# Ophthalmological aspects of the effect of selected physical, chemical and biological agents

**PhD Thesis**

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VIII. ***Hári-Kovács A,*** Soós J, Facskó A, Végh M. Acetazolamid orális alkalmazása mellett jelentkező chorioidea leválás: ismert idioszinkráziás hatás szokatlan megjelenési formája? (Case report on choroidal effusion after oral acetazolamide administration: an unusual manifestation of a well-known idiosyncratic effect?) *Orv. Hetil. (Hungarian Medical Journal)* 2017; 158(50): 2005-2009. **(IF/2016: 0,349)**

IX. ***Hári-Kovács A,*** Zeffer T, Gyetvai T, Soós J, Szabó Á, Vass A, Kovács A, Lovas P, Hadarits F, Kiss T, Baranzi N, Végh M. Cornea érzékenység vizsgálata kettős ellenoldali corneális metszést követően (Changes in corneal sensitivity following phacoemulsification with opposite site clear corneal incision). *Szemészet (Ophthalmologia Hungarica*) 2017; 154:213-216.

## INTRODUCTION

The eye as one of the organs that build up our body can become the target of the effect of different enviromental factors, physical, chemical and biological agents. The present dissertation includes five studies that aim to present the results of the investigations of three below listed agents seemingly selected arbitrarily from all of the others but which are rather determined by the opportunities provided by the everyday work of a practicing clinician. These are as follows:
PHYSICAL AGENT: ***Surgical trauma*** caused by phacoemulsification (PhE) on the eye surface, primarily on the corneal innervation. The intraoperative pain perception and the central corneal sensitivity (CS) were the investigated variables (Study 1-3).

CHEMICAL AGENT: The ciliochoroidal effusion syndrome as an *opthalmic idiosyncrasy* caused by orally administered ***sulfonamid-derived drugs*** (Study 4).

BIOLOGICAL AGENT: Opthalmo-filariasis, an opthalmic disease caused by ***Dirofilaria repens*** (DRep) that has become endemic in Hungary primarily because of the climatic changes in the past decades (Study 5).

## I., SURGICAL TRAUMA DURING PHACOEMULSIFICATION AS A PHYSICAL AGENT AFFECTING THE EYE

With more than 20 million interventions per year, PhE is one of the surgical procedures being performed in the greatest number worldwide. With both of the dramatically reduced corneal wound size and the topical anesthesia employed in the vast majority of cases comply with the world-wide conquering concept of the minimally invasive surgery. Although the surgical trauma to the ocular tissues are reduced to a great extent, some acute and long-term alterations occur in both the structure (edema, astigmatism) and the function (pain, decreased sensitivity, dryness) of the cornea. The functional effects are greately related to the corneal innervation of which density is the highest of any surface epithelium of the body, and contains centrally 3,500–7,000 nerve terminals/mm$^2$. It has been hypothesized that injury of a single epithelial cell may be sufficient to trigger pain perception. However, the experience of pain is characterized by an immense inter-individual and group variability with numerous contributing factor such as age, gender, previous experiencies, anticipated pain and anxiety for a procedure, race, ethnicity etc. Although there is no consensