today, 20 years after the publication of my thesis, new medications for lowering IOP, as well as an alternative laser treatment, selective laser trabeculoplasty, have been introduced. They have reduced the need for classic argon laser trabeculoplasty, but it still remains an effective and safe method for lowering IOP when topical medication is contraindicated or not effective enough.

*Harri Rouhiainen, MD, is currently in private practice and docent in ophthalmology at the University of Kuopio*

# 1988

## GENETIC AND EPIDEMIOLOGIC STUDIES OF OPEN ANGLE (SIMPLE AND CAPSULAR) AND ANGLE CLOSURE GLAUCOMA

**Jaakko Teikari, Helsingin yliopisto – University of Helsinki**

The aim was to examine a possible association of the amount of sunshine and risk for acute closed-angle glaucoma, and genetic and environmental factors in the etiology of closed-angle and primary open-angle glaucoma (POAG) and capsular glaucoma.

Epidemiologic data was collected using hospital discharge registry data, linked to meteorological data for the same period. Material for clinical studies was obtained with a nationwide record linkage of the Finnish Twin Cohort Study (FTCS) with the Hospital Discharge Registry and the Registry of Rights for Free Medication.

A peak incidence of acute closed-angle glaucoma was noted whenever the number of hours without sunshine increased. Sex and sunshine hours best explained the variation in incidence in a covariate model. Cup/disc-ratio of the optic nerve head was studied using 10 monozygotic (MZ) and 7 dizygotic (DZ) random pairs from the FTCS. Results confirm a genetic determination in cup/disc area ratio in normal eyes. POAG was observed to be determined by genetic and environmental factors (multifactorial). Chronic closed-angle glaucoma was also found to be determined both by genetic and environmental factors using clinically studied MZ and DZ cases obtained from the FTCS.

**Author's Comment:**
Last 20 years of studies have gone further trying to find the genes responsible for the genetic influences in the expression of POAG. Acid Phosphatase gene located in the 2p23 chromosome has been associated with POAG. Association of closed angle glaucoma to female sex has later been confirmed but the seasonal association of the disease has not been consistent in countries were days are longer and nights shorter in wintertime.

*Jaakko Matias Teikari, MD, MPH, EBOD, ABOC, NCLC,*
*is currently in private practice*

# 1988

## AN OPHTHALMOLOGICAL STUDY ON WORKERS WITH LONG-TERM OCCUPATIONAL EXPOSURE TO INDUSTRIAL SOLVENTS

**Henrik Teir, Helsingin yliopisto – University of Helsinki**

The widespread use of organic solvents has caused increased concern because of the health hazards these substances present. The nervous system, in particular, is vulnerable to the toxic effects of solvents. Even long-term, low-level exposure to solvents is known to cause various neurological disturbances in the central and peripheral nervous system. The poorly known effects of long-term, low-level exposure to solvents on the structure and function of the eye was investigated among 71 industrial workers with long-term exposure to solvents and symptoms causing suspicion of solvent intoxication as compared to 71 age-matched control subjects.

The ophthalmological examinations included measurements of visual acuity, refraction and orthoptic balance, tonometry, biomicroscopy of the anterior segment, measurement of the amplitude of accommodation, perimetry, colour discrimination by Farnsworth-Munsell 100 hue test, electroretinography (ERG), visual evoked potentials (VEP) and fluorescein angiography (FAG).

A slightly increased frequency of microscopic subcapsular opacities of the lens cortex was found in the exposed group, but the opacities did not affect visual acuity. A significantly increased frequency of low amplitudes of accommodation was observed among the exposed workers younger than 50 years of age, compared to the controls. Colour discrimination showed a significant shift toward higher total error scores among the exposed workers; colour discrimination was impaired for raw as well for the square root scores, indicating a disturbance of the ganglion cells or optic nerve fibres. Slightly lowered amplitude of the b-wave of the ERG among the exposed workers indicated a disturbance of the bipolar and Müller cells of the retina. FAG showed a higher frequency of delayed peripapillary or segmental filling in the exposed workers, indicating an increased rigidity of the vascular bed possibly due to arteriosclerotic changes.

Long-term exposure to solvents seems to accelerate processes in the eye which normally occur with increasing age.

*Henrik Teir, MD, is currently in private practice*

# 1988

## GYRATE ATROPHY OF THE CHOROID AND RETINA

**Kaarina Vannas, Helsingin yliopisto – University of Helsinki**

Jacobsohn was the first one to publish a case of gyrate atrophy (GA) in 1888. A definite and accurate diagnosis became possible in 1973, as Simell and Takki detected the accompanying hyperornithinemia and ornithuria. The cause was found to be a defect in the major enzyme which catabolises ornithine, ornithine aminotransferase (OAT). This milestone stimulated research in GA as it now had a specific biochemical marker.

An answer has been sought to the question what is detrimental to the function of the retina in this slowly blinding disease, with a defect in ornithine metabolism in which patients are otherwise clinically healthy? Because no eyes had been available for histopathological evaluation of the choroid and retina, understanding of the ocular disease process relied on the clinical and physiological examination of the eye.

The other aspect of the disease is in its biochemistry. Several theories have been suggested for the pathomechanism of GA, and treatment modalities have been proposed correspondingly. Gene technology provides the potential to determinate the defects causing the altered gene expression in GA, and thus cure could possibly be pinpointed to that cause instead of replacement of the whole gene.

The thesis consisted of works where the pathology and pathomechanism of GA was investigated by the three approaches described above: ocular investigation, biochemistry and gene technology.

**Author's Comment:**
In the future we may hopefully approach the treatment of GA more efficiently by gene transfer therapy.

*Kaarina Vannas, MD, is currently ophthalmic surgeon at the Helsinki University Eye Hospital*

# 1989

## ENDOPHTHALMITIS FOLLOWING CATARACT SURGERY: CLINICAL ASPECTS AND EVALUATION OF RISK FACTORS

**Tuomo Puustjärvi, Kuopion yliopisto – University of Kuopio**

The goal was primarily to find out risk factors for endophthalmitis following cataract surgery and, secondarily, to evaluate their mutual role in causality. The retrospective study comprised 3 275 patients operated for cataract at the Kuopio University Hospital during the years 1976 to 1986.

A total of 43 cases (1.3%) of postoperative endophthalmitis were observed. Specimens for microbic cultures from intraocular fluids were obtained from 24 of the 43 inflamed eyes, and of these 7 cultures (29%) were positive, 14 cultures (58%) were negative and the remaining 3 cultures (13%) were equivocal. The number of confirmed culture positive infections, 7 of 3 275 operated eyes, equalled a prevalence of 0.2%.

The most common microbial agent was coagulase negative staphylococci (6 cultures). In one culture, *Proteus mirabilis* was found. Additionally, in 1 of the 7 vitreous taps both coagulase negative *Staphylococcus* and *Aspergillus fumigatus* were isolated.

Males were 2 to 3 times more prone to develop endophthalmitis than females. The age from 60 to 67 years carried a 3- to 4-fold risk. Beyond that age the risk slowly deceased. However, the greatest risk rate was associated with peroperative vitreous loss: irrespective of the surgical technique, the risk of endophthalmitis was 7- to 8-fold. Exfoliation syndrome and myopia as factors precipitating vitreous loss increased the risk about 1.8-fold. On the other hand, the general health status, e.g. diabetes, did not play a notable role among the risk factors of postoperative endophthalmitis.

**Author's Comment:**
During the study period, cataract surgeons were rapidly adapting from intracapsular to extracapsular surgery. This is reflected in the exceptionally high rate of endophthalmitis. The learning period brought along an increased risk of surgical complications, and the new technique did not prevent vitreous loss. Indeed, peroperative vitreous loss was the leading risk factor of postoperative endophthalmitis identified. The large proportion of Gram positive microbes as cause of endophthalmitis still holds true. Twice as frequent rate of culture negative than positive endophthalmitis may reflect the practice of that period. Today, the risk of endophthalmitis following cataract surgery is 0.1% or less.

*Tuomo Puustjärvi, MD, is currently docent in ophthalmology and chief medical officer at the Department of Ophthalmology, Kuopio University Hospital*

# 1989

## VITREORETINAL SURGERY IN DIABETIC EYE DISEASE: PROGNOSTIC INDICATORS AND LONG-TERM FOLLOW-UP

**Paula Summanen, Helsingin yliopisto – University of Helsinki**

The outcome and complications among the first 105 patients (124 eyes) undergoing vitrectomy for diabetic eye disease (DED) at the Helsinki University Eye Hospital from 1978 to 1985 were retrospectively analysed. Their mean age was 39 years (range, 18 to 73) and the mean duration of diabetes (DM) was 23 years (range, 6 to 43); 85% were younger than 30 years when DM was diagnosed and all but one were on insulin therapy. Two thirds had cardiovascular disorders, nephropathy or both.

Vitrectomy was performed for non-resorbed vitreous haemorrhage (VH) in 62% of eyes, central traction retinal detachment (TRD) in 17%, and a combination (VHTRD) thereof in 21%. At its best, visual acuity (VA) had improved in 67% of the eyes, was unchanged in 29% and worse in 4%. Corresponding figures for the latest VA after a mean follow-up of 3.7 years were 52%, 26% and 23%, respectively. VA was better in eyes operated for VH than TRD or VHTRD: it improved in 71%, 10% and 8% and was 0.3 or better in 40%, 10% and 12%, respectively. Conversely, light perception was lost in 16%, 33% and 23%, respectively. Main causes of permanent visual loss were RD in 19% of eyes and neovascular glaucoma (NVG) in 15%. The major risk indicators for NVG were total retinal detachment (RD; odds ratio [OR] 9.9) and aphakia (OR 4.6).

Electrophysiological tests had some value in predicting outcome. An early age at onset of DM was prognostically favourable. Patients with TRD had DM and DED at an earlier age than those with non-resorbed VH and the worst visual outcome was related to a shorter duration of DM and DED, indicating an aggressive form of disease. Presence of RD was the most important predictor of a poor visual outcome and preoperative VA of counting fingers at 1 m or better predicted a favourable visual outcome. Time from VH to surgery did not influence long-term visual outcome but long duration of RD worsened it. The 5-year cumulative survival was 82%. By December 1987, 17 patients had died, 12 of cardiac disease. Proportion of patients without ambulatory vision tended to be higher for those who died than among survivors (47 % vs. 21 %).

**Author's Comment:**
Non-resorbed VH and traction RD threatening the macula remain the main causes for diabetic vitrectomy but photographic screening of diabetic retinopathy and timely laser treatment seem to decrease the need of surgical intervention. Studies from other centers show that new surgical equipment, especially endolaser, has improved prognosis.

*Paula Summanen, MD, is currently head of diabetic eye and retinal vaso-occlusive disease section and docent in ophthalmology at the Helsinki University Eye Hospital*

# 1990

## NÄKÖ JA TYÖ: KLIINIS-EPIDEMIOLOGINEN TUTKIMUS AMMATTIMAISTEN AUTONKULJETTAJIEN, NÄYTTÖPÄÄTE- JA ELEKTRONIIKKATYÖNTEKIJÖIDEN NÄKÖAISTISTA

**Esko Järvinen, Helsingin yliopisto – University of Helsinki**

Tutkimuksessa selvitettiin ammattimaisten autonkuljettajien, näyttöpäätetyöntekijöiden ja elektroniikkatyöntekijöiden näkökykyä ja heidän kokemaansa silmiin ja näkemiseen liittyviä ongelmia. Lisäksi arvioitiin näön muuttujien merkitystä liikenteessä sekä suoritettujen työterveyshuollon ja muiden näkötarkastusten merkitystä.

Suurin näöntarkkuutta alentava tekijä oli korjaamaton taittovirhe. Alentunut näöntarkkuus ei vaikuttanut koettuihin silmiin ja näkemiseen liittyviin ongelmiin työoloissa. Refraktiiviset erot eri ammatti- ja ikäryhmissä selittyvät iän, valikoitumisen ja mahdollisesti koulutuksen eroilla. Autonkuljettajan alentunut näöntarkkuus oli suhteellisen yleinen löydös, joskaan se ei aiheuttanut oireita eikä ollut lisännyt kolaritiheyttä viimeisen viiden vuoden aikana. Näöntarkkuus häikäisyoloissa, häikäisystä toipuminen ja liikkuvan kohteen havaitseminen heikkenivät iän myötä, mutta ne eivät lisänneet kolarialttiutta.

Päätetyöntekijöiden kokemille, silmiin ja näkemiseen liittyville ongelmille ei löytynyt selvää objektiivisesti mitattavissa olevaa syytä. Sisäänpäinkarsastus ja fuusiolaajuus divergenssin suuntaan korreloivat näihin oireisiin. Heidän akkommodaatiokapasiteettinsa oli alentunut tilastollisesti merkitsevästi verrattuna verrokkeihin.

Elektroniikkatyöntekijät olivat silmistään vähäoireisimpia nyt tutkituista ammattiryhmistä. Todetut oireet eivät korreloineet mihinkään kliiniseen muuttujaan. Akkommodaatiokapasiteetti oli elektroniikkatyöntekijöillä merkitsevästi alempi kuin naisverrokeilla. Useammat näkötarkastukset ja yleisempi silmälasien käyttö sekä tiheämpi silmälasien uusiminen selittivät ainakin osaksi muita ryhmiä vähäisemmät subjektiiviset ongelmat.

Työterveyshuollon näöntarkastuksilla oli selvä vaikutus autonkuljettajien näöntarkkuutta parantavana tekijänä. Työterveyshuollossa tutkituilla näyttöpäätetyöntekijöillä oli vähemmän subjektiivista silmäoireistoa kuin muilla joskaan ei tilastollisesti merkitsevästi. Elektroniikkatyöntekijöiden vähäiset ongelmat selittyvät pitkälle useampien työterveyshuollon tarkastusten ja herkästi jatkotutkimuksiin lähettämisen pohjalta.

Tutkittujen ammattiryhmien osalta ei ollut syytä ryhtyä sen hetkistä laajempiin silmien ja näön rutiininomaiseen tutkimiseen tai seurantaan. Elektroniikka- ja näyttöpäätetyöntekijöiden erillisten työlasien tarvetta voitiin perustella vain poikkeustapauksissa. Ajokortin myöntämisen näöntarkkuuden kriteerejä olisi voinut turvallisesti laskea esimerkiksi EU-maiden suositusten tasolle.

*Esko Järvinen, MD, is currently a head of anterior segment surgery at the Helsinki University Eye Hospital*

# 1990

## GLAUCOMA IN INSTITUTIONALIZED GERIATRIC PATIENTS

**Ritva Peräsalo, Helsingin yliopisto – University of Helsinki**

Glaucoma was diagnosed in 11% of 1576 subjects living in the centralised institution for the elderly in the City of Helsinki. These people had been institutionalised because their daily living activities were impaired for medical reasons or because of old age.

Altogether 213 glaucoma patients, 149 with bilateral and 64 with unilateral glaucoma, and 100 controls without glaucoma were compared. The mean age of the study group was 83 years and that of the control group 81 years; the former included 15% men and the latter 16%.

Primary open-angle glaucoma occurred in 39%, narrow-angle glaucoma in15% and capsular glaucoma in 44% (combinations included) of the patients; 35% of the glaucoma patients had low vision (visual acuity [VA] 0.05 to <0.3 in the better eye) and 28% were blind (VA <0.05). Capsular glaucoma was the most difficult to control. Of 42 eyes that had been treated with filtering surgery 71%, and of 39 eyes that underwent cataract surgery 44% were without glaucoma medication.

When the systolic blood pressure in the glaucoma patients was above 160 mmHg, it correlated significantly with intraocular pressure. There was no similar correlation in the control patients. Severe visual field changes were most common in patients with low systolic pressure (120 mmHg and under).

Electrocardiographic changes suggesting coronary heart disease occurred more often in the glaucoma patients (77%) than in the controls group (62%), which suggests that a vascular component is part of the mechanism of glaucoma in the elderly.

Arrythmias were seen twice as often in the glaucoma patients as in the control group. It is possible that, at least in the elderly, atrial fibrillation decreases the blood flow to the eye. Patients with this condition should have an ophthalmological examination.

**Author's Comment:**
The common occurrence of glaucoma among geriatric patients (11% in the institutionalised geriatric population) emphasises that each elderly person should undergo an ophthalmological examination when entering the institution.

*Ritva Peräsalo, MD, is glaucoma and low vision specialist retired from the Helsinki University Eye Hospital*

# 1990

## PERFORATING EYE INJURIES: EPIDEMIOLOGY, LONG-TERM FOLLOW-UP AND THE ROLE OF VITRECTOMY IN THE TREATMENT

**Eeva Punnonen, Helsingin yliopisto – University of Helsinki**

The retrospective study analysed 387 consecutive patients treated for perforating eye injury (PEI) at the Helsinki University Eye Hospital from 1980 to 1986. Of these patients, 86% were male. The main causes of 290 PEI without intraocular foreign body (IOFB) were domestic and occupational accidents, and assaults. The main causes of 95 PEI with an IOFB were occupational, domestic and shooting accidents.

After a mean follow up of 31 months, 61% of the eyes had good vision, 8% had low vision, 31% were blind and 14% had been enucleated (15% of those without an IOFB and 11% of those with an IOFB). The outcome was fairly similar in eyes with and without IOFB. Retinal attachment was maintained or achieved in 85% of eyes. Retinal detachment was the main cause of blindness (21%); the main cause of low vision was a corneal scar (35%). The percentage of blind eyes was lower than in earlier studies in Finland (50% to 34% in the 1950's to 1970's) before the era of vitreoretinal surgery. The percentage of eyes with good vision had increased (61% as compared to 34% to 49% in the 1950's to 1970's).

Vitrectomy was considered indicated only in more severely damaged eyes; therefore the outcome was usually better if vitrectomy had not been done. Of eyes without an IOFB, those with anterior segment injuries complicated by vitreous haemorrhage benefited most from vitreoretinal surgery. Of eyes with an IOFB and posterior segment injury, functional result was better with vitrectomy.

Use of intravitreal silicone oil resulted in anatomical success in 27% of eyes in which complicated retinal detachment could not be otherwise treated. Despite the anatomical success, one third of the eyes remained blind. Anterior segment complications related to the use of silicone oil included keratopathy in 12%, increased intraocular pressure in 16%, and cataract in 67% of the eyes.

On histopathologic examination of the enucleated eyes, the most marked finding was severe fibrous proliferation in eyes enucleated 1 month after injury or later. Proliferation of retinal pigment epithelial cells was seen 9 days, fibrous proliferation in the vitreous 10 days and epiretinal membranes 1 month after injury.

**Author's Comment:**
The current features of PEI in Finland have not been analysed but one might expect that the more sophisticated surgical techniques available and the greater experience in the use of silicone oil would have improved the final outcome.

*Eeva Punnonen, MD, is currently in private practice*

# 1991

## EPIDERMAL GROWTH FACTOR, PLASMIN AND PLASMINOGEN ACTIVATOR IN TEAR FLUID

**Gysbert van Setten, Helsingin yliopisto – University of Helsinki**

This study showed that epidermal growth factor (EGF) is a constant component of the human tear fluid. It was shown that even though intense tearing does lead to a significant decrease in growth factor concentrations, EGF remains always detectable in tears. New parameters were established such as tear fluid flow, measured in µl/min, which allowed to gain an idea about the secretion parameters of the lacrimal glands. Histological studies confirmed the anticipated origin of EGF in tears to be the lacrimal gland.

Studies with tears from both humans and animals gave proof that not only cytokines are constantly present in tears but they also might be exposed to an environment with rather high enzymatic activity. This was shown for some types of contact lens wear. The simultaneous presence in tears of both systems, the cytokines and enzymes, and the model of their kinetic interaction in the control of re-epithelialisation of the cornea provided the basis for understanding of corneal wound healing events and a hypothesis of a sensitive balance between the two systems during contact lens wear. An observed relation between the presence and intensity of corneal neovascularisation and plasmin-like activity in the tears offered a new approach to understanding possible side effects of contact lens wear.

A model was created that showed a link between proteolytic degradation of extracellular matrix of an exposed wound surface by the plasmin-like activity of tears. The idea of controlled destruction of this extracellular matrix during cellular migration, partially stimulated by EGF, was one of the most applicable results of the study.

**Author's Comment:**
The finding of EGF was followed by the detection of a large number of other cytokines and proteins in human tear fluid. In these subsequent studies many of the methods used in the original thesis are applied, confirming their scientific applicability. Tear fluid research has gained significant attention in the scientific community which emphasizes that tears are a human body fluid of major importance.

*Gysbert van Setten, MD, is currently corneal specialist and docent in ophthalmology at St.Erik's Eye Hospital, Stockholm, Sweden*

# 1991

## CATARACT SURGERY IN DIABETES

**Petri Tommila, Helsingin yliopisto – University of Helsinki**

The influence of the two types of cataract extraction used in the 1980's, intracapsular (ICCE) and extracapsular (ECCE), on progression of diabetic retinopathy (DR), postoperative iris neovascularisation and neovascular glaucoma (NVG) was studied retrospectively in 69 insulin-treated (IT) and 12 oral drug-treated (OT) diabetic patients operated in 1982–1985. Of the IT patients 42% and 58% had juvenile (age <30 y) and adult-onset (age >30 y) diabetes, respectively. The type of surgery was ICCE in 57 eyes (30%) and ECCE in 133 eyes (70%). An intraocular lens (IOL) was implanted in 54% of ECCE eyes. The follow-up time was 1.2 to 5.9 y (mean 3.2 y).

The latest visual acuity (VA) was 0,5 or better in 69% (in 54% vs. 79% for IT and OT, respectively) of eyes, and 11% (14% vs. 8%, respectively) of eyes had a VA less than 0.1. In 46% of patients the reason for low vision or blindness was DR.

The prevalence of DR, mainly non-proliferative, increased both in IT (from 63% to 92%) and OT (from 9% to 41%) patients. The risk of progression was 2.5-fold higher in IT patients matched for duration of diabetes. Progression was not significantly more common than in the non-operated fellow eye (36% vs. 24%). Progression of DR did not correlate with the type of surgery or presence of an IOL. Results for progression of diabetic maculopathy were similar. Cataract surgery did not increase progression of DR significantly, but in those eyes in which progression was observed it was more profound in IT patients. Posterior capsule opacification developed in 75% of ECCE eyes, similarly in IT and OT patients. The tendency was highest in juvenile-onset diabetics.

Iris neovascularisation was found in 6% of eyes in IT and in 1% in OT patients. All but one eye with postoperative iris neovascularisation had either peroperative complications or postoperative underlying factors such as retinal detachment. NVG was found in 3 eyes after ECCE complicated by posterior capsule rupture in IT patients. All these eyes had had vitrectomy either peroperatively or postoperatively.

**Author's Comment:**
Today, the techniques of cataract surgery have changed and the risk for progression of DR after cataract surgery may be even smaller. Iris neovascularisation and NVG were 20 years ago speculated to develop because of chemical mediators diffused from the retina to the iris, triggered by retinal ischemia or ocular inflammation. ICCE and a posterior capsule tear made it easier for the mediators the reach the target tissue. Today, we know a lot more of these vascular growth mediators and have several means of blocking their action. Speculation has turned into knowledge and clinical practice.

*Petri Tommila, MD, is currently retinal specialist at the Helsinki University Eye Hospital*

# 1992

## ATOPIC CONJUNCTIVITIS WITH SPECIAL REFERENCE TO TEAR FLUID ANALYSIS AND CONJUNCTIVAL CYTOLOGY

**Osmo Kari, Helsingin yliopisto – University of Helsinki**

Atopic IgE mediated conjunctivitis is a common disease. Twenty three patients with atopic conjunctivitis underwent measurement of tear fluid IgE and specific IgE determinations. In the tear fluid, IgE was detected in 56% of the patients. Specific IgE was less common and was detected in 35% of the patients. Tear fluid IgE seemed to be an unreliable indicator for allergy.

Histamine has a central role in allergy. An ocular challenge test with a specific allergen was made to 14 allergic patients. All patients showed a positive reaction. In two thirds of the patients a rapid increase of histamine level in tear fluid was detected in both eyes. This speaks in favour of a sympathetic mechanism between the lacrimal gland and the conjunctiva.

Eosinophils and mast cells have a central role in allergic conjunctivitis. In conjunctival scrapings a significant difference in the number of eosinophils was observed between pollen allergic patients at symptom free stage and healthy controls, but not between patients with atopic and non-atopic conjunctivitis. Over 50% of all atopic patients had eosinophils not only during the pollen season but also outside of the pollen season. In an allergen challenge test, the eosinophils increased up to one hour both in conjunctival scrapings and in the tear fluid.

Presence of conjunctival eosinophils was studied in 152 atopic patients, 484 non-atopic patients with various external eye symptoms and in 333 healthy controls. Eosinophils were observed in 7% to 15% of subjects in different diagnostic groups without signs of atopy, compared with 6% of healthy control subjects.

Tolerance to contact lenses was studied in atopic and non-atopic subjects. Conjunctival eosinophilia found before the use of contact lenses increased the risk to get external eye symptoms, and atopy alone increased the risk 5-fold.

*Osmo Kari, MD, is currently ophthalmologist at the Department of Dermatology and Allergology in the Helsinki University Central Hospital*

# 1992

## PIGMENTARY GLAUCOMA

**Ilkka Lehto, Helsingin yliopisto – University of Helsinki**

Characteristics of eyes with pigment dispersion syndrome (PDS) and pigmentary glaucoma (PG) were studied in a group of patients who were either treated at the Helsinki University Eye Hospital during a ten-year period or seen by private ophthalmologists in the region. The longitudinal study included 9 patients (18 eyes) with PDS, 42 patients (81 eyes) with PG, and 28 controls (56 eyes). In PDS the mean follow-up time was 2.8 years (range, 1–5 years) and the PG patients had been followed up for a mean of 10.7 years (range 2–30 years).

The anterior chamber depth was measured with a soft-tip A-scan ultrasound ruler. The depth did not change when measured in a supine as compared to the prone position in either the PDS or the PG group. In controls, the anterior chamber was deeper in the prone than in the supine position. Glaucomatous eyes treated with pilocarpine reacted like the control eyes and the anterior chamber was deeper in the prone position.

A distinct variation in endothelial cell size and shape was observed in the PDS and PG groups, most likely due to the pigment deposited on the posterior corneal surface, but no significant difference in the endothelial cell density was found as compared to control eyes.

The initial pressure lowering effect of trabeculoplasty in 9 treated eyes was 56%. This effect wore off in three months, after which the intraocular pressure settled to a level 14% (4 mmHg) lower than before treatment.

The outcome of PG in this study was that 2 of 38 patients (5%) were visually impaired in a socio-economic sense because of visual field defects caused by PG, being entitled to compensation, but they were not professionally handicapped. No malignant course of PG was observed.

A mild burning sensation and redness of the eyes were the main complains of topical treatment (timolol with or without dipivephrine, pilocarpine or both); 23% of patients had no side effects from their topical medication. Patients neglecting their treatment once a month and once a week amounted to 43% and 17%, respectively. Forgetfulness and haste were the main reasons for not applying the drops.

*Ilkka Lehto, MD, is glaucoma specialist retired from the Helsinki University Eye Hospital*

# 1993

## REGIONAL ANAESTHESIA OF THE EYE: STUDIES ON TECHNIQUE, MECHANISM AND COMPLICATIONS

**Auli Ropo, Helsingin yliopisto – University of Helsinki**

The technique, mechanism and complications of regional anaesthesia of the eye were investigated. Adequate globe akinesia could be achieved with both extra- and intraconal injections. With the retrobulbar technique, an additional nasal extraconal injection improved the akinesia because of medial rectus and levator muscle blocks but, with regard to lid akinesia, this was less effective than the electrostimulation or infiltration techniques were.

The good akinesia achieved with both extraconal and intraconal injections depends on diffusion. After a periocular injection, the anaesthetic diffuses rapidly from the extraconal to the intraconal space, whereas after a retrobulbar injection, the reverse happens. Thus diffusion results in similar distributions of the anaesthetic within a few minutes despite the difference in the position of the needle. Absorption of the anaesthetic agent by the optic nerve causes clear changes in visual evoked potentials (VEP) after retrobulbar injections. As only part of the injected anaesthetic reaches the optic nerve after periocular injections, the changes in VEP are smaller.

The study confirmed the beneficial effect of ocular compression. The use of compression counteracted the rise in intraocular pressure (IOP) caused by the volume of the anaesthetic and even resulted in a further decrease in IOP, which improved the surgical conditions. Although no difference in globe akinesia could be detected between cases in which compression was or was not used, compression is essential, especially in the large volume techniques. Compression improved diffusion of the anaesthetic away from the levator muscle and resulted in smaller decrease in the palpebral aperture in the early postoperative period. However, the volume and myotoxicity of the anaesthetic cannot be the sole cause of postoperative ptosis, as this was found to be common after both regional and general anaesthesia.

It is concluded that regional blockade of the eye can be achieved with both intraconal and extraconal injections. The diffusion of the anaesthetic makes it possible to use shorter needles, whichever route is used, to deposit the anaesthetic in a safer site far from the ciliary ganglion and the vascular apex, so as to achieve an effective and safe block.

*Auli Ropo, MD, is currently director of clinical research, Santen Oy, Helsinki*

# 1994

## STUDIES ON VENTILATORY EFFECTS AND PHARMACOKINETICS OF OPIOIDS IN CHILDREN

**Katri Hamunen, Helsingin yliopisto – University of Helsinki**

The ventilatory effects of six commonly used opioid analgesics (i.e. morphine, buprenorphine, pethidine, oxycodone, methadone and pentazocine) in children aged 2 to 10 years were investigated after elective ophthalmic surgery using non-invasive methods (i.e. ventilatory rate, end-tidal carbon dioxide and oxygen concentrations [$EtCO_2$ and $EtO_2$] and peripheral oxygen saturation [$SpO_2$]). In addition, pharmacokinetics of intravenous and rectal pethidine, and intravenous oxycodone and pentazocine were studied. The study took place in 1989–1992 at the Helsinki University Eye Hospital.

$EtCO_2$ and $SpO_2$ were the best indicators of ventilatory depression when clinically comparing opioid effects. Ventilatory changes after each drug had distinctive profiles. For all opioids studied, time, duration and magnitude of maximal change in measured variables varied appreciably between individuals. After morphine, the changes in the ventilatory variables were moderate and recovered back to predrug values in about 30 min. All patients given morphine maintained $SpO_2$ over 90%. Ventilatory depression after buprenorphine was greater. Buprenorphine and methadone both produced ventilatory changes of long duration. Compared to morphine, pethidine and pentazocine produced changes which were steeper but of shorter duration. Oxycodone produced fast and clinically significant ventilatory depression in several patients. The oxycodone dose studied (0.1 mg/kg) was therefore not recommended for clinical use in children without careful monitoring.

In children aged 4 to 8 years, intravenous pethidine and pentazocine are eliminated approximately as fast as in adults. Elimination of intravenous oxycodone in children aged 2 to 9 years is faster than in adults. Rectal administration of pethidine produced unpredictable and highly variable concentrations and was not recommended for management of acute pain in children.

**Author's Comment:**
Morphine has maintained its position in daily management of acute postoperative pain in children. In Finland, oxycodone is probably the most commonly used strong opioid for adult postoperative pain. It is used increasingly in children. The currently used dose is smaller than the one used in the thesis. Further pharmacodynamic studies would still be needed in the analgesic and ventilatory dose responses of oxycodone in children.

*Katri Hamunen, MD, is currently anaesthesiologist*
*at the Department of Surgery,*
*Helsinki University Central Hospital*

# 1994

## CATARACT SURGERY. SOCIODEMOGRAPHIC ASPECTS AND GENERAL HEALTH OF PATIENTS, RISK FACTORS FOR COMPLICATIONS AND SHORT-TERM VISUAL OUTCOME

**Pirkko Lumme, Oulun yliopisto – University of Oulu**

The aim was to evaluate characteristics of patients undergoing cataract surgery and to analyze factors determining the outcome of extracapsular cataract extraction (ECCE) with implantation of a posterior chamber intraocular lens (IOL). Sociodemographic and the general health aspects of the patients as well as peroperative ocular findings and their role as risk factors for per- and postoperative complications were evaluated.

The prospective study included 351 consecutive surgeries for adult non-traumatic cataract performed at the Oulu University Central Hospital in 1990. The mean age of the patients was 70 years. Although significantly more women than men were operated, sex proportions in the different age groups in the underlying population were similar. Of the study patients, 17% had diabetes which was at least twice as common as in the general population. Exfoliation syndrome was observed in 31% and glaucoma in 18%. According to the WHO classification, 25% of the patients were blind or had low vision before surgery. The need for help in daily living correlated with impaired vision.

Peroperative complications were registered in 18% of the eyes (bleeding in 9%, zonular or posterior capsule rupture in 8% and vitreous loss in 3%). An anterior chamber IOL was implanted in 3%. Early postoperative complications in the form of more frequent or more serious anterior chamber reactions, corneal edema or increased intraocular pressure were seen in half of the eyes. Exfoliation and small pupil size associated with it, and glaucoma, were the most common risk factors for per- and postoperative complications. Anticoagulant and antiplatelet therapy increased intraoperative bleeding, and acetylsalicylic acid the frequency of fibrin reaction in anterior chamber.

Visual acuity of the operated eye 3 months after surgery was 0.5 or better in 75%, but 12% of patients had low vision and 2% were blind. Poor vision was related to the age and other eye diseases, not to per- or postoperative complications. Cataract surgery provided great benefit for visual rehabilitation of the elderly.

**Author's Comment:**
The study was carried out before the era of phacoemulsification, and the complications reported are not comparable with those observed with current technology, e.g. per- and postoperative problems related to acetylsalicylic acid do not seem to be a problem with small incision cataract surgery. A high frequency of exfoliation in cataract patients continues to be the leading risk factor for intra- and postoperative complications.

*Pirkko Lumme, MD, is currently in private practice*

# 1994

## REGIONAL ANESTHESIA FOR CATARACT SURGERY: STUDIES ON TECHNIQUE, LOCAL ANESTHETICS, HYALURONIDASE, AND EPINEPHRINE

**Johanna Sarvela, Helsingin yliopisto – University of Helsinki**

Eye blocks were studied using retrobulbar and peribulbar anaesthesia, different anaesthetic agents in different concentrations and combinations, and with added adjuvants in 609 cataract patients. For complete lid and globe akinesia, approximately 15% to 20% of patients required supplemental injections.

With a two-site injection technique for regional ophthalmic anaesthesia, satisfactory globe akinesia without supplemental injection was obtained in nearly two thirds of the patients using either a periconal 22-mm-long or an intraconal 31-mm-long needle for inferolateral injection. In spite of a smaller intraorbital volume of the anaesthetic, superior akinesia was achieved more often with the 31-mm needle. With the 22-mm needle, lid akinesia was initially better than with the intraconal one.

Profound muscle relaxation is required for satisfactory globe akinesia; a 0.75% concentration of pH-adjusted bupivacaine was needed to reach this goal. With a mixture of equal volumes of bupivacaine 0.75% and lidocaine 2.0% complete globe akinesia was achieved more often and faster than with bupivacaine 0.75%. With etidocaine 1.0%, in spite of adequate motor blockade, 30% of patients felt intraoperative pain. Even etidocaine 1.5% did not seem to produce good enough intraoperative analgesia. No differences in injection pain scores were recorded between etidocaine 1.0% and 1.5%, pH-adjusted bupivacaine 0.5% and 0.75% or bupivacaine with lidocaine.

Adding hyaluronidase 7.5 IU/ml to etidocaine 1.5% increased the number of patients with satisfactory globe and lid akinesia and sensory block. Doubling the dose of hyaluronidase produced no further improvement. With bupivacaine, hyaluronidase gave superior lid akinesia compared with plain bupivacaine. Epinephrine increased the number of complete lid blocks and lengthened the duration of the block with pH-adjusted bupivacaine 0.75%. When two-site injection technique is used, addition of both epinephrine and hyaluronidase is advocated in medial periconal injection.

**Author's Comment:**
At the time of the thesis, the cataract surgical technique mandated that, in addition to analgesia, a full eyelid and ocular akinesia was obtained. With the advent of small incision cataract surgery, the requirements are no longer the same; a cataract can now be extracted under analgesia induced only by topical anaesthetic eye drops.

*Johanna Sarvela, MD, is currently anaesthesiologist at the Department of Gynaecology and Obstetrics, Helsinki University Central Hospital*

# 1994

## SURGICAL TREATMENT OF GLAUCOMA: STUDIES ON TRABECULECTOMY AND CYCLOCRYOTHERAPY

**Eija Vesti, Helsingin yliopisto – University of Helsinki**

The outcome of trabeculectomy was investigated in 99 consecutive eyes (49 with exfoliation glaucoma [EG], 38 with primary open-angle glaucoma [POAG], and 12 with other type of glaucoma) after a one year follow-up period. The results were more favourable in EG than in POAG: IOP decreased more (46% vs. 37%), the mean IOP was lower (15.5 mmHg vs. 16.8 mmHg), and a greater proportion of EG eyes had an IOP <22 mmHg without glaucoma medication (64% vs. 58%). However, these differences were statistically not significant.

Correlation of the appearance of a filtering bleb to the outcome of trabeculectomy was investigated in a series of 88 eyes after a mean follow-up of 32 months. A diffuse bleb indicated a more favourable outcome than a flap sized bleb or non-detectable bleb. A diffuse bleb type was achieved more easily in an elderly patient whose eye had not been treated with miotics or by argon laser trabeculoplasty, and in which trabeculectomy had not been complicated by early postoperative hypotony.

Progression of cataract after trabeculectomy was investigated in 67 eyes which had either EG (47 eyes) or POAG (20 eyes), no prior intraocular surgery, and preoperative pupillary dilatation of at least 4 mm. The indicators for cataract were: decrease in visual acuity by ≥2 lines, myopic shift in refraction (≥0.25 D), increase in lens opacity and number of cataract extractions. The mean follow-up time was 26 months. Patients who were over 61 years of age with EG had the highest risk, which was further increased by early postoperative hypotony or IOP rise > 30 mmHg.

The outcome of transillumination guided cyclocryotherapy was investigated in a series of 38 consecutive eyes with therapy resistant glaucoma. 25 eyes were treated with sight saving indication and 16 of them (64%) achieved IOP control (from 9 to 23 mmHg). The best results were obtained in eyes with chronic uveitis. 13 eyes were treated to achieve pain relief. The treatment was successful in all but one eye (92%).

**Author's Comment:**
Today cryocoagulation has been replaced by cyclophotocoagulation which has less side effects but the results seem to be quite comparable.

*Eija Vesti, MD, is currently glaucoma specialist and docent in ophthalmology at the Helsinki University Eye Hospital*

# 1994

## RESULTS OF AMBLYOPIA TREATMENT IN A CLINICAL POPULATION: A RETROSPECTIVE STUDY

**Sinikka Vänttinen, Kuopion yliopisto – University of Kuopio**

The results of amblyopia treatment of 397 patients managed from 1979 to 1989 were evaluated retrospectively. The occlusion treatment was the method of choice but other therapies such as penalisation, pleoptics, CAM (from Campbell *et al*.) Vision Stimulator treatment and atropine eye drops were applied when necessary.

The mean age of the patients at the beginning of treatment was 5.4 years. The mean treatment time was 2.7 years. The mean initial visual acuity (VA) of the amblyopic eye was 0.3, increasing to 0.8 at the end of the treatment. A good result (classified as the VA of 0.8 or better at the end of treatment) was achieved in 66% of the 397 patients, and a difference of one line or less between the amblyopic and the good eye was registered in 50%. At a follow-up of one year or more after treatment, the good result was confirmed in 70% of 205 patients.

The percentage of patients with good result was highest in the anisometropic (77 %), cause unknown (71%), strabismic-anisometric (65%) and strabismic (60%) patients; the poorest results were obtained in the deprivation group (31%).

The most significant factors in the logistic regression analysis predicting a good result at the end of the treatment were compliance to the treatment, the type of amblyopia, the neurological status, the initial VA of the amblyopic eye, the age of the patient at the beginning of the treatment, and the type of fixation. The factors explaining a good result at the latest examination were VA of the amblyopic eye and the age of the patient, both measured at the end of the treatment.

**Editor's Comment:**
The treatment of amblyopia can permit many compliant patients to attain useful VA in the amblyopic eye. However, the time required to achieve and maintain the results is quite long and demands therefore support and encouragement from the clinical personnel.

*Sinikka Vänttinen, MD, deceased in 2006*
*Thesis is abridged by the Editors*

# 1995

## A HISTOPATHOLOGICAL AND LECTIN HISTOCHEMICAL STUDY OF EXFOLIATION SYNDROME

**Jaana Hietanen, Helsingin yliopisto – University of Helsinki**

The primary aim was to analyse the thickness of the lens capsule by measuring it from formalin-fixed and paraffin-embedded histological specimens obtained during intracapsular cataract surgery in eyes with and without exfoliation syndrome. No significant difference in capsule thickness was found between the groups. The results confirmed that the thinnest area of the lens capsule is the central posterior capsule which should be handled with great caution during cataract surgery.

The secondary aim was to develop lectin histochemical tools for detection of exfoliation material in histological specimens. In addition, lectin binding profiles of various tissues in eyes with and without exfoliation syndrome were compared with that of exfoliation material in order to clarify the origin of the exfoliation deposits.

Of the many lectins used, seven were useful markers of intraocular exfoliation material in histological specimens. When comparing the lectin binding profile of exfoliation with that of neighbouring tissues, similar reactions were detected in non-pigmented ciliary epithelium. Interestingly, the lens capsule was essentially unstained with all the lectins used. These findings suggested that exfoliation material may be produced by the non-pigmented ciliary epithelium.

The third aim was to look for labelling similar to that of intraocular exfoliation material in conjunctival biopsy specimens of patients with and without exfoliation syndrome by light microscopy using lectins and three monoclonal antibodies to the HNK-1 carbohydrate epitope. No difference in lectin binding profile or immunoreactivity was detected between these patients. The findings indicate that exfoliation-like fibres often detected in the conjunctiva by electron microscopy differ from the carbohydrate composition of intraocular exfoliation material.

**Author's Comment:**
At the time of the thesis, a hunt for the origin of exfoliation material was ongoing in many laboratories. We had recently shown that the HNK-1 carbohydrate epitope was a specific label for exfoliation material and also was associated with elastic fibres. Others independently made the link with the elastin system. Last year Icelandic investigators linked exfoliation with polymorphisms of the lysyl oxidase-like 1 gene. The cell of origin and the relationship between intraocular and extraocular exfoliation deposits remain open issues. Thinness of the lens capsule remains an important issue even in modern cataract surgery.

*Jaana Hietanen, MD, is currently in private practice*

# 1995

## VISUAL FUNCTION AND OCULAR DISEASE IN THE ELDERLY: THE OULU EYE STUDY

**Heli Hirvelä, Oulun yliopisto – University of Oulu**

The Oulu Eye Study was a cross-sectional population-based survey of inhabitants aged 70 years or older in three rural communities in the county of Oulu, Finland. Of the 560 eligible subjects, 500 (89%) were examined. Visual acuity and contrast sensitivity were measured and related to subjective visual problems, and the prevalence of impaired vision and its causes were recorded. The distribution and prevalence of lens opacities and cataract, macular changes, intraocular pressure and glaucoma and their impact on visual functions were evaluated.

A visual acuity of 1.0 or better in both eyes was found in 7% of subjects, and 59% had an acuity of 0.7 or better in the better eye. The correlation between visual acuity and contrast sensitivity was pronounced (r=0.47 to 0.79 for various diseases). By World Health Organisation criteria, 10% of subjects had low vision and 2% were blind.

The diagnosis of lens opacities was based on clinical biomicroscopy, and the findings were compared to standard photographs of the Lens Opacification Classification System II (LOCS II). Of those examined, 34% had a clear lens in both eyes, and cataract (LOCS II grades higher than C1, P0, N1 or NC1), aphakia or pseudophakia was recorded in one or both eyes in 64% of the participants.

Exfoliation syndrome in one (8%) or both (14%) eyes was diagnosed in 22% of participants, and glaucoma defined as previously diagnosed glaucoma (8%) or glaucomatous optic disc on photographs or ophthalmoscopy (4%) occurred in 12% of subjects.

Fundus photographs were obtained from 76% of eyes. Photography, ophthalmoscopic evaluation of the macula or both in at least one eye was possible for 96% of subjects. No macular pathology in either eye was found in 46% of examined participants. Early age-related macular degeneration (ARM) was found in 37%, geographic atrophy in 4% and disciform degeneration in 4% of those examined.

Of visually handicapped persons, 68% had ARM, 75% had cataract and 21% had glaucoma. In 39% of these persons ARM was considered the main cause of visual deterioration, whereas in 11% the main cause was cataract and in 18% both early dry ARM and cataract were present without clear dominance by either.

In addition to untreatable age-related and other eye diseases, a considerable number of treatable causes of visual impairment afflict the elderly. According to this study up to one third of all eyes in subjects aged 70 years or more may need cataract surgery.

*Heli Hirvelä, MD, is currently in private practice*

# 1995

## EXFOLIATION SYNDROME: A RISK FACTOR FOR GLAUCOMA AND LENS OPACIFICATION

**Päivi Puska, Helsingin yliopisto – University of Helsinki**

A computerized 3-dimensional image analysis of optic nerve head (ONH) stereophotographs was performed for the paired eyes of 66 non-glaucomatous subjects (mean age 69 years) with unilateral exfoliation syndrome (ES). The intraocular pressure (IOP) was significantly higher in the exfoliation-positive eye (EP) than in the exfoliation-negative (EN) fellow eye (17 vs. 15 mmHg). The paired eyes did not differ in ONH topography measured by disc area, rim area, cup area, rim/disc area ratio, or cup volume.

A detailed analysis of ONH configuration was performed in 37 subjects by measuring the rim-to-disc radius ratio at intervals of 30°. In 16 subjects in whom IOP was at least 2 mmHg higher in the EP eye (mean, 18 mmHg) than in the EN eye (mean, 14 mmHg) the EP eyes had significantly smaller rim-to-disc radius ratios at the inferotemporal rim (0.38 vs. 0.49) and the inferior rim (0.43 vs. 0.55) than the EN fellow eyes. No such differences in ONH configuration were found in another group of 21 subjects in whom the IOP difference between the paired eyes was less than 2 mmHg. ONH change was concluded to be pressure-dependent, but the effect of ES could not be ruled out.

In the EP eye, IOP correlated significantly with the degree of chamber angle pigmentation. The EP eye with at least grade 2 trabecular pigmentation had significantly smaller rim area (1.49 vs. 1.61) and rim/disc area ratio (0.71 vs. 0.74) than the fellow eyes. In non-glaucomatous EP eyes, dense trabecular pigmentation was an important prognostic sign of a rise in IOP and ONH damage.

ES as a risk factor for lens opacification was investigated in 63 subjects with unilateral ES and 42 patients with unilateral exfoliation glaucoma (EG). Increased lens opacification was associated with EG even when the effect of glaucoma therapy was ruled out. The likelihood of such an association was also seen in ES.

**Author's Comment:**
Re-examination of the same patients 10 years later showed that 38% of formerly non-glaucomatous subjects with previously unilateral ES had now converted to bilateral ES. Conversion rate to EG was 32% in the initially EP eyes and 38% in the initially EN fellow eyes. The EP eyes that converted to glaucoma had a higher initial IOP, a poorer pupillary dilatation, and a greater difference in IOP between the two paired eyes than those EP eyes that remained non-glaucomatous.

*Päivi Puska, MD, is currently head of the glaucoma outpatient clinic and docent in ophthalmology at the Helsinki University Eye Hospital*

# 1995

## THE HNK-1 CARBOHYDRATE EPITOPE IN THE ANTERIOR SEGMENT OF THE EYE: THE INNER CONNECTIVE TISSUE LAYER OF THE HUMAN CILIARY BODY AS A DISTINCT ELEMENT

**Marita Uusitalo, Helsingin yliopisto – University of Helsinki**

The study was a histopathological investigation of the distribution of the cell-adhesion related HNK-1 carbohydrate epitope in the anterior segment of the eye. The material consisted of fetal and postnatal normal human eyes, eyes with exfoliation syndrome (ES), glaucoma, iridocyclitis, and uveal melanoma, pseudophakic eyes, and eyes from 18 different fish, bird and mammalian species. The specimens were studied by immunohistochemistry using the avidin-biotinylated peroxidase-complex method with three antibodies to the HNK-1 epitope.

In normal human eyes and pseudophakic eyes, an immunoreaction for the HNK-1 epitope was seen in the inner connective tissue layer of the ciliary body, located between the ciliary epithelia and ciliary muscle. The immunoreaction delineated cell processes of a population of dendritic-like cells. The immunoreaction appeared in this area during the 20th gestational week and remained constant throughout life. In eyes with ES or glaucoma, the immunoreaction was partly granular, and in eyes with advanced glaucoma, it was grossly diminished. Immunoreaction for the HNK-1 epitope was also seen in the ciliary epithelia, the posterior pigmented layer of the iris epithelium, the zonular lamella of the lens, the ciliary nerves, the sclera, and in some blood vessels of the iris.

Immunohistochemical staining using antibodies to the HNK-1 epitope provided indirect evidence of a hitherto unrecognized population of dendritic cells in the inner connective tissue layer of the human ciliary body. The changes in the HNK-1-reactivity in this region in eyes with exfoliation syndrome and glaucoma and the HNK-1-reactivity in the blood vessels of the iris seem to be related to these disease processes. Immunoreaction of exfoliation material provided one of the first specific tools to label this abnormal deposit by immunohistochemistry.

**Author's Comment:**
After this thesis other researchers became interested in these findings. They confirmed them and further clarified the presence of the epitope in other parts of the eye. The HNK-1 epitope became a good marker of intraocular exfoliation material and we e.g. demonstrated that exfoliation syndrome is a bilateral disease although it may clinically sometimes seem unilateral. Our immunoelectron microscopic findings using antibodies to the HNK-1 epitope further localised it to the elastic fiber system of the ciliary body and suggested that this epitope has a role in structurally stabilizing the ciliary body.

*Marita Uusitalo, MD, is currently head of the outpatient clinic and docent in ophthalmology at the Helsinki University Eye Hospital*

# 1995

## VISUAL SIGNAL PROCESSING MECHANISMS IN THE DIPTERAN COMPOUND EYE: THE ROLE OF THE FIRST VISUAL SYNAPSE AND THE FIRST VISUAL INTERNEURON

**Raimo Uusitalo, Oulun yliopisto – University of Oulu**

The visual signal processing mechanisms in the first visual synapse and the first visual interneurons or the large monopolar cell (LMC) of the fly *(Calliphora vicina*) compound eye were investigated *in situ* by using various stimulation paradigms: 1. contrast steps; 2. pseudorandom modulated contrast sequences and 3. discontinuous single electrode current clamp with current steps. To study the involvement of ion channels and ion exchangers to signal transmission through the synapse and LMC, ionophoretical injections of different ions and blockers were applied.

Increased light adaptation gradually changed the synaptic signal transfer at the first visual synapse from low-pass to band-pass filtering. This was accompanied by decreased synaptic delay and increased contrast gain. The overall synaptic gain and the intrinsic noise (transmission noise) were reduced. During light adaptation, the reversal potential of the transmitter-gated conductance ($Cl^-$) in post-synaptic LMC was found to depolarize considerably by about 20 mV, indicating a probable substrate saturation of the $Cl^-$-extrusion mechanism that contributed to light-adapting in this synapse. After light-adaptation, the LMC showed a marked enhancement of about 10 mV of the light-on responses. This depended on the coinciding hyperpolarization of presynaptic photoreceptors. The mechanism for the post-adaptive potentiation (PAP) involved tonic transmitter release that was reduced drastically to 11 mV below the presynaptic dark resting potential, and a tonic $Cl^-$-extrusion mechanism. Their simultaneous effect led to hyperpolarization of the reversal potential of the synaptically driven conductance ($Cl^-$) and thus to enhanced responses. A possible function of this PAP may be to reduce rapidly the period of sensitivity loss after light-adaptation.

In the axon part of the LMC (L3 and L1) a normally inactivated voltage sensitive conductance, probably sodium, was found to be activated after the hyperpolarizing light-on responses. The action of this conductance was to boost the high frequency band of the visual signal under transmission through these cells. This mechanism was probably to counterbalance the low-pass nature of the graded transmission of visual signals in the axon part of this pathway. Partial activation was also produced by the hyperpolarization of the LMC resting potential during light adaptation; thus it can at least partly be behind the non-linear and band-pass nature of LMC responses during light-adaptation.

The results show a complex nature of processes operating in the first visual synapse and visual interneuron to adjust this visual system to changing visual environment.

*Raimo Uusitalo, MD, is currently chief physician at the Helsinki University Eye Hospital*

# 1996

## OCCURRENCE, NATURAL HISTORY AND RISK FACTORS OF RETINOPATHY IN DIABETIC CHILDREN AND ADOLESCENTS

**Aura Falck, Oulun yliopisto – University of Oulu**

In a cross-sectional study of the pediatric diabetes population, 216 children younger than 17 years of age living in the Oulu County in 1989–1990, 194 children (90%) with insulin-dependent diabetes mellitus were examined by fundus photography for diabetic retinopathy (DR). Their median age was 12 years (range, 4 to 16 years), and the median duration of diabetes was 4.5 years (range, 0 to 14 years). Of these patients, 11% had minimal or mild background DR. Nine had changes in one eye only. A follow-up study 2 to 3 years later was performed on 182 patients. During the follow-up period, DR had appeared in 33 children and disappeared in 2 children.

Changes in vascular calibre over the study period were searched in 45 diabetic children by microdensitometry and digital image analysis. Vasodilation associated with elevated glycated hemoglobin on the date of the follow-up study.

Long duration of diabetes, including both the duration prior to and after the onset of pubertal changes, hyperglycemia in terms of elevated glycated hemoglobin and glucosuria index, female sex and high diastolic blood pressure appeared to be risk factors for DR in adolescence. Of the genetic markers studied, HLA-DR1 seemed to be a predictor of retinopathy, while HLA-A9 and the HLA-A9,B40 haplotype were protective.

**Author's Comment:**
Childhood diabetes is more prevalent in Finland than anywhere else in the world, the prevalence is continuously increasing, and the onset of diabetes has shifted to younger children during the past years. At the same time, ways to manage diabetes and its complications have developed. In 2007, follow-up data on these by now adult patients was gathered, and the diabetic children currently living in the Oulu County underwent fundus photography for diagnosing DR. This follow-up study will give epidemiological data on DR and will help to identify the risk factors for severe retinopathy. Tools for improving the diabetes eye health care system to prevent visual impairment and blindness are still needed.

*Aura Falck, MD, is currently chief of the visual rehabilitation centre at the Department of Ophthalmology, Oulu University Hospital*

# 1996

## NORMAL TENSION GLAUCOMA: ASPECTS ON IOP-LOWERING MEDICATION AND ETIOLOGY AND PATHOGENESIS OF OPTIC NEUROPATHY

**Kristina Jämsén, Helsingin yliopisto – University of Helsinki**

The IOP lowering effect of 2.0% pilocarpine hydrochloride, 0.5% timolol maleate and 0.5% betaxolol hydrochloride was investigated in a series of 23 eyes with normal tension glaucoma (NTG). The IOP lowering effect of pilocarpine did not achieve statistical significance. The effect of β-blockers was significant but rather small, 16% for timolol and 11 % for betaxolol measured at 7.30 a.m. before instilling the morning dose.

The occurrence of asymmetry in optic disc size and the occurrence of asymmetry of IOP level, and whether these correlated with an asymmetry in the visual field, were investigated in 26 patients with NTG. The results indicated that the cumulative effect of a large optic disc size and a slightly elevated IOP in myopic and long eyes can cause damage. The individual risk factors did not reach a level at which they could cause damage alone.

In 13 NTG patients with asymmetrical visual field loss of at least 2.5 dB in the mean defect, the differences in visual field defects were compared with the differences in optic disc configuration measured from stereophotographs with a computerised image analysis system. The results indicated that the early optic disc damage in NTG usually occurs in the inferior part of the optic disc extending to the upper parts as the disease progresses.

Six out of 25 patients with NTG were found to have thyroid disease. The mean refraction was more hyperopic and the mean IOP tended to be higher in the thyroid group. The IOP fluctuations were higher in the non-thyroid eyes. The pattern visual evoked potentials and the visual field defect in one patient with NTG were reversed after treatment of the hypothyroidism alone. These findings indicate that thyroid disease is a risk factor for optic neuropathy mimicking NTG.

The topography of the optic disc and the configuration of the peripapillary nerve fibre layer were investigated in 12 NTG patients (6 with and 6 without thyroid disease) and in 6 voluntary controls using the Heidelberg Retina Tomograph™. The profile of the peripapillary retinal nerve fibre contour line differed between the groups. Further investigation will be needed to decide whether these profiles and possible contour line height variation ratios can be used in the diagnosis of NTG at an early stage.

*Kristina Jämsén, MD, is currently in private practice*

# 1996

## SYSTEMIC ABSORPTION AND EFFECTS OF TOPICALLY APPLIED OCULAR ANTICHOLINERGIC DRUGS

**Kimmo Lahdes, Turun yliopisto – University of Turku**

A modification of the radioreceptor assay (RRA) was used to investigate the systemic absorption of atropine, scopolamine and cyclopentolate after ocular application. This modification of RRA provided a sensitive method for detecting picogram quantities of anticholinergic drugs in plasma.

Ocular atropine, scopolamine and cyclopentolate are absorbed into the systemic circulation. The peak plasma levels were reached within 30 minutes in most subjects. The atropine and scopolamine absorption from eyedrops is as rapid as that reported after intramuscular injections. The peak plasma levels recorded after a single atropine or scopolamine eyedrop are of the same order of magnitude as those previously reported after intramuscular injection when different doses are taken into account. In children, interindividual variation in systemic absorption of ocular cyclopentolate was found to be remarkable.

Cyclopentolate was eliminated from plasma with a mean half-life of about 100 min, a value which was somewhat shorter than that reported earlier for atropine or scopolamine. Elimination half-life for cyclopentolate in plasma was reported for the first time.

Incorporating cyclopentolate into polygalacturonate polymers which had mucoadhesive properties produced no effect on the rate or the magnitude of the systemic absorption of cyclopentolate in humans. Also the effect of polygalacturonate complexes on mydriatic or cycloplegic responses was negligible.

The canthal application method is a clinically applicable alternative to the traditional one when delivering ocular cyclopentolate eyedrops. The systemic absorption of the drug was equal after both techniques.

*Kimmo Lahdes, MD, is currently neuro-ophthalmologist*
*at the Department of Ophthalmology,*
*Turku University Central Hospital*

# 1996

## CORNEAL WOUND HEALING AFTER MODERN REFRACTIVE SURGERY: EXPERIMENTAL STUDIES ON EXCIMER LASER PHOTOREFRACTIVE KERATECTOMY AND LASER IN SITU KERATOMILEUSIS

**Terho Latvala, Helsingin yliopisto – University of Helsinki**

Corneal wound healing after two types of refractive surgical procedures, photorefractive keratectomy (PRK) and laser in situ keratomileusis (LASIK), was investigated. The study included experimental excimer laser PRK or surgical wounds performed on rabbit and cat corneas and experimental LASIK operations on voluntary patients prior to enucleation of the blind eye for medical reasons. The corneas were analysed using indirect immunohistochemistry for detection of the hemidesmosome marker integrin subtypes $\alpha_6$ and $\beta_4$, the basement membrane marker laminin, the extracellular matrix glycoproteins fibronectin and tenascin, SPARC (Secreted Protein, Acidic and Rich in Cysteine), transforming growth factor β1 (TGF-β1). and $\alpha$-smooth muscle actin ($\alpha$-SMA). Also acetylcholinesterase (AChE) histochemistry was used to visualise corneal nerves.

Characteristic distributions for each investigated glycoprotein were found. The expressions varied between types of operations and different time-points during experimental corneal wound healing. The results indicated activity of fibronectin, tenascin, and SPARC in epithelial cell migration, wound healing process, and impaired corneal transparency. Cells in LASIK corneas were negative for $\alpha$-SMA but immunoreactive for TGF-β1. Integrin and laminin showed a slow reassembly process lasting almost 12 months after PRK. The results indicated that interaction of corneal epithelium and stroma plays an important role in the regulation of corneal wound healing and scar formation. Experiments in corneal nerve morphology after PRK and LASIK revealed differences in the neural recovery processes.

*Terho Latvala, MD, is currently associated chief physician and neuro-ophthalmologist at the Department of Ophthalmology, Tampere University Hospital*

# 1996

## TAUSTAN VALAISTUS NÄKÖKENTTÄTUTKIMUKSESSA

**Markku Leinonen, Turun yliopisto – University of Turku**

Väitöskirjatutkimus osoitti, että osa näkövioista jää nykyisillä tutkimusmenetelmillä paljastumatta. Näkökenttätutkimus on tärkeä tutkimusmenetelmä selvitettäessä eri silmäsairauksien aiheuttamia vikoja näössä. Nykyisin nämä tutkimukset tehdään yksinomaan hämärässä valaistuksessa. Tässä valaistustasossa ei kuitenkaan kaikkia eri silmäsairauksien aiheuttamia näkövikoja ole mahdollista löytää. Verkkokalvon kahdesta aistinsolutyypistä vain tappijärjestelmään rajoittuvan vian löytämiseksi näkökenttätutkimus olisi tehtävä kirkkaassa valaistuksessa. Pelkän sauvajärjestelmän toiminnan mittaamiseksi näkökenttätutkimus tulisi tehdä täysin pimeässä.

Tutkimusta varten kehitettiin menetelmä, jossa näkökenttätutkimuksia tehtiin kirkasta päivänvaloa vastaavassa valaistustasossa käyttäen testivalona punaista laseria. Menetelmän avulla saatiin mitattua verkkokalvon kahdesta valoaistinsolutyypistä pelkästään värien näkemisestä vastuussa olevan ja päivänvalossa toimivan tappijärjestelmän viallisuutta. Menetelmän avulla tutkittiin mm. erityyppisten täydellisesti värisokeiden henkilöiden näkökentän laajuutta. Synnynnäisessä täydellisessä värisokeudessa (akromatopsia) ja etenevässä verkkokalvon tappijärjestelmää vioittavassa silmäsairaudessa (tappidystrofia) näkökentän laajuus poikkesi normaalista ja toisistaan merkittävästi vaikka hämärässä tehdyssä tavallisessa tutkimuksessa näkökentät olivat lähes normaalit.

Näissä sairauksissa normaalissa päivänvalossa esille tulevan näkökenttävian löytäminen nykyisin rutiinikäytössä olevilla näöntutkimusmenetelmillä on puutteellista. Väitöstutkimuksessa käytetyllä menetelmällä kirkkaassa valaistuksessa erot olivat selviä: synnynnäisesti täydellisesti värisokea henkilö ei kyennyt näkemään testivalona käytettyä punaista laservalotäplää missään kohdassa näkökenttää, kun taas tappijärjestelmää viottavassa silmäsairaudessa vikaa oli laservalolla tutkien vain aivan näkökentän keskellä. Synnynnäisessä täydellisessä värisokeudessa silmän verkkokalvon aistinsoluista päivänvalonäöstä vastaavat tapit ovat viallisia koko näkökentän alueella, kun etenevässä verkkokalvon tappijärjestelmää vioittavassa silmäsairaudessa tauti on vahingoittanut verkkokalvon tappitoimintaa vain näkökentän keskeltä.

Tutkimuksessa mitattiin myös hämärässä ja pimeässä näkemiseksi välttämättömän sauvajärjestelmän toimivuutta tähän tarkoitukseen muunnetulla laitteella käyttäen sinivihreää testivaloa. Menetelmällä mitattiin periytyvää näköhermosurkastumaa (dominantti infantiili optikusatrofia) sairastavien potilaiden näkökenttää pimeässä. Käytetyllä menetelmällä todettiin paikallisia sauvatoiminnan vajauksia, vaikka edeltävässä tutkimuksessa rutiinikäytössä olevalla menetelmällä sauvatoiminnan vajausta oli löydetty vain osalla tätä tautia sairastavista potilaista.

*Markku Leinonen, MD, is currently strabismologist and low vision specialist at the Department of Ophthalmology, Turku University Central Hospital*

# 1996

## OCCURENCE OF GENERALIZED PERIPHERAL IRIS TRANSLUMINANCE IN EYES WITH PSEUDOEXFOLIATION SYNDROME: ASSOCIATIONS WITH CEREBROVASCULAR DISEASE AND OCULAR BLOOD FLOW

**Leo Repo, Kuopion yliopisto – University of Kuopio**

Transluminance of the iris is a phenomenon detectable by illuminating the eye either transpupillary or transsclerally. More translucent areas appear owing to degenerative changes in the stroma and pigment epithelium of the iris. We examined the prevalence of generalized peripheral iris transluminance (GPIT) in eyes of patients with exfoliation syndrome (ES). We also examined the possible associations of ES with cerebrovascular disorders and changes in orbital blood circulation by investigating prevalence of GPIT and ES among patients with a history of transient ischemic attack (TIA) and by measuring possible changes in the blood flow of the ophthalmic artery with a color Doppler unit. Histological changes in the pupillary area of the iris were examined in connection with poorly dilating pupils.

GPIT was significantly more common in ES patients as compared to healthy controls of the same age. The frequency of ES among TIA patients was 2 to 4 times higher than is reported in previous Finnish population studies on the prevalence of ES. The frequency of ES was especially high in eyes of TIA patients who showed positive GPIT. On the basis of color Doppler, these eyes showed impaired ciliary circulation, which supports the theory that hypoxia plays an important role in the development of ES. Histological findings showed degenerative changes in the stromal tissue and the sphincter muscle of the iris in ES eyes, which implies involvement of different structures of the human iris in connection with poorly dilating pupils.

Transillumination of the iris as a clinical diagnostic method is easy to perform using a biomicroscope and transscleral transilluminator. Positive GPIT in an elderly person may suggest the presence or future risk of ES and, in the long run, exfoliation glaucoma.

*Leo Repo, MD, is currently in private practice*

# 1996

## DETECTION, CONSEQUENCES AND RISK FACTORS OF EARLY LENS OPACITIES: A THREE-YEAR FOLLOW-UP STUDY

**Päivi Rouhiainen, Kuopion yliopisto – University of Kuopio**

This study was carried out as a part of The Kuopio Atherosclerosis Prevention Study concerning the effect of pravastatin on carotid and femoral atherosclerosis. As some compounds belonging to the statin family had been reported to have a cataractogenic effect in animal studies, it was considered necessary to follow the lens status of the study participants.

Altogether 410 hypercholesterolemic men underwent an ophthalmological examination 3 times at 18-month intervals. A special emphasis was upon the detection and development of lens opacities, which were assessed by two different methods, the Lens Opacification Classification System II (LOCS II) and Opacity Lensmeter™ 701 (OLM). LOCS II is a subjective grading method introduced by Chylack *et al.*; it is based on grading the opacity level by comparing the microscopic finding to standard photographs. OLM is a commercially available apparatus which sends a light beam in the eye and calculates the amount of scattered light giving a numerical value of the amount of opacification.

Progression of pre-existing and development of new lens opacities was detected by LOCS II in 9% of the eyes in the category of nuclear sclerosis, 5% in cortical and 0,5% in the category of posterior subcapsular opacities. OLM detected existing nuclear opalescence well, but was less good in detecting cortical and posterior subcapsular opacities. It was unable to discover most of the progression detected by LOCS II.

Age and cigarette smoking were associated with an increased risk of progression of cortical opacities, but high plasma vitamin E level was associated with a deceleration in cortical opacity progression. Participants belonging to the lowest quartile of plasma vitamin E had a 3.7-fold risk for cortical opacity progression when compared with participants in the highest quartile.

Pravastatin treatment had no statistically significant effect on lens opacity development or progression during the follow-up, although a trend towards new cortical opacities to appear more often in pravastatin-treated participants was observed.

*Päivi Rouhiainen, MD, is currently in private practice*

# 1997

## STRUCTURAL AND FUNCTIONAL ALTERNATIONS IN EARLY DIABETIC RETINOPATHY, WITH SPECIAL REFERENCE TO DIABETIC PREGNANCY

**Timo Hellstedt, Helsingin yliopisto – University of Helsinki**

The structural and functional changes that accompany mild diabetic retinopathy (DR) were studied. Diabetic pregnancy was chosen as an experimental model because previous studies had suggested that mild retinopathy progressed during pregnancy.

Initially, a computerised system for the detection of diabetic lesions from fundus photographs was developed. The rates of formation and disappearance of microaneurysms (MA) were investigated in 24 males and non-pregnant females with mild DR during a 2-year follow-up. Three fluorescein angiograms (FAG) were taken at 1-year intervals, and MA were identified in 2 separate sessions. Of 298 MA found at baseline, 58% were present at the 1 year and 48% at the 2 year follow-up. In patients whose glucose control was good, MA formation rate tended to be lower. MA disappearance rate was not correlated with glucose control.

In a further study, MA were compared between FAG and simultaneous colour and red-free photographs. In 24 patients, 394 MA were detected in FAG, 95 in red-free and 62 in colour photographs. Of the MAs detected in FAG, only 7% were seen as a red dot in colour photographs and 13% in red-free photographs. On the other hand, corresponding MA in FAG was found for about 50% of the dots classified as MA in colour and red-free photographs.

Longitudinal changes in macular blood flow velocity, contrast sensitivity and MA dynamics were investigated during pregnancy and postpartum. In diabetic women, the capillary blood flow velocity was lowest at term, whereas in the non-diabetic controls the velocity increased until the end of pregnancy and then decreased. When MA formation and disappearance rates were investigated during pregnancy it appeared that the MA count increased during pregnancy and after delivery, being highest 3 months postpartum and decreased thereafter gradually up to 1 year postpartum.

Contrast sensitivity at low to mid spatial frequencies was lower in the diabetic patients than in non-diabetic controls throughout pregnancy. These neurosensory defects may result from functional retinal vascular or metabolic abnormalities.

*Timo Hellstedt, MD, is currently corneal specialist and ophthalmic surgeon at the Helsinki University Eye Hospital*

# 1997

## TENASCIN AND CYTOKINES IN CORNEAL WOUND HEALING: TEAR FLUID STUDIES ON PHOTOREFRACTIVE KERATECTOMY

**Minna Vesaluoma, Helsingin yliopisto – University of Helsinki**

The wound healing process after photorefractive keratectomy (PRK) is regulated by a number of modulators produced by the lacrimal glands, inflammatory cells, extracellular matrix, nerves, corneal epithelial cells and stromal keratocytes, or deriving from conjunctival vessels.

The presence of tenascin and cytokines (hepatocyte growth factor [HGF], transforming growth factor [TGFβ1], vascular endothelial growth factor [VEGF], platelet-derived growth factor [PDGF-BB] and tumor necrosis factor [TNFα]) in human tear fluid was investigated using enzyme or radioimmunoassay. Changes in their concentrations following PRK were assayed on day 1-2 and on day 7 postoperatively in 70 patients (38 woman and 32 men, mean age 31 years). Tear fluid samples were collected from the lower fornix using scaled microcapillary tubes.

The study showed that excluding PDGF-BB all substances were present in normal human tear fluid in the following concentrations: tenascin 0.85 µg/ml, HGF 0.44 ng/ml, TGFβ1 7.8 ng/ml, VEGF 18.6 ng/ml and TNFα 0.36 ng/ml. On day 1-2, the concentration of PDGF-BB increased, the concentrations of TGFβ1, and TNFα remained relatively stable, and the concentrations of HGF and VEGF decreased significantly. On day 7, all concentrations had returned to the preoperative level, except that of HGF.

Because PRK induces a remarkable hypersecretion of tears, any tear fluid component would easily get diluted after PRK. The mean tear fluid flow in the microcapillary (volume dived by the tear collection time) increased significantly on day 1-2 and it decreased to preoperative level by day 7. Therefore, we introduced a release parameter (concentration multiplied by tear fluid flow), which takes tear fluid flow changes into account and better reflects the change in synthesis or release of the substance. Immediately postoperatively, on day 1-2, the release rates (g/min) of all substances increased significantly, but they returned to the preoperative level by day 7.

The bioavailability of tenascin and cytokines on the ocular surface is likely to increase during the first days after PRK, before completed re-epithelialization of the wound. The increased release rates suggest that they may be involved in corneal healing after PRK.

*Minna Vesaluoma, MD, is currently docent in experimental ophthalmology at the University of Helsinki and corneal specialist at the Moorfields Eye Hospital, London, United Kingdom*

# 1997

## TEAR FLUID PLASMIN ACTIVITY AND FIBRONECTIN CONCENTRATION: EFFECT OF CONTACT LENS WEAR, SJÖGREN'S SYNDROME AND PHOTOREFRACTIVE KERATECTOMY

**Tuula Virtanen, Helsingin yliopisto – University of Helsinki**

Plasmin activities in tear fluid (TF) of contact lens (CL) wearers with and without tear deficiency, as well as in Sjögren's syndrome (SS) and during healing of human corneal photorefractive keratectomy (PRK) wounds, were investigated with a fluorometric assay. TF cellular fibronectin (cFn) concentration during healing of corneal PRK wounds was measured with an enzyme immunoassay.

In 32 healthy CL wearers, the TF plasmin activity was nearly 2-fold compared with that seen in control subjects. In nine CL wearers with tear deficiency and lacrimal plugs, the increase in plasmin activity was even higher, 7-fold, and the highest of any seen in the study. Canalicular plugs induced a short-term decrease in the TF plasmin level to 58% of normal. The effect lasted only for 1 month. Similarly, a transient improvement of conjunctival hyperaemia, fluorescein and Rose Bengal staining, and subjective irritation scores was observed.

The TF plasmin activities of 16 patients with verified SS and a dry eye were more than 10 times higher than in healthy controls. The increase might have been even higher, because the topically added balanced salt solution needed for TF sample collection of dry eye patients appeared to lower plasmin activities about 40% in the control group.

On the first two postoperative days following PRK, the TF flow was highly increased because of reflex tearing resulting from the irritation caused by a persistent epithelial defect. The TF plasmin activity was decreased, but the level of plasmin release was increased 4- to 6-fold compared with the preoperative level. Both the activity and the release normalised in 1 week, after re-epithelization was completed. The cFn concentration was increased 1.5-fold during postoperative days 1, 2, and 7 compared with preoperative values. The release levels were increased during the first 2 postoperative days, and reached normal levels in 1 week.

TF proteolytic activity related to plasmin plays a potential role in the pathology of CL wear and dry eye syndrome. CL wear with tear deficiency appeared to potentiate this effect whereas lacrimal occlusion with a plug prevents the proteolytic effect. PRK appears to represent a normal corneal wound healing process in which the proteolytic system is needed, but high TF proteolytic activities related to plasmin are prevented by the dilution effect of reflex tearing.

*Tuula Fyhrqvist, MD, is currently in private practice*

# 1998

## STRONTIUM PLAQUE IRRADIATION FOR EXUDATIVE AGE-RELATED MACULAR DEGENERATION

**Aino Jaakkola, Helsingin yliopisto – University of Helsinki**

Age-related macular degeneration (AMD) is the leading cause of visual disability in the industrialized countries. In Finland, 54% of visual disability among people 64 years of age or older is caused by AMD. In the most devastating form of the disease choroidal neovascular membranes (CNVM) grow beneath the macula. The only established form of treatment when the study started had been laser photocoagulation, but only 13% of patients with exudative AMD met the laser treatment criteria.

A possible new therapy for the treatment of subfoveal CNVM associated with AMD was introduced. We treated a group of 20 patients with subfoveal CNVM not amenable to laser therapy with local episcleral radiotherapy using a strontium (90Sr) applicator. The fellow eyes and 12 patients who refused 90Sr treatment or had been examined before the start of this study served as controls. The applicator was applied to the posterior sclera under the macula and held there tightly for 54 min to obtain a dose of 15 Gy at a depth of 1.75 mm. The main outcome measures evaluated after 3, 6, 12 and 24 months were visual acuity (VA) and change in fluorescein angiography (FA). Also other retinal functions such as contrast sensitivity, retinal sensitivity and reading speed were evaluated. Changes in macular topography were studied with confocal scanning laser tomography.

It was shown that local radiotherapy with $^{90}$Sr plaque can arrest growth and even induce regression of a CNVM in AMD. The CNVM showed signs of regression by FA in 74% of irradiated eyes at 12 months. VA improved or remained unchanged in 45% of the irradiated eyes as compared to only in 25% of the control eyes at 12 months.

**Author's Comment:**
To further evaluate the new $^{90}$Sr treatment, a larger, prospective, randomized clinical trial was done at the Helsinki University Eye Hospital, enrolling 86 eyes of 86 patients between 1996 and 2000. Strontium brachytherapy reduced the short term (6 month rate) visual loss in AMD, but there was no long-term benefit at 3 years. More recently, intravitreally injectable anti-vascular endothelial growth factor agents were approved and are now widely used in the treatment of exudative AMD. They have shown to be effective and well-tolerated short term. More studies are needed to find a treatment with long-term efficacy for AMD with CNVM.

*Aino Jaakkola, MD, is currently retinal specialist in private practice*

# 1998

## OPHTHALMIC FINDINGS IN NEPHROPATHIA EPIDEMICA (PUUMALA VIRUS INFECTION): A CLINICAL, PATHOPHYSIOLOGICAL AND EPIDEMIOLOGICAL STUDY

**Matti Kontkanen, Kuopion yliopisto – University of Kuopio**

Nephropathia epidemica (NE) is a human zoonosis caused by the Puumala virus. The main reservoir of the virus is the bank vole. Puumala virus causes a hemorrhagic fever. The occurrence and pathogenesis of the ophthalmic manifestations of NE was investigated among 37 participants collected during a NE epidemic in the Savonlinna area in the Eastern Finland in winter 1992–1993.

Ophthalmic symptoms and signs were common in patients hospitalised for NE, and the most characteristic features were myopic shift in refraction and a decrease in intraocular pressure (IOP). The mechanism of myopic shift (based on A-scan ultrasonography) was a combination of two factors: forward movement of the lens-iris diaphragm and thickening of the lens. We found a slight decrease of IOP during the acute phase of NE, but it is easy to understand that the forward movement of the iris-lens diaphragm may sometimes paradoxically lead to angle closure attacks with elevated IOP. Manifestations resulting from increased capillary permeability included lid edema, conjunctival chemosis and hemorrhage as well as retinal hemorrhage. Furthermore, spontaneously subsiding inflammatory cells were occasionally seen in the anterior chamber.

The symmetry of ocular manifestations of NE reflects the systemic nature of the viral infection. In concert with the systemic manifestations of the disease, the ophthalmic symptoms and signs resolved rapidly and spontaneously without any specific therapy.

A seroepidemiological study of 351 subjects carried out between 1993 and 1996 aimed to evaluate the seroprevalence of Puumala virus antibodies and to determine whether this disease represents a risk factor for cataract. The seropositivity rate for the elderly (70 years or older) population in the Savonlinna area was 30 %. Men were significantly more often seropositive than women, but no significant difference was found in seropositivity between cataract patients and controls.

*Matti Kontkanen, MD, is currently chief physician*
*at the Department of Ophthalmology,*
*Pohjois-Karjala Central Hospital, Joensuu*

# 1998

## EPIDEMIOLOGICAL STUDY OF ENDOGENOUS UVEITIS IN SOUTH-WESTERN FINLAND

**Taina Päivönsalo-Hietanen, Turun yliopisto – University of Turku**

Epidemiological aspects of endogenous uveitis were studied in south-western Finland. The charts of all patients with endogenous uveitis seen at the University Eye Clinic of Turku from 1980 to 1982 and in 1988 were reviewed. A total of 1122 uveitis patients were seen, of whom 51% were men and 49% were women; 92% had anterior uveitis, 1% had intermediate uveitis, 6% had posterior uveitis, and 1% had panuveitis.

Of the patients seen, 37% were new cases of uveitis. The annual incidence and prevalence rates for anterior uveitis were 213 and 697 per 1 000 000 population, for intermediate uveitis 3 and 14, for posterior uveitis 8 and 46, for panuveitis 2 and 8, and for all uveitis cases 226 and 754, respectively. The incidence of uveitis was significantly higher in the age group 20 to 69 years than in the age groups 0 to 19 years and 70 years or older. The incidence of uveitis was higher in lower than in higher socioeconomic groups. The incidence rates did not differ between men and women in any age or socioeconomic group. There was significant seasonal variation in the incidence of uveitis; it was significantly higher in the warm and transitional months from April to November than in the cold months from December to March.

The most common uveitis entity was idiopathic acute anterior uveitis accounting for 66% of patients; the incidence and prevalence rates were 171 and 485 per 1 000 000, respectively. Ankylosing spondylitis was the most frequent associated disease in these patients (incidence rate 20; prevalence rate 103) and occurred significantly more often in men than in women. The incidence rates of other anterior uveitis entities were more than 30 times smaller than that of idiopathic acute anterior uveitis. Toxoplasmic retinochoroiditis was the most common posterior uveitis entity (incidence rate 3; prevalence rate 24 per 1 000 000 population).

The incidence and prevalence rates of uveitis were significantly lower in children under 16 years of age than in adults (incidence rate 43; prevalence rate 279 per 1 000 000 population). The distribution of children with uveitis by location of the inflammation resembled the distribution of adults. The most common entity in children was juvenile rheumatoid arthritis-associated anterior uveitis (incidence rate 11; prevalence rate 139 per 1 000 000 population), which was more frequent in girls than in boys.

*Taina Päivönsalo-Hietanen, MD, is currently in private practice*

# 1998

## SURGICAL MANAGEMENT OF REFRACTORY GLAUCOMA WITH MOLTENO IMPLANT

**Juha Välimäki, Oulun yliopisto – University of Oulu**

The long-term outcome of Molteno implantation in refractory glaucoma and especially its usefulness in controlling intraocular pressure (IOP) in glaucoma secondary to juvenile rheumatoid arthritis (JRA) was determined. Factors influencing surgical outcome, the frequency and outcome of excision of an encapsulated bleb after implantation, the feasibility of measuring the rate of collagen synthesis in the aqueous humour samples in eyes with glaucoma surgery, and the possibility of improving the surgical outcome of Molteno implantation with postoperative oral prednisolone treatment were additionally studied.

A retrospective study included 87 patients (100 eyes) with refractory glaucoma. The success rates of Molteno implantation by the life-table method were 90%, 75% and 50% at 1, 2 and 4.5 years, respectively. The results of 27 eyes with glaucoma secondary to JRA showed an excellent 90% life-table success rate in patients with JRA at 4.5 years after Molteno implant surgery with an average IOP reduction of 62%. Postoperative hyphema, suprachoroidal haemorrhage and the number of systemic medications before surgery were significantly associated with failure to control IOP. Most of complications were short-lived. Of the operated patients, 15% required excision of an encapsulated filtration bleb, and in 50% of them the excision resulted in a normal IOP.

The prospective study showed that immunoassays of the carboxyterminal propeptide of type I procollagen (PICP) and the aminoterminal propeptide of type III procollagen (PIIINP) can be used to measure the activity of collagen synthesis in the aqueous humor after glaucoma surgery. Peak values were measured 2 to 3 months after surgery. Administration of systemic corticosteroid after Molteno implantation during the maximum activity of collagen synthesis did not lead to more favorable surgical results. It seems that collagen synthesis after Molteno implantation is under the influence of local factors.

The favourable results indicated that the Molteno implant is useful and well tolerated in controlling IOP without adjunctive postoperative systemic corticosteroid treatment in patients with refractory glaucoma, especially secondary to JRA.

*Juha Välimäki, MD, is currently chief physician*
*at the Department of Ophthalmology,*
*Päijät-Häme Central Hospital, Lahti*

# 1999

## THE REFRACTIVE COMPONENTS IN BINOCULARITY DISTURBANCES

**Laura Lindberg, Helsingin yliopisto – University of Helsinki**

The refractive components of strabismic and amblyopic patients were determined so as to shed light on whether refractive aberrations in these patients may be associated with a disturbed active emmetropisation process because of their deficient binocularity. The background of the refractive aberrations in each group of patients was additionally studied.

Between 1995 and 1998, 306 patients operated for strabismus, 50 patients receiving pleoptic treatment for amblyopia and 50 healthy control children participated in the study. An automatic refractokeratometer was used to measure total refraction, corneal refractive power, astigmatism, residual astigmatism and anisometropia under cycloplegia. A-scan ultrasonography was used to measure the anterior chamber depth, lens thickness, vitreous chamber depth, and axial length.

The strabismic eyes were shorter, mostly due to shortness of the vitreous cavity, and more hyperopic and astigmatic when compared to their fellow eyes and the controls. The cylinder axes in the strabismic eyes tended toward oblique astigmatism. These findings were more pronounced in constant unilateral strabismus and even more so if combined with amblyopia or esotropia, i.e. with a more pronounced prior binocularity disturbance. The results were accentuated in those older than six years.

The fellow eyes of the strabismic patients also showed aberrations in their refractive components when compared to the controls. Findings in pleoptically treated amblyopic patients were more pronounced than in surgically treated strabismic patients. Those who had had patching in addition to surgery displayed no noteworthy differences when compared with the pleoptically treated amblyopic patients. These findings support the hypothesis of the influence of binocularity disturbances on the normal development of refraction and emmetropisation.

*Laura Lindberg, MD, is currently strabismologist-in-chief at the Helsinki University Eye Hospital*

# 1999

## OCULAR LYME BORRELIOSIS: DIAGNOSIS AND CLINICAL CHARACTERISTICS

**Helena Mikkilä, Helsingin yliopisto – University of Helsinki**

The diagnosis and clinical characteristics of ocular Lyme borreliosis, its role as a cause of uveitis, and the value of screening uveitis patients for serum antibodies to *Borrelia burgdorferi* were evaluated.

The diagnosis and clinical characteristics of ocular Lyme borreliosis were evaluated in 20 patients in whom Lyme borreliosis was diagnosed on the basis of medical history and laboratory confirmation of *B. burgdorferi* infection; 17 of them had elevated antibodies to *B. burgdorferi* in their serum or cerebrospinal fluid by enzyme-linked immunosorbent assay (ELISA) and 7 patients, including 2 with a negative ELISA, had a positive immunoblot. Seven patients had a positive polymerase chain reaction (PCR) for *B. burgdorferi*. Of the 20 patients, 10 had intraocular inflammation, 5 had external ocular inflammation, 4 had neuro-ophthalmic disease and one developed a branch retinal vein occlusion.

The role of Lyme borreliosis as a cause of uveitis was evaluated in 160 consecutively examined uveitis patients. Lyme borreliosis was considered to be the most probable cause of uveitis in 4% of patients, all of whom had posterior segment inflammation.

The significance of serum antibodies to *B. burgdorferi* in diagnostic work-up was examined in 161 uveitis patients. Elevated antibodies were detected in 16% of patients, with elevated IgG in 42% of them. In only 5 of 26 patients with elevated antibodies was uveitis suggested to be associated with *B. burgdroferi* infection on the basis of the medical history or a positive PCR reaction.

*Helena Pelkonen, MD, is currently in private practice*

# 1999

## LENS AUTOFLUORESCENCE IN AGING AND CATARACTOUS HUMAN LENSES: CLINICAL APPLICABILITY

**Seppo Siik, Oulun yliopisto – University of Oulu**

The in vivo the changes of the human lens autofluorescence (AF) with aging and cataractogenesis were investigated. Measurements were performed in the blue-green AF range (495 nm/520 nm) using a fluorometer designed, built and clinically tested in our department.

Altogether 43 healthy volunteers (43 eyes chosen randomly) aged 6 to 86 years, five representing each decade of age, were studied for effects of aging, and 84 patients (84 eyes) with cortical, nuclear, posterior subcapsular or mixed lens opacities were additionally examined. The results were compared with the widely used subjective lens opacities classification system (LOCS II and III). Lens AF was measured also from 122 smoking males aged 57 to 76 years who participated in a cancer prevention study.

Lens AF exponentially increased with age. By extrapolation, AF appeared to be absent at birth. The lens transmission for blue-green light, determined from the lens AF curve, was almost constant with ages up to 60 years. Thereafter, it decreased rapidly and the interindividual variation increased.

In cataractous lenses, the mean AF differed significantly from those of age-matched controls. The highest AF values were measured in nuclear cataracts, where AF was also related to visual acuity and an increasing yellow-brown colour of the nucleus. We could demonstrate how yellowing of the lens, determined by the lens AF, had an actual effect on retinal nerve fibre layer visibility in black-and-white images taken with a blue monochromatic filter.

In cortical cataracts, the AF curve was low and flattened and the maximum AF value was significantly lower than in the age-matched control eyes. Central cortical opacities may interfere with the measurement of nuclear AF in the blue-green range. On the other hand, an early development of cortical opacity may shield the lens nucleus from photochemical browning.

The results suggested that lens fluorometry together with a subjective grading system may be a useful additional tool in the follow-up of optical changes occurring in the nuclear region of the lens.

*Seppo Siik, MD, is currently in private practice*

# 1999

## EXCIMER LASER SURGERY FOR CORNEAL DISEASES AND MYOPIA

**Tiina Tuunanen, Helsingin yliopisto – University of Helsinki**

This study was initiated when excimer laser technique had just become available. The aim was to investigate the results of phototherapeutic keratectomy (PTK) in various corneal diseases and its potential role in reducing refractive errors in corneal grafts. It also evaluated the potential and safety of photorefractive keratectomy (PRK) in reducing myopia and combined myopic astigmatism. In addition, the role of dry eye and its effect on the outcome of PRK was evaluated. In an animal model, the potential effect of excimer laser corneal sculpting on the accuracy of IOP measurement was evaluated.

PTK was effective in corneal degenerations located in the anterior third of the stroma. Deep corneal scars did not perform well, although in most patients corneal clarity improved. An improvement in individualized goal (i.e. increase in visual acuity, improvement in corneal clarity or decrease in ocular discomfort) was attained in 50% of the eyes. In recurrent erosion syndrome, the symptom-free period with PTK was longer than otherwise would be typical. Treatment of pterygia did not prevent recurrences.

In 10 eyes with astigmatism after penetrating keratoplasty (PKP), the initial net reduction in astigmatism was favourable, but a regression of the effect was noted in addition to an intense corneal haze. At 1 year, mean reduction of astigmatism was 48% (range, 0% to 100 %). Uncorrected visual acuity (UCVA) improved by 2 Snellen lines in 6 of 10 eyes, and decreased by 3–7 lines in 4 eyes.

The predictability and efficacy of PRK in correcting low (-1.50 D to -6.00 D), moderate (-6.10 D to -8.00 D) and high (-8.10 to -11.50 D) myopia were studied. Both were satisfactory: 58% achieved a correction within 0.5 D of the attempted in low myopia, 50% in moderate, and 29% in high myopia; the corresponding values for a correction within 1.0 D of the attempted were 87%, 79% and 67%, respectively. To elucidate the effect of relative tear deficiency on results of PRK, 62 eyes were matched by age and attempted correction. At 1 year, an intended correction within 1 D and an UCVA of 0.5 or better were more common and the mean overcorrection was smaller in eyes with a higher preoperative Schirmer test value (10 mm in 5 min or better). These differences were not statistically significant.

The possible alterations in corneal structure after PRK may affect measurement of IOP. In the animal model, the manometric measurements correlated with the results obtained by pneumotonometry. No significant differences in pressure readings were detected either in eyes with a 5 D or in eyes with a 15 D myopic correction.

*Tiina Tuunanen, MD, is currently in private practice*

# 1999

## DACRYOCYSTORHINOSTOMY: PROSPECTIVE COMPARISON OF THREE DACRYOCYSTORHINOSTOMY TECHNIQUES IN TREATMENT OF PRIMARY ACQUIRED NASOLACRIMAL SAC AND DUCT OBSTRUCTION IN ADULTS

**Jouko Hartikainen, Turun yliopisto – University of Turku**

The traditional surgical treatment of obstruction within the nasolacrimal sac and duct is external dacryocystorhinostomy (EXT-DCR). We conducted a prospective comparison of XDCR and two modern endonasal techniques: endonasal endoscopic (EESC-DCR) and endonasal laser-assisted (ENL-DCR) dacryocystorhinostomy (DCR)

In our hands, EXT-DCR appeared to give a superior success rate after primary operation, the success rates being 91% for EXT-DCR, 75% for EESC-DCR and 63% for ENL-DCR with a follow-up time of one year. After revision surgery, the success rates were nearly similar for all three DCR techniques, indicating that all are acceptable alternatives in treating nasolacrimal sac and duct obstruction in adults. The major advantages of both endonasal DCR techniques were short operation time and avoidance of a skin wound, as well as direct access to the obstructed rhinostomy site during revision DCR.

In our anatomical study, we demonstrated that the lacrimal bone at the lacrimal sac fossa, at the site where the creation of the DCR osteotomy is begun, is composed of a thin plate, 0.1 mm in mean thickness, of lamellar cortical-type compact bone that can easily be perforated with most surgical instruments.

The bacteriology of obstructed nasolacrimal sac and duct in adults consisted mostly of Gram-positive bacteria, which were isolated in 62% of the specimens. *Staphylococcus epidermidis* was the most frequently cultured bacterial species. Chronic dacryocystitis was associated with an increased proportion of Gram-negative bacteria and *Streptococcus* species, whereas they were nearly absent in simple stenosis of the nasolacrimal sac and duct.

*Jouko Hartikainen, MD, is currently in private practice*

# 2000

## CLINICAL AND MICROBIOLOGICAL STUDIES ON EDG AND BEN22 DETERGENTS IN SOFT CONTACT LENS CARE SOLUTIONS

**Hanna Vaahtoranta-Lehtonen, Turun yliopisto – University of Turku**

Two detergents, ethyl-6-*O*-decanoylglucoside (EDG) and 50:50 mixture of L-α-rhamnopyranosyl-β-hydroxydecanoyl-β-hydroxydecanoate and 2-*O*-α-L-rhamnopyranosyl-α-L-rhamnopyranosyl-β-hydroxydecanoyl-β-hydroxydecanoate (BEN22), were tested for their ability to enhance cleaning and disinfection in contact lens care.

A commercial contact lens care solution containing 0.00025% of chlorhexidine acetate (CHX) could not sterilise contact lenses heavily contaminated with *Serratia marcescens* and *Pseudomonas aeruginosa*, but 0.005% EDG together with CHX enhanced killing of these bacteria significantly.

Two commercial contact lens care solutions and 0.05% and 0.005% BEN22 were examined for efficacy in removing adherent *Acanthamoeba castellanii* and *A. polyphaga* trophozoites from contact lenses; 0.05% BEN22 detached adhered trophozoites from the lenses to an equal extent to the two commercial solutions ReNu Multi-Purpose™ (Bausch & Lomb Inc., Italy) and BioSoak™ (Finnsusp Ltd., Finland) and to significantly greater extent than saline used as a control did.

EDG and 0.005% BEN22 were added to CHX and used in three clinical studies. The use of CHX+EDG resulted in diminished contact lens protein content as compared to Multi-Purpose™, but on ionic lenses only. Users of CHX+EDG had fewer positive conjunctival bacterial cultures and a significantly smaller rate of papillary hypertrophy as compared to controls using Multi-Purpose™. In the second study, however, CHX+EDG did not result in diminished rate of pre-existing papillary hypertrophy as compared to CHX. A significant correlation between tear tryptase levels and grade of papillary hypertrophy was noted. In the third clinical study, CHX+BEN22 had no effect on papillary hypertrophy. In giant papillary conjunctivitis, tear lactoferrin levels were noted to be low.

EDG and BEN22 were found to be well tolerated in contact lens care. In some users, they can assist cleaning and reduce the rate of papillary hypertrophy. However, these detergents can not reverse papillary hypertrophy in subjects who have a long history of contact lens wear.

*Hanna Vaahtoranta-Lehtonen, MD, is currently head of the ophthalmological outpatient clinic of the City of Turku*

# 2000

## EXCIMER LASER REFRACTIVE SURGERY WITH SPECIAL REFERENCE TO CORNEAL WOUND HEALING AND NERVE REGENERATION AFTER MYOPIC PHOTOREFRACTIVE KERATECTOMY AND LASER IN SITU KERATOMILEUSIS

**Tuuli Valle, Helsingin yliopisto – University of Helsinki**

Corneal wound healing and nerve regeneration following photorefractive keratectomy (PRK) and laser in situ keratomileusis (LASIK) were evaluated with experimental LASIK surgery on rabbit corneas and in humans undergoing PRK and LASIK. Rabbit corneas were analysed by indirect immunohistochemistry for extracellular matrix glycoproteins cellular fibronectin (cFn) and tenascin (Tn), and with acetylcholinesterase (AChE) histochemistry for visualisation of corneal nerves. The wound healing reactions of human corneas that had undergone PRK or LASIK were assessed with *in vivo* confocal microscopy. Cochet-Bonnet esthesiometry was performed on post-LASIK corneas to examine the association between corneal nerve recovery and corneal sensitivity.

In post-LASIK rabbit corneas the central optical zone was virtually devoid of scar tissue. The stromal cells located in the periphery of the flap and in relatively close contact with the epithelium were surrounded by scar tissue expressing immunoreactivity for both cFn and Tn. An initial major loss of epithelial, subbasal, and superficial stromal nerves was observed in the flap, excluding its hinge, but at 2.5 months the innervation had reached an almost normal density and architecture.

Confocal microscopy of human corneas clinically confirmed histological data presented earlier concerning healing of excimer laser wounds after PRK and LASIK. After PRK, the anterior stroma showed keratocyte changes and extracellular matrix alterations for several months after surgery. The first long subbasal nerve fiber bundles appeared at one month. After LASIK, the corneal areas with no nerve images or with short unconnected bundles were associated with lower sensitivities than were corneal areas showing long nerve fibre bundles with or without interconnections.

The sensitivity of the post-LASIK corneas was at its lowest after 1 to 2 weeks, but the decrease was not as marked in the nasal hinge area. Near normal sensitivity thresholds were obtained in patients examined at 6 months or later. Healing problems were observed after repeat LASIK surgeries, which suggested that corneal healing may be compromised and neural damage may increase after multiple operations.

*Tuuli Valle, MD, is currently corneal specialist and ophthalmic surgeon at the Helsinki University Eye Hospital*

# 2001

## EXFOLIATION GLAUCOMA: STUDIES ON INTRAOCULAR PRESSURE, OPTIC NERVE HEAD MORPHOMETRY, AND OCULAR BLOOD FLOW

**Mika Harju, Helsingin yliopisto – University of Helsinki**

Risk factors for progression of glaucoma were studied in 139 patients (139 eyes) with exfoliation syndrome (ES), ES associated with ocular hypertension (EOHT) and exfoliation glaucoma (EG). Multivariate survival analysis detected increased age, increased mean weighted intraocular pressure (IOP) and increased stage of glaucoma as risk factors for progression. History of trabeculectomy was associated with decreased relative risk for progression even when statistically adjusted for mean weighted IOP.

The use of automated optic nerve head (ONH) analysis with the Heidelberg Retina Tomograph (HRT) was studied in 80 patients with EG. Most HRT parameters were associated with the disc area, and when the effect of disc area was taken into account, all HRT parameters showed a significant association with the amount of visual field (VF) damage.

In a prospective follow-up study of 56 patients, change in one VF index (mean defect) was shown to be associated with subsequent change in one of the HRT parameters, the cup shape measure. This suggests that cup shape measure may be an indicator for progression of glaucoma.

Reversal of ONH topography was studied with the HRT. Decrease in IOP was associated with reversal changes in most HRT parameters.

Ocular blood flow in eyes with EOHT, EG and ES was measured with the Heidelberg Retina Flowmeter and blue-field entoptoscopy. Results indicated that more advanced glaucomatous damage was associated with reduced flow in the ONH. In the macula, leukocyte velocity was significantly lower in EG eyes than in non-glaucomatous fellow eyes. The results indicate that alterations in ocular blood flow occur in EG.

*Mika Harju, MD, is currently glaucoma specialist and ophthalmic surgeon at the Helsinki University Eye Hospital*

# 2001

## UVEITIS IN JUVENILE IDIOPATHIC ARTHRITIS

**Kaisu Kotaniemi, Helsingin yliopisto – University of Helsinki**

The occurrence, characteristics and prognosis of uveitis in patients with juvenile idiopathic arthritis (JIA) was studied. Uveitis occurred in 16% of 114 subjects receiving specially reimbursed medication for JIA in 5 of 21 central hospital districts in Finland during years 1980, 1985 and 1990. Uveitis was chronic in 9 patients, and most severe when it appeared at the onset of arthritis.

In 49 sibling pairs with JIA, uveitis occurred in 26%. The concordance rate for uveitis (3 pairs) did not differ from that expected (3.4 pairs).

Among 426 patients with newly diagnosed JIA, the main determinants of associated uveitis were onset of arthritis at the age of 2 to 4 years and a positive antinuclear antibody (ANA) test. During 4.5 years, 24% of these children with JIA developed uveitis, which was asymptomatic in 95% of them. Complications of uveitis occurred in 24% of patients, but none became blind.

In a cohort of 372 JIA children, the activity of arthritis was compared between patients with associated uveitis and without it. The erythrocyte sedimentation rate was higher and the hemoglobin value was lower at the diagnosis of arthritis in the 96 JIA patients with uveitis than in the 276 patients without. The arthritis seemed to be more active in JIA patients with uveitis: treatment with prednisolone, injections of glucocorticoid and methotrexate was more common and clinical remission of arthritis was less frequent among patients with uveitis than among those without.

A patient with juvenile-type chronic polyarthritis and late-onset severe chronic uveitis controlled with prednisolone, cyclosporin A and methotrexate was described. The successful treatment was carried out in close co-operation with rheumatologists.

In the Finnish Register of Visual Impairment, 174 patients with uveitis leading to visual impairment during 1980−1996 were found. Arthritis or a comparable condition was detected in 22% of them: JIA in 8%, followed by spondyloarthropathy in 6%, sarcoidosis in 3% and seronegative rheumatoid arthritis in 2%. Legally blind were 65 patients of whom 8 were totally blind. Uveitis led to visual impairment within a mean of 18 years.

Treatment of chronic uveitis in JIA is difficult, and collaboration of ophthalmologists and pediatric rheumatologists and rheumatologists is quite essential in determining the optimal management early in the disease course.

*Kaisu Kotaniemi, MD, is currently uveitis specialist at the Heinola Hospital for Rheumatoid Patients*

# 2001

## *IN VIVO* CONFOCAL MICROSCOPY AND ESTHESIOMETRY FOR CLINICAL ASSESSMENT OF CORNEAL PATHOLOGY

**Maria Rosenberg, Helsingin yliopisto – University of Helsinki**

Corneal epithelial adhesion problems are distressing and their underlying mechanisms are unclear. Because it is known that corneal nerves influence epithelial cells, corneal innervation was evaluated by confocal microscopy and corneal sensitivity in a total of 74 patients (121 eyes) with recurrent corneal erosion syndrome; basement membrane dystrophy (BMD); diabetes mellitus (DM); familial amyloidosis, Finnish (FAF), with corneal lattice dystrophy, type II; and prior herpes simplex virus (HSV) keratitis.

A thin epithelium was noted in diabetics with severe neuropathy. The basal epithelium showed changes related to the genesis of adhesion defects: deposits (BMD, DM, FAF) and folding of Bowman's layer (BMD, recurrent corneal erosion syndrome, DM, HSV). Subbasal nerve density was decreased in DM and FAF, and dendritic particles (presumably Langerhans cells) in the basal epithelium were observed in corneas with HSV. Increased stromal extracellular matrix was observed in all conditions. In FAF, straight stromal filaments (presumably lattice lines), and undulating denser structures, possibly new local amyloid deposits, were observed.

Both Cochet-Bonnet esthesiometry in 44 eyes and non-contact gas esthesiometry in 20 eyes were used to measure corneal sensitivity. Subbasal nerve density in DM appeared to correlate with mechanical sensitivity and inversely with the degree of neuropathy. In FAF, mechanical, and to some extent also thermal, sensitivity were reduced. Subbasal nerve density was correlated with mechanical and cold sensitivity.

Confocal microscopy provided descriptive information on corneal sublayers, although few individual findings were clinically relevant. Basal epithelial deposits and subbasal nerve density were amenable to quantitative analysis.

*Maria Lamberg, MD, is currently glaucoma specialist at at the Helsinki University Eye Hospital*

# 2001

## THE SANDWICH THEORY: A BIOACTIVITY BASED EXPLANATION FOR POSTERIOR CAPSULE OPACIFICATION AFTER CATARACT SURGERY WITH INTRAOCULAR LENS IMPLANTATION

**Reijo Linnola, Oulun yliopisto – University of Oulu**

Mechanisms of adhesion of the intraocular lens (IOL) to the capsular bag was studied after cataract surgery and IOL implantation. The sandwich theory was presented. If the IOL is made of a bioactive material it would allow a single lens epithelial cell (LEC) layer to bond both to the IOL and the posterior capsule at the same time. A 90º edge of the IOL optic against the posterior capsule would hinder or direct the proliferating LEC to form a monolayer between the IOL and the posterior capsule. This would produce a sandwich pattern including the IOL, the cell monolayer and the posterior capsule. The sealed sandwich structure would prevent further LEC ingrowth. The degree of bioactivity of the IOL would explain the difference in the incidence of posterior capsule opacification (PCO) and capsulotomy rates with different IOL materials.

The sandwich theory was put forward on the basis of a search for a keratoprosthesis material, which would allow maximal adhesion of the prosthesis to corneal tissue. Titanium and glass-ceramic coated titanium were found to develop better adhesion than poly(methyl methacrylate) [PMMA].

The differences between various IOL materials were tested on rabbit corneal tissue cultures. Corneal tissue adhered stronger to soft, hydrophobic acrylate than to PMMA, heparin surface modified (HSM)-PMMA, silicone or hydrogel IOL. In a further study, 75 lenses of different materials were incubated with radioactive iodine labeled fibronectin, laminin or collagen type IV. Soft hydrophobic acrylate (AcrySof™) showed the highest binding to fibronectin. Finally, in 70 pseudophakic autopsy eyes immunohistochemical analyses were performed for fibronectin, vitronectin, laminin and collagen type IV. Soft hydrophobic acrylate lenses showed significantly more adhesion of fibronectin to their surfaces than PMMA or silicone lenses did.

The study suggested that fibronectin may be the major extracellular protein responsible for attachment of an acrylate IOL to the capsular bag with a true bioactive bond.

**Author's Comment:**
No contradictory reports have appeared on the role of fibronectin. The exact binding mechanism of fibronectin to soft hydrophobic acrylate has not been published. The role of a sharp, 90° IOL edge, was part of the sandwich theory. The sharp edge has been shown to hinder PCO even with other IOL materials than soft hydrophobic acrylate. Today, essentially all the lenses in the market have a sharp edge.

*Reijo Linnola, MD, is currently in private practice*

# 2001

## PROGNOSTIC INDICATORS IN CHOROIDAL AND CILIARY BODY MELANOMA

**Teemu Mäkitie, Helsingin yliopisto – University of Helsinki**

A population-based, clinicopathologic study was undertaken to explore prognostic factors of patients who had an eye removed because of choroidal or ciliary body melanoma between years 1972 to 1981. The specimens were studied using periodic-Acid Schiff stain for microvascular patterns and immunohistochemistry for the Factor VIII-related antigen, CD34 and CD68 epitopes and ezrin.

A total of 167 consecutive patients were enrolled from files of the Ophthalmic Pathology Laboratory of the Helsinki University Eye Hospital. During median follow-up time of 22 years, 80 deaths occurred from metastatic uveal melanoma. Patients with large primary tumour, nonspindle tumour cell type or a tumour involving the ciliary body died statistically significantly more often of metastatic disease than patients without such characteristics.

The study confirmed previously controversial findings regarding prognostic significance of tumour microcirculation in uveal melanoma: the presence of specific microvascular patterns (loops with and without networks) and high microvascular density were associated with increased melanoma-specific mortality.

Moreover, immunohistochemical analysis of tumour-infiltrating macrophages and ezrin (an actin-plasma membrane ptotein linker) generated two novel prognostic indicators: the high number of tumour-infiltrating macrophages and presence of ezrin immunoreactivity were statistically significantly associated with melanoma-specific mortality.

**Author's Comment:**
The onset of metastatic disease is still today an unfortunate occurrence, and this study was conducted to help to understand factors that are associated with the development of uveal melanoma metastasis and which have adverse effect on the clinical course of the disease. The findings have later been independently confirmed by other investigators. Recently, chromosomal abnormalities, in particular monosomy 3, have proven to be associated with a high risk for metastasis from uveal melanoma.

*Teemu Mäkitie, MD, is currently in private practice*

# 2001

## EFFECT OF CATARACT SURGERY ON VISUAL OUTSOME, INTRAOCULAR PRESSURE AND POSTERIOR CAPSULAR OPACIFICATION IN NORMAL AND GLAUCOMATOUS EYES

**Tuula Pohjalainen, Helsingin yliopisto – University of Helsinki**

Initially, the effect and complications of extracapsular cataract extraction and intraocular lens implantation (ECCE-IOL) were compared in 37 eyes with primary open angle glaucoma (POAG) and 66 eyes with exfoliation glaucoma (EG) operated on from 1987 to 1988. Rupture of the posterior capsule (7.6%) and vitreous loss (4.5%) did occur only in EG. Postoperative intraocular pressure (IOP) rise and fibrinous exudation did not differ been the groups. After 1 to 3 years, IOP was controlled in 19 % of the POAG and in 37 % of the EG without medication.

A subsequent study evaluated the effect of phacoemulsification and intraocular lens implantation (PHACO-IOL) performed from 1995 to 1996 in open angle glaucoma patients (OAG, i.e. POAG and EG combined). The complications were less frequent than previously with ECCE: posterior capsular rupture with vitreous loss occurred in 0% vs. 4.7% of eyes and without vitreous loss in 2.6% vs 4.7% of eyes, respectively. In the first postoperative day, IOP rise over 30 mmHg occurred in 30% of the eyes in ECCE-IOL and in 40% of the eyes in PHACO-IOL group. The long-term (mean, 2.8 years) IOP control after PHACO-IOL surgery was improved or unchanged in 86% and worse in 14% of the preoperatively well controlled OAG eyes.

The effect of PHACO-IOL on IOP was studied in 160 non-glaucomatous eyes with (23 eyes) and without (137 eyes) exfoliation syndrome (ES). One day after surgery, transient IOP peaks to 30 mmHg or higher were more common in eyes with ES than without (17% vs. 6%, respectively). In both groups, IOP decreased and remained significantly lower (23% vs. 21%, respectively) at 1 to 2.7 years of follow-up.

After ECCE-IOL, 58% of glaucomatous eyes reached a visual acuity (VA) of at least 0.4. After PHACO-IOL, 87% of glaucomatous eyes and 88% of non-glaucomatous eyes reached a VA of 0.4 or more. VA was less than 0.3 in 13% of glaucomatous and 12% of non-glaucomatous eyes, most often because of age-related macular degeneration.

Posterior capsular opacification (PCO) was compared in 40 eyes having a silicon IOL and 40 eyes having an acrylic IOL 1-2.4 years after cataract surgery; 25% of eyes with a silicon and 10% of eyes with an acrylic IOL had PCO.

*Tuula Pohjalainen, MD, is currently in private practice*

# 2001

## EFFECTS OF ANTIEPILEPTIC DRUGS ON VISUAL FUNCTION, WITH SPECIAL REFERENCE TO VIGABATRIN

**Iiris Sorri, Kuopion yliopisto – University of Kuopio**

The new antiepileptic drugs (AED) vigabatrin and tiagabine entered the market in the 1990's as a result of rational drug development. They increase the amount of an inhibitory neurotransmitter, gamma-amino butyric acid (GABA), in the central nervous system. Since 1997, reports of severe bilateral concentric visual field defects that were associated with the use of vigabatrin were published.

The causality, prevalence, risk factors and prognosis of visual field defects were determined in 35 patients treated with initial vigabatrin monotherapy and 25 patients treated with add-on therapy. Visual functions were assessed with psychophysical tests. The effect of tiagabine monotherapy on different visual functions was examined in 15 patients in order to detect any possible class effect of GABAergic AED; 18 patients who were treated with carbamazepine monotherapy and 18 healthy volunteers served as controls.

Bilateral visual field constriction was found with the kinetic Goldmann perimetry in 40% of patients treated with vigabatrin therapy. The constriction was severe in 13% and mild in 27% of the patients. No difference was found between patients on monotherapy or on add-on therapy. After a follow-up of 4 to 38 months (mean, 15), visual field defects were neither reversible after cessation of the drug nor progressive with continued treatment. We could not find any specific risk factors, such as sex, dose or duration of therapy. The patients treated with tiagabine or carbamazepine had normal visual fields. Acquired colour vision defects were found in all patient groups. Colour vision and contrast sensitivity were significantly impaired in patients with vigabatrin-associated visual field defects.

The study confirmed the relationship between the treatment with vigabatrin and concentric visual field defects in patients with initial vigabatrin monotherapy and showed that the phenomenon is not a class effect of this GABAergic AED. The results concur with other studies which have shown that vigabatrin is retinotoxic. In animal studies, vigabatrin exposure is associated with high GABA concentrations and accumulation of the drug in the retina. However, the exact mechanism of retinotoxicity is still unclear.

*Iiris Sorri, MD, is currently retinal specialist*
*at the Department of Ophthalmology,*
*Kuopio University Hospital*

# 2001

## OCULAR MANIFESTATIONS IN TYPE 2 DIABETES: CONTROLLED TEN-YEAR FOLLOW-UP STUDY

**Raija Voutilainen, Kuopion yliopisto – University of Kuopio**

The visual acuity (VA), diabetic retinopathy (DRP) and maculopathy (DMP), age-related macular degeneration (AMD) and their risk factors in 133 newly diagnosed patients with type 2 diabetes referred from health centers and in 144 nondiabetic controls recruited from the population register were examined. Additionally, iris transluminance and the hypothesis that the Leu7Pro-polymorphism in the signal peptide part of neuropeptide Y gene could be a risk marker of DRP were investigated.

In this 10-year-long prospective study, the frequencies of DRP and DMP were determined by grading of stereoscopic fundus photographs and fluorescein angiograms. The subjects were studied at baseline and after 5 and 10 years. Iris transluminance was determined by using transscleral transillumination and by grading black-and-white iris photographs at the 10-year examinations.

By 10 years, the diabetic patients had a lower VA than the controls. The impairment of VA correlated inversely with HbA1c values at 5 years. The frequency of DRP and DMP increased sharply after 5 years and by 10 years 55% and 21% of diabetic patients had signs of DRP and DMP, respectively. Poor glycemic control was the most important predictive factor for the development of DRP and DMP. Controls with retinopathy had higher blood pressure levels and more frequently microalbuminuria than those without.

The frequency of AMD was nearly the same in both groups. It reduced the VA of diabetic patients earlier than that of the controls. AMD at baseline was more frequent in those type 2 diabetic patients who died from a cardiovascular cause than in those who did not, and this association persisted after adjustment for other risk factors. Abnormal iris transluminance was more frequent in diabetic patients than in controls, and it tended to associate with more severe and short-term DRP. At 10 years, the frequency of DRP in patients with Leu7Pro-polymorphism was higher than in those without it.

DRP and DMP are frequent complications of type 2 diabetes, threatening vision. Poor glycemic control is the most important predictor of the development of DRP and MRP. AMD predicted cardiovascular mortality in type 2 diabetics, but the mechanisms behind this association are unknown. Hypoxia due to impaired microvascular circulation of the iris presumably is responsible for defects in the iris pigment layer. Iris transluminance may serve as a marker for rapidly progressive DRP. The genes regulating neuropeptide Y expression may increase the risk for DRP.

*Raija Voutilainen, MD, is currently strabismologist at the Department of Ophthalmology, Kuopio University Hospital*

# 2001

## ACUTE ANTERIOR UVEITIS AND HLA-B27: INFECTIOUS BACKGROUND, SYSTEMIC INFLAMMATION, AND PROGNOSIS OF THE PATIENTS

**Minna Huhtinen, Helsingin yliopisto – University of Helsinki**

The use of HLA-B27 typing in the diagnostic work-up of uveitis was evaluated, and the infectious background, systemic inflammation and innate immune responsiveness of patients with previous acute anterior uveitis (AAU) were studied.

Of 220 consecutive patients with undetermined uveitis, 85% were tested for HLA-B27 antigen from 1993 to 1996. Other laboratory and radiologic examinations were performed as indicated by the clinical picture. In 1999, 64 patients with a previous AAU were examined. Serum antibodies to bacteria were measured using either enzyme-linked immunosorbent assay (ELISA) or microimmunofluorescence test, antibodies to *Chlamydia pneumoniae* heat shock protein 60 (Cpn Hsp60) were measured using enzyme immunoassay of patients and matched controls, serum C-reactive protein (CRP) levels were determined using an immunonephelometric high-sensitivity CRP assay, tumor necrosis factor (TNF)-alpha production in response to bacterial lipopolysaccharide (LPS) was measured by whole blood culture assay, and levels of TNF-$\alpha$ were measured by chemiluminescent immunoassay.

HLA-B27 antigen was present more often in patients with unilateral acute or recurrent anterior uveitis than in bilateral or chronic uveitis patients. The levels of immunoglobulin IgA antibodies to Cpn Hsp60 were significantly higher in the AAU patients than in controls. A high number of recurrences of AAU was independently related to the presence of single or multiple antibacterial antibodies. The CRP level and the TNF-$\alpha$ concentration were significantly higher in patients with previous AAU than in controls.

The presence of HLA-B27 in conjunction with uveitis entities other than unilateral AAU is of the same level or less than in the population of Finland in general. The presence of single or multiple antibodies in patients with many recurrences of AAU compared with patients with none or few recurrences may be a sign of repeated infections, antigen persistence or elevated innate immune responsiveness. The high frequency of IgA antibodies to Cpn Hsp60 in patients with past AAU may indicate persistent or recurrent infections caused by *C. pneumoniae.* The elevated CRP suggests low-grade inflammation and increased TNF-$\alpha$ production denotes enhanced innate immune responsiveness in patients with a history of AAU.

*Minna Huhtinen, MD, is currently in private practice*

# 2002

## A TRANSGENIC MOUSE MODEL FOR HUMAN ARTHRO-OPHTHALMOPATHIES

**Tapio Ihanamäki, Turun yliopisto – University of Turku**

Ocular abnormalities in transgenic mice harbouring mutations in type II collagen gene (COL2) were systematically characterized using light and electron microscopy and molecular biologic analyses. Total mRNA extracted from mouse eyes was used to study the expression of different matrix proteins during embryogenesis, growth and aging in normal mouse eyes. Based on these studies, selected *in situ* hybridisation and immunohistochemical analyses were performed.

Two different types of engineered mutations in COL2 transgenes were found to result in genotype-dependent ocular changes already during embryogenesis with characteristic vitreoretinal abnormalities. The severity of the resultant phenotypes was dependent on the dose of the transgenes. Analysis of COL2 gene expression during embryogenesis confirmed production of both variants of COL2 mRNAs (type IIA and IIB) in the mouse eye. Alternative splicing of exon 2 was not altered by the transgenes. *In situ* hybridisation demonstrated that the expression of the transgenes did not affect the distribution of COL2 mRNA in the eye.

During aging, the production of total COL2 mRNA underwent marked down-regulation in normal and transgenic Del1 mouse eyes. In the presence of transgenes, the levels of COL2 mRNA, which initially were higher than in non-transgenic controls, were reduced even faster, possibly indicating premature degeneration of the Del1 mouse eye. The production of other matrix components during embryonic development, growth and aging were less affected. This demonstrates that the effect of the transgenes is predominantly seen in the production of COL2.

In the ultrastructural analyses, dilation of the rough endoplasmic reticulum was seen in COL2-producing cells of transgenic Del1 mice, which suggested a defect in the final processing of collagen molecules for transport into the Golgi complex and subsequent secretory pathway. This is analogous with observations in human patients with arthro-ophthalmopathies. Together with this cellular "constipation" the main pathogenetic consequence of the transgenes in the eyes of Del1 animals seemed to be a reduction in the amount of fibrils containing COL2. In the presence of transgenes the vitreoretinal degenerative changes were more pronounced and earlier than in normal controls.

Co-expression of transcription factor Sox9 and type IIA procollagen suggested that Sox9 regulates expression of the *Col2a1* gene in the eye. Reactivation of Sox9 transcription upon aging may imply an ongoing tissue repair process and may also provide a model for therapeutic interventions to slow down vitreoretinal degeneration.

*Tapio Ihanamäki, MD, is currently neuro-ophthalmologist and ophthalmic surgeon at the Helsinki University Eye Hospital*

# 2002

## RED LASER CYCLOPHOTOCOAGULATION FOR TREATMENT OF THERAPY-RESISTANT GLAUCOMA

**Virpi Raivio, Helsingin yliopisto –University of Helsinki**

Red laser cyclophotocoagulation (CPC) with 647 nm krypton and 670 nm diode laser is a method developed at the Helsinki University Eye Hospital. The usefulness and the complications of red laser CPC in patients with therapy-resistant glaucoma and uncontrolled intraocular pressure (IOP) in spite of maximal tolerated medication and surgical treatment were studied.

In posttraumatic glaucoma, an IOP of 8 to 21 mmHg was achieved in 56% of patients. Repeated treatments were given to 44% of patients. In long-term follow-up, excessive decrease in IOP developed in one patient. In young patients, success was achieved in 41% (IOP 8 to 21 mmHg) to 64% (>30 mmHg decrease in IOP or IOP <22 mmHg) of patients. Repeated treatment was given to 64% of the eyes. In long-term follow-up, none of the patients developed excessive decrease in IOP.

The combination of CPC with retinal cryocoagulation was studied in neovascular glaucoma. IOP decreased to 21 mmHg or less in 62% of patients after krypton laser and in 71% after 670 nm diode laser CPC. Repeated CPC treatments were given to 27%. In 43% of patients, iris neovascularization regressed or disappeared during follow-up. In long-term follow-up, excessive decrease in IOP developed in one patient.

After 670 nm diode CPC, confocal microscopic examinations did not reveal any significant reduction in corneal nerve density. There were no statistically significant changes in corneal sensitivity values or in the Schirmer tear test. Postoperative complications tended to be mild probably due to the low power and the long duration of the red laser exposure.

Red laser cyclophotocoagulation appeared to be a safe and well-tolerated means of treating therapy-resistant glaucoma.

*Virpi Raivio, MD, is currently vitreoretinal surgeon at the Helsinki University Eye Hospital*

# 2002

## RETINAL DETACHMENT AFTER NEODYMIUM: YTTRIUM-ALUMINUM-GARNET LASER POSTERIOR CAPSULOTOMY

**Päivi Ranta, Helsingin yliopisto – University of Helsinki**

The purpose of the study was to better understand the etiology, pathogenesis, characteristics and outcome of pseudophakic retinal detachment (RD) after Nd:YAG laser posterior capsulotomy (LCT). The main principle was to compare RD of eyes with an intact posterior capsule with RD in eyes that had a LCT at the time of RD after uncomplicated cataract surgery. The hypothesis was that a significant number of asymptomatic retinal breaks might exist in eyes scheduled for LCT, possibly later causing RD.

In a retrospective cohort study of 129 eyes with pseudophakic RD, the mean number of peripheral retinal breaks was higher in the LCT group (1.7 vs. 1.1). The breaks were located preferentially in the upper quadrants in the LCT group, and tended to be more frequently atrophic holes than horseshoe breaks (34 of 103 vs. 15 of 77).

In a two-stage prospective study of 220 eyes an asymptomatic retinal break was found in 1.7% of eyes before LCT. Also in 2 additional eyes (0.9%) an undiagnosed RD was found. One month after LCT a new break was found in 0.4% of eyes. During five-year follow-up 2.3% of eyes had developed a RD. Axial length was statistically significantly associated with RD after LCT.

Differences in outcome of pseudophakic RD were assessed in a cross-sectional analysis of 101 patients. The retina remained attached long-term in 91% of the patients. The median BCVA was 0.08 before surgery and 0.4 at re-examination. No statistically significant difference was observed between the LCT and control groups.

**Author's Comment:**
This series of studies, although based on relatively small numbers of patients, supported the concept that in some eyes, pre-existing retinal breaks may underlie pseudophakic RD after LCT. Especially when dealing with patients with pre-existing vitreoretinal pathology and risk factors for RD, such as high axial length, history of fellow RD and vitreous loss during cataract surgery, a careful retinal examination and follow-up before and after LCT may be recommended.

*Päivi Ranta, MD, is currently in private practice*

# 2002

## GROUP IIA PHOSPHOLIPASE A2 IN TEARS OF HEALTHY AND DISEASED EYES

**Valtteri Aho, Turun yliopisto – University of Turku**

Tears contain several anti-microbial proteins, which include group IIA phospholipase $A_2$ ($GIIAPLA_2$),an enzyme capable of killing a broad spectrum of gram-positive bacteria.

By using a time-resolved fluoroimmunoassay, $GIIAPLA_2$ content of tears was measured in 160 normal subjects of different age and sex, at different times of the day and in basal, non-stimulated and reflex tears. The $GIIAPLA_2$ content was also determined in tears of 21 patients with senile cataract, 23 patients with primary open-angle glaucoma (POAG), 20 patients with keratoconjunctivitis sicca (KCS) and in 20 contact lens (CL) wearers.

The mean $GIIAPLA_2$ content of tears in healthy subjects was 54 µg/ml. The $GIIAPLA_2$ concentration decreased with increasing age and showed a discernible diurnal rhythm. It was significantly lower in reflex than in basal tears, but there was no significant difference between basal and non-stimulated tears. In CL-wearers, the $GIIAPLA_2$ content of tears decreased after CL use for 4 or 8 hours. The $GIIAPLA_2$ content of tears was elevated in patients with KCS but normal in patients with senile cataract or POAG.

$GIIAPLA_2$ content of normal human tears is one of the highest reported in human secretions. This finding indicates a substantial antibacterial role for $GIIAPLA_2$ in tears. The decreased $GIIAPLA_2$ content of tears may increase the risk of older subjects and CL wearers to local eye infection.

*Valtteri Aho, MD, is currently consultant for Orion Pharma, Orion Oyj, Helsinki*

# 2003

## THE DEVELOPMENT AND EARLY DIAGNOSIS OF PRIMARY AND DISSEMINATED UVEAL MELANOMA

**Sebastian Eskelin, Helsingin yliopisto – University of Helsinki**

A population-based study was undertaken to increase understanding of development of metastatic uveal melanoma and to improve treatment and prognosis of patients.

Annual screening programs are carried out to detect metastases when they are small and potentially easier to treat. Two thirds of 34 patients were diagnosed with metastases as asymptomatic when screening was annual; semiannual screening would have detected up to 98% as asymptomatic. Abdominal ultrasound (US) revealed metastases or led to a diagnostic scan or fine needle aspiration biopsy in 89% of patients. Regular chest radiograms were not helpful if US and liver enzyme tests were done.

Tumour doubling times were calculated to roughly predict the behaviour of metastases in the period prior to diagnosis. The calculated time of micrometastasis relative to the time of treatment of the primary tumour showed that the majority of primary tumours, assuming a constant growth rate, metastasized within 1 to 3 years before treatment. The primary tumour would then be small but detectable by ophthalmoscopy.

Estimating lead-time bias and, in clinical trials, stratification by estimated prognosis has not been possible. A multivariate model was built and a table of predicted median survival time after diagnosis of metastases was compiled for clinically relevant combinations of Karnofsky index, serum alkaline phosphatase level and the largest dimension of the largest metastasis of 91 patients, which were found to have independent predictive value. A table for clinical use was developed for staging.

Two thirds of 159 patients with uveal melanoma sought help from an ophthalmologist whether they had symptoms or not. Their chance of being immediately referred and correctly diagnosed at first visit was 88% and 71%, respectively. One eight of all patients were asymptomatic, and the tumour was detected during a routine check-up.

The inability of modern to notably improve prognosis calls for efforts to develop adjuvant therapies to be used at the time of the treatment of the primary uveal melanoma.

**Author's Comment:**
Many screening programs elsewhere have been modified according to this study. The tumour doubling times published have given rise to a lively debate on the potential benefit of treating small suspicious uveal melanocytic lesions early, and it was highlighted in an editorial when originally published.

*Sebastian Eskelin, MD, is currently ophthalmic surgeon and ocular oncologist at the Helsinki University Eye Hospital*

# 2003

## EFFECTS OF NITRIC OXIDE DONORS AND CYCLIC GMP ON INTRAOCULAR PRESSURE AND AQUEOUS HUMOR DYNAMICS

**Hanna Kotikoski, Helsingin yliopisto – University of Helsinki**

The effects of nitric oxide (NO) donors and cyclic GMP on intraocular pressure (IOP) were investigated in rabbits. Furthermore, the mechanisms underlying the effects of NO donors and cyclic GMP on aqueous humor dynamics was clarified by measuring aqueous humor outflow facility in rabbits and aqueous humor flow in healthy volunteers. The value of a novel tissue incubation method for screening potential NO donors and guanylate cyclase (GC) activators was evaluated using porcine iris and ciliary body. The possible connection of NO in aqueous humor dynamics in glaucoma patients was studied.

Topically and intravitreally used NO-cyclic GMP pathway-affecting compounds lowered IOP in normotensive rabbits. Intracamerally administered sodium nitroprusside (SNP), nitrosocaptopril and 8-Br-cGMP enhanced aqueous humor outflow facility in anesthetized rabbits. Aqueous humor flow did not change significantly after a single oral dose of the NO donor, isosorbide-5-mononitrate (ISMN), as compared to placebo in healthy subjects. Since IOP after placebo and ISMN intake were similar, the rate of aqueous humor flow can be regarded as an indicator of the formation of the aqueous. Because ISMN, as a model of systemic NO donors, did not influence the rate of aqueous humour flow, enhanced aqueous humor outflow facility mainly explain the IOP lowering effect of NO releasing compounds.

Various NO donors and GC activators increased cyclic GMP production in a novel tissue incubation model of the porcine iris and ciliary body. ODQ, an inhibitor of GC, totally inhibited the production of cyclic GMP after the administration of NO donors SNP and nitrosocaptopril. Captopril had no effect on cyclic GMP production, whereas the GC activators atriopeptin III and YC-1 increased the production dose-dependently.

The concentrations of NO metabolites (NO, nitrite and cyclic GMP) in aqueous humour were slightly higher in glaucoma patients than in the matched control patients, but the difference was not significant. However, the glaucoma medication may have masked any real change in variables, which are possibly unbalanced in untreated patients.

*Hanna Kotikoski, MD, is currently specialist at the Department of Ophthalmology, Tampere University Hospital*

# 2003

## DIABETIC RETINOPATHY AND PREGNANCY

**Sirpa Loukovaara, Helsingin yliopisto – University of Helsinki**

The pathogenesis of diabetic retinopathy (DR) during pregnancy is multifactorial, but the pathogenetic mechanisms are not fully known. Several factors related to metabolic changes, diabetes itself, pregnancy physiology and pregnancy complications seem to play important roles in the progression of DR during pregnancy.

Retinal capillary blood flow in type I diabetic women was measured both by blue field entoptoscopy, a psychophysical system, and Heidelberg Retinal Flowmeter™, a confocal scanning laser Doppler flowmeter (Heidelberg Engineering, Heidelberg, Germany). It appeared that retinal capillary hyperperfusion may play a role in the development of DR during pregnancy and postpartum. Furthermore, the retinal capillary blood flow seemed to depend on the grade of DR.

Because we suggested that hyperdynamic retinal capillary blood flow may act as a pathogenetic mechanism in early DR during pregnancy, we suspected that perturbations in one or more vasoactive system, either vasoconstrictive or vasodilatory, might contribute and play a role in this process. Therefore, markers of the renin-angiotensin system (plasma renin activity, angiotensin II, aldosterone, natriuretic peptides and adrenomedullin) were measured. However, these systemic vasoactive factors did not seem to play a significant role in development or progression of DR during pregnancy.

The retina is known to be a source of many growth factors. It has been suggested that various circulating and local growth factors may contribute to the progression of DR during pregnancy. We evaluated the role of circulating angiopoietic factors (angiopoietin-1, angiopoietin-2, human vascular endothelial growth factor A, and total soluble receptor of vascular endothelial growth factor type 1). These factors seemed to have a minor role in the development of DR during pregnancy.

Hormonal changes together with fluid overload might affect retinal thickness and lead to macular edema during pregnancy. Macular topography in pregnant women with type I diabetes was measured by confocal scanning laser tomography (Heidelberg Retinal Tomograph™, Heidelberg Engineering) and correlated with contrast sensitivity measured with the Vistech™ 6500 contrast test system. According to this study, macular thickness was higher and contrast sensitivity lower in diabetic women who showed clear progression of DR during pregnancy.

*Sirpa Loukovaara, MD, is currently vitreoretinal surgeon at the Helsinki University Eye Hospital*

# 2005

## LONG-TERM OUTCOME OF TRABECULECTOMY IN PRIMARY OPEN-ANGLE GLAUCOMA AND EXFOLIATION GLAUCOMA

**Pia Ehrnrooth, Helsingin yliopisto – University of Helsinki**

The long-term outcome of trabeculectomy in patients with either primary open-angle glaucoma (POAG) or exfoliation glaucoma (EG) at the Helsinki University Eye Hospital was evaluated in a consecutive series of 138 single-surgeon trabeculectomies performed between November 1994 and August 1996. The mean age at surgery was 70 years. The proportion of EG was 60%. Preoperative visual field (VF) defect was considered severe in 40%.

During a mean follow-up of 3.5 years (range, 2–5 years) the intraocular pressure (IOP) reducing effect of trabeculectomy gradually decreased. At one year, 82% of the operated eyes had an IOP of <21 mmHg without or with a single topical medication; at 4 years the corresponding percentage was 52%. At the latest examination, 53% of eyes were on glaucoma medication and 12% had had further glaucoma surgery during the follow-up period.

Patients with EG were significantly older and had a higher preoperative IOP than those with POAG and postoperative hyphema was more common in EG, but none of these factors was an independent predictor of failure. Early postoperative complications were common, but did not predict poor outcome. Insufficient filtration at the end of the first postoperative month predicted long-term failure.

In this consecutive series of eyes progression of FV defects was fairly common (41%). Progression was associated with the severity of initial VF defect. Association between stability of VF and the amount of IOP reduction after surgery indicate that a lower target IOP level would be needed, particularly in eyes with initially severe VF defect. Glaucoma-related low vision in the operated eye increased from 6% to 7%, and blindness from 4% to 10% during the follow-up period, according to World Health Organisation criteria.

Patient age was the only significant risk indicator for cataract surgery after trabeculectomy. In eyes having cataract surgery, the best corrected visual acuity was reduced already before trabeculectomy, possibly related to higher age.

These results emphasize the importance of proper postoperative control and therapy and regular long-term follow-up of patients after trabeculectomy.

*Pia Ehrnrooth, MD, is currently in private practice*

# 2005

## OPHTHALMIC BETAXOLOL: STUDIES ON PHARMACOKINETICS AND CLINICAL EFFICACY IN THE TREATMENT OF GLAUCOMA WHEN COMPARED TO TIMOLOL

**Elina Vainio-Jylhä, Turun yliopisto – University of Turku**

The pharmacokinetics of betaxolol applied to the eye was studied. The clinical efficacy of betaxolol compared to timolol in glaucoma treatment was also evaluated, because previously it had been suggested that betaxolol might prevent glaucomatous progression more effectively than timolol, probably because of its neuroprotective or vascular effects.

The pharmacokinetics was studied by measuring concentration of betaxolol in aqueous humour and in plasma at different time points after application to the eye. The correlation of intraocular pressure (IOP) reduction and concentration of betaxolol in aqueous humour were examined preoperatively in cataract patients. A prospective study was carried out to compare the clinical efficacy of 0.5% betaxolol and 0.25% timolol in glaucoma treatment. The visual field examination and retinal nerve fiber layer photography were used to evaluate glaucomatous progression.

After drug application measurable concentrations of betaxolol in aqueous humour were found all through the 48-hour follow-up period. The concomitant use of mydriatics preoperatively prevented IOP reduction. Betaxolol absorbed rapidly into the systemic circulation. Small plasma concentrations of betaxolol were measured 12 hours after a single topical ocular dose. Some accumulation obviously occurred during maintenance therapy, exposing patients to systemic adverse effects. After repeated dosing a biphasic concentration vs. time curve was seen. Interindividual variability in drug absorption was large.

In a follow-up study of glaucoma patients, reduction of IOP was similar in betaxolol- and timolol-treated groups. Treatment with betaxolol seemed to prevent the progression of glaucoma slightly better than treatment with timolol, but the difference was not statistically significant.

**Author's Comment:**
Today the neuroprotective effects of β-adrenergic antagonists are still under investigations. Concentrations of betaxolol in ocular tissues have also been studied further, and it has been shown that topically applied betaxolol is bioavailable to the posterior segment of the eye.

*Elina Vainio-Jylhä, MD, is currently specialist in glaucoma and medical retina at the Department of Ophthalmology, Turku University Central Hospital*

# 2005

## SCREENING FOR DIABETIC RETINOPATHY: ASPECTS OF PHOTOGRAPHIC METHODS

**Gunvor von Wendt, Karolinska Institutet**

Fundus photography with 45° images from one or two fields using colour transparencies or Polaroid™ pictures has so far been the predominant photographic screening method for diabetic retinopathy (DR). Furthermore, field definitions have varied. Photography with 60° images offers large field coverage and might improve detection of DR. Using a monochromatic green filter (red-free light) enhances the contrast of the retinal blood vessels and haemoglobin containing structures, and thus might improve detection of red lesions.

In this methodological study, varying photographic screening methods were evaluated. Using 60° cameras, it was studied whether DR was more easily detected from red-free film-based or digital black-and-white pictures as compared to corresponding colour transparencies. Furthermore, it was evaluated whether two 60º photographic fields were needed for screening purposes. The field coverage of one and two 60º fields was compared with that of the gold standard (30° seven-field photography). We also studied how retinal neovascularization (NVE) was detected from one and two 45° fields, and compared the results with that of one and two field 60° photography. Furthermore, in order to find out whether any of three varying 45° macular fields was superior in detecting NVE, the number of NVE lesions detected in each of them was compared with the number detected from the 60° fovea-centred field.

The results showed that especially early DR lesions, red dots, but also intraretinal microvascular abnormalities and venous beading, both indicating severe DR, were more easily detected from monochrome red-free digital images and photographs, compared to colour transparencies. "White lesions", e.g. cotton wool spots, were the only abnormalities which were less easily detected with the red-free technique.

Single field 60° photography is advocated only when the finding in this field is normal; otherwise severe lesions can be missed. One and two field 60° photography covers 60% and 80%, respectively, of the areal coverage of 30° seven-field photography (gold standard). One and two field 45° photography disclosed 53% and 77%, respectively, of the NVE lesions which were detected from two field 60° photography. Of the 45° macular fields investigated, the field centred most temporally turned out to disclose NVE lesions most appropriately.

*Gunvor von Wendt, MD, is currently retinal specialist at the St. Erik's Eye Hospital, Stockholm, Sweden*

# 2006

## PREOPERATIVE VISUAL ACUITY OF CATARACT PATIENTS. REPEATABILITY OF VISUAL ACUITY AND REFRACTIVE ERROR MEASUREMENTS IN CLINICAL SETTINGS

**Jaakko Leinonen, Helsingin yliopisto – University of Helsinki**

Visual acuities at the time of referral and on the day before surgery were compared in 124 patients operated for cataract. During an average waiting time of 13 months, the average decrease in visual acuity (VA) in the operated eye was 0.27 logMAR units per year. In the fastest worsening quartile, VA change was 0.75 logMAR units per year.

Preoperative VA was compared in samples of consecutive cataract surgeries performed in 1982, 1985, 1990, 1995 and 2000. From 1982 to 2000, the annual rate of cataract surgery increased from 1.0 to 7.2 surgeries per 1 000 population in the Vaasa region in Western Finland. The average preoperative VA in the operated eye increased by 0.85 logMAR units (from 0.03 to 0.2 in Snellen values) and that in the fellow eye increased by 0.27 logMAR units (from 0.23 to 0.43 in Snellen values) over this period. The proportion of patients profoundly visually handicapped (VA less than 0.1 in the better eye) before surgery fell from 15% to 4%.

Repeatability of VA and refractive error determination in a clinical environment in cataractous, pseudophakic and healthy eyes was estimated by re-examining the VA and refractive error of patients referred to cataract surgery or consultation. The repeatability of VA measurement estimated as the coefficient of repeatability was ±0.18 logMAR units for all eyes, and the standard deviation of measurement error was 0.06 logMAR unit. Eyes with the lowest VA had the largest variability.

Repeatability of refractive error measurement was calculated as 3-dimensional vector values and spherical equivalents and expressed by coefficients of repeatability. These coefficients for all eyes for vertical, torsional and horizontal vectors were ±0.74 D, ±0.34 D and ±0.93 D, respectively, and for spherical equivalent ±0.74 D. Eyes with lower VA had larger variability. If a change of ±0.5 D (measured in defocus equivalents) is accepted as a basis for change of spectacles for eyes with good vision, the basis for eyes in the visual acuity range of 0.3−0.65 (Snellen values) would be ±1 D.

This study measured the degree of random variation in the measurement of VA and refractive error. This gives clinicians a tool to estimate whether the observed change is real or can be explained by random variation. This is a very usual clinical situation. The study also gives an estimate of the probability of misclassification in borderline cases in medico-legal situations (e.g. driving licence). The study also gives an estimate of the average rapidity and variation of VA decrease in a cataractous eye during a given time.

*Jaakko Leinonen, MD, is chief physician retired from the Department of Ophthalmology, Vaasa Central Hospital*

# 2006

## IODINE BRACHYTHERAPY FOR LARGE UVEAL MELANOMAS

**Ilkka Puusaari, Helsingin yliopisto – University of Helsinki**

Uveal melanoma is the most common primary intraocular malignancy in adults. Vision is threatened by both the tumor and the side-effects from the currently available treatments. Prognosis for saving vision becomes worse with increasing tumor size, and thus enucleation has been the treatment of choice for large melanomas. Evidence suggests, however, that no survival benefit is gained (or lost) by enucleation as compared to eye conserving methods.

The Helsinki University Eye Hospital has since 1990 offered $^{125}$iodine plaque brachytherapy (IBT) for patients not willing to undergo enucleation for a large uveal melanoma. Survival, local tumor recurrence and preservation of the eye and vision after IBT was assessed in a population-based series of 96 patients with uveal melanomas classified as large by the Collaborative Ocular Melanoma Study (COMS) criteria. The incidence of side effects and their association with ocular dose distribution and clinical risk factors were studied. Means to improve current treatment were sought by using computer models to compare existing plaques with collimating ones, and by comparing the outcome of patients with thick tumors with similar eyes managed with transscleral local resection (TSR) in Liverpool, United Kingdom.

Melanoma-specific survival at 5 years after IBT was 65% and comparable with the survival experience of patients after enucleation in COMS. Local recurrence developed in 6% of eyes, and 84% of eyes were conserved. The 5-year incidence of cataract was 79% and that of glaucoma 60%, optic neuropathy 46%, and maculopathy 52%. Legal blindness (loss of 20/400 vision) of the tumor eye was avoided by 26% at 2 years. Dose to the optic disc was independently associated with optic neuropathy, and both dose to the optic disc and dose to the macula predicted vision loss after IBT. Simulated treatment using collimating plaques resulted in clinically meaningful reduction in both optic disc and macular doses. Preservation of 20/400 vision was more often achieved with TSR in the patients with thick tumors (32% vs. 5% at 5 years). No cases of secondary glaucoma were observed after TSR, and optic neuropathy was rare. However, local tumor recurrence was more common after TSR (41% vs. 7% at 5 years).

In terms of survival, IBT seemed to be a safe alternative to enucleation in managing large uveal melanomas. Local tumor control was no worse than with medium-sized tumours and the chances of avoiding secondary enucleation were good. Unfortunately, side-effects from radiotherapy are frequent, especially with thick tumors, and long-term prognosis of saving vision is consequently guarded. Some complications can be limited by using collimating plaques and by managing uveal melanomas that are large because of tumor height with TSR instead of IBT.

*Ilkka Puusaari, MD, is currently in private practice and a research fellow at the Helsinki University Eye Hospital*

# 2007

## ROLE OF BASEMENT MEMBRANE AND EXTRACELLULAR MATRIX PROTEINS IN THE ADHESION AND SPREADING OF IMMORTALIZED HUMAN CORNEAL EPITHELIAL CELLS

**Sissi Katz, Helsingin yliopisto – University of Helsinki**

The repair of corneal wounds requires epithelial cell adhesion and migration. Basement membrane (BM) and extracellular matrix (ECM) proteins function in these processes via integrin and non-integrin receptors. We have studied the adhesion, spreading and migration of immortalised human corneal epithelial (HCE) cells and their interactions with the laminins (Lms), fibronectins and tenascins (Tn) produced.

Human corneal BM expresses Lm-332 and -511. HCE cells produced both processed and unprocessed Lm-332, but not Lm-111 or Lm-511. Also extradomain-A fibronectin, oncofetal fibronectin and Tn-C were produced. Because HCE cells did not produce Lm-511, although it was present in corneal BM, we suggested that Lm-511 is produced by stromal keratocytes.

The cells adhered via integrin $\alpha 3\beta 1$ to both purified human Lm-332 and -511 as well as to endogenous Lm-332. However, only integrin β1 subunit participated in HCE cell adhesion to mouse Lm-111. The adhesion of HCE cells to Lm-511 was also mediated by the Lutheran (Lu) receptor. Since Lm-511 did not induce Lu into focal adhesions in HCE cells, we suggested that Lm-511 serves as an ECM ligand enabling cell motility.

During early adhesion, HCE cells co-deposited Lm-332 and the large subunit of Tn-C beneath the cells. Integrin β4 subunit, which is a hemidesmosomal component, did not mediate the early adhesion of HCE cells to Lm-332 or Lm-332/Tn-C. Based on these results, we suggested that the adhesion of HCE cells is initiated by Lm-332 and modulated by the large subunit of Tn-C, as it has been reported to prevent the assembly of hemidesmosomes.

*Sissi Katz, MD, is currently resident at the Helsinki University Eye Hospital*

# 2007

## EPIDEMIOLOGICAL, CLINICAL AND HISTOPATHOLOGICAL STUDY ON BASAL CELL CARCINOMA OF THE EYELID

**Ville Paavilainen, Turun yliopisto – University of Turku**

The incidence of basal cell carcinoma (BCC) of the eyelid in Finland was studied on the basis of 6 241 patients reported to the nation-wide Finnish Cancer Registry. This is the first nationwide study of the BCC of the eyelid based on register data within Caucasian population. In addition, the case records of 218 patients with malignant neoplasms of the eyelid other than melanoma were gathered from the Turku University Eye Clinic from years 1977 to 1997. Histopathological characteristics of neoplasms from patients treated at this clinic from 1988 to 1997 were re-evaluated and classified.

The mean annual incidence rates of BCC of the eyelid showed a statistically significant increase from 7 to 3 per 1 000 000 men and from 5 to 28 per 1 000 000 women during from 1953 to 1997 in Finland. The annual incidence rates of BCC of the eyelid increased from 8 to 29 per 1 000 000 population in south-western Finland from 1977 to 1997. The incidence rate of BCC of the eyelid rose significantly with age. Statistically significant differences in the incidence rates of BCC of the eyelid between urban, semi-urban and rural populations were not detected, and the standardized incidence ratios between different social classes and occupational categories were comparable.

During the study period 90% of patients diagnosed with BCC of the eyelid at the Turku University Eye Clinic from 1977 to 1997 were treated surgically. The recurrence rate of all surgically treated tumours was 14%. Other treatment methods were radiation therapy and cryotherapy. The most frequent histopathological subtype of BCC of the eyelid was nodular BCC in 85%. Only the nodular subtype showed recurrences.

The results showed that the incidence of BCC of the eyelid increased remarkably during the study period. According to the literature, the nodular subtype is regarded as the least aggressive subtype of BCC. However, in this study, the nodular BCC showed high recurrence rate in spite of surgical treatment. Thus, histopathological examination and subtyping of all BCC tumours of the eyelid is recommended.

*Ville Paavilainen, MD, is currently ophthalmic surgeon in the Central Hospital of Satakunta, Pori*

# 2007

## RETINAL PIGMENT EPITHELIUM AS A BARRIER IN DRUG PERMEATION AND AS A TARGET OF NON-VIRAL GENE DELIVERY

**Leena Pitkänen, Kuopion yliopisto – University of Kuopio**

The limiting barriers after intravitreal non-viral gene delivery were identified. *In vitro* experiments with bovine vitreous and retina demonstrated that both vitreous and neuroretina restrict the uptake of cationic gene complexes into the retinal pigment epithelium (RPE). The large size and especially the positive charge of the complex are the reasons for its limited access into the RPE although the exact mechanisms remain unclear. Oligonucleotides in solution were efficiently taken up by RPE cells, but the neural retina limited their permeation. The uptake of naked plasmid into the RPE was very low even without the presence of vitreous or neuroretina.

The influence of lipophilicity (β blocking drugs) and size (fluorescein isothiocyanate-dextrans) of the permeants were assessed using isolated bovine choroid-RPE. For hydrophilic compounds, the choroid-RPE was 10 to 100 times less permeable than the sclera, whereas for lipophilic compounds the choroid-RPE and sclera were equal barriers, emphasizing the important role of the RPE in permeation.

The present study demonstrated that melanin isolated from bovine ocular tissue and synthetic melanin differed in terms of size, surface area, shape, aggregation properties and drug binding. It was estimated that the choroid-RPE contains 3 to 19 times more melanin bound betaxolol and metoprolol compared to the free drug. In contrast, phosphodiesterase oligonucleotides and carboxyfluorescein did not bind to melanin. Thus, melanin binding modifies the pharmacokinetics of betaxolol and metoprolol at the cellular level in the posterior segment of the eye.

*Leena Pitkänen, MD, is currently clinical instructor and specialist at the Department of Ophthalmology, Kuopio University Hospital*

# 2007

## VISUAL IMPAIRMENT IN FINNISH CHILDREN: PREVALENCE, CAUSES AND MORBIDITY OF FULL-TERM AND PRETERM CHILDREN WITH VISUAL IMPAIRMENT BORN FROM 1972 THROUGH 1989

**Sirkka-Liisa Rudanko, Helsingin yliopisto – University of Helsinki**

The prevalence and causes of childhood visual impairment in Finland during the period 1970 to 1980's were investigated, with special attention to risk factors and further prevention of visual impairment in children. The primary data on children with visual impairment were obtained from the Finnish Register of Visual Impairment and supplemented from other health registers and patient records in Finnish hospitals.

Visual impairment had been registered in 556 children from a population of 1,138,326 children between the ages of 0 to 17 years, born from 1972 through 1989. The age-specific prevalence of registered visual impairment was 49/100,000 in total. Of them, 23/100,000 were blind children and 11/100,000 were children born prematurely. Boys were impaired more often and more severely than girls. Congenital malformations (52%), systemic diseases (48%) and multiple impairments (50%) were common.

Genetic factors (42%) were the most common etiologies of visual impairment, followed by prenatal (30%) and perinatal (21%) factors. Risks for visual impairment associated with preterm births, low gestational age and low birth weight, prenatal infections, birth asphyxia, neonatal respiratory difficulties, mechanical ventilation over two weeks, and hyperbilirubinemia. The proportion of blind and multi-impaired children was increasing, owing to the higher survival of extremely preterm and very sick infants.

The main ophthalmic groups of visual impairment were retinal diseases (35%), ocular malformations (29%) and neuro-ophthalmological disorders (29%). The most common diagnoses of visual impairment were optic nerve atrophy (22%), congenital cataract (11%), retinopathy of prematurity (10%) and cerebral visual impairment (8%). Retinopathy of prematurity had afflicted children born at 32 gestational weeks or earlier.

The study results serve as basic data for follow-up studies of childhood visual impairment in Finland. Some diseases that are part of the Finnish disease heritage have remained common causes of childhood visual impairment, owing to the lack of cure. In consequence of new methods introduced into pediatric ophthalmology in the 1980's, a significant reduction has been seen in visual impairment due to retinopathy of prematurity and congenital cataract. The persisting increase in visual and other impairment associated with brain injuries requires continuous improvements in antenatal, neonatal and ophthalmologic care, efficient early intervention programs and long-term multimodal rehabilitation.

*Sirkka-Liisa Rudanko, MD, is currently chief of the Finnish Register of Visual Impairment, Finnish National Agency for Welfare and Health, Helsinki*

# Hakemisto

# Index

# TEKIJÄHAKEMISTO – AUTHOR INDEX


Aho Valtteri 68
Ehrnrooth Pia 72
Eskelin Sebastian 69
Falck Aura 35
Fyhrqvist, kts. Virtanen Tuula 44
Hamunen Katri 25
Harju Mika 56
Hartikainen Jouko 53
Hellstedt Timo 42
Hietanen Jaana 30
Hirvelä Heli 31
Huhtinen Minna 64
Ihanamäki Tapio 65
Jaakkola Aino 45
Jämsén Kristiina 36
Järvinen Esko 17
Kari Osmo 22
Katz Sissi 77
Kivelä Tero 8
Kontkanen Matti 46
Kotaniemi Kaisu 57
Kotikoski Hanna 70
Lahdes Kimmo 37
Lamberg, kts. Rosenberg Maria 58
Latvala Terho 38
Lehto Ilkka 23
Leinonen Markku 39
Leinonen Jaakko 75
Lindberg Laura 49
Linnola Reijo 59
Loukovaara Sirpa 71
Lumme Pirkko 26
Mikkilä Helena 50
Mikkonen Pentti 9
Mäkitie Teemu 60
Mäntyjärvi Maija 10
Paavilainen Ville 78
Pelkonen, kts. Mikkilä Helena 50
Peräsalo Ritva 18
Pitkänen Leena 79
Pohjalainen Tuula 61
Punnonen Eeva 19
Puska Päivi 32
Puusaari Ilkka 76
Puustjärvi Tuomo 15
Päivönsalo-Hietanen Taina 47
Raivio Virpi 66
Ranta Päivi 67
Repo Leo 40
Ropo Auli 24
Rosenberg Maria 58
Rouhiainen Harri 11
Rouhiainen Päivi 41
Rudanko Sirkka-Liisa 80
Sarvela Johanna 27
van Setten Gysbert 20
Siik Seppo 51
Sorri Iris 62
Summanen Paula 16
Teikari Jaakko 12
Teir Henrik 13
Tommila Petri 21
Tuunanen Tiina 52
Uusitalo Marita 33
Uusitalo Raimo 34
Vaahtoranta-Lehtonen Hanna 54
Vainio-Jylhä Elina 73
Valle Tuuli 55
Vannas Kaarina 14
Vesaluoma Minna 43
Vesti Eija 28
Virtanen Tuula 44
Voutilainen Raija 63
Välimäki Juha 48
Vänttinen Sinikka 29
von Wendt Gunvor 74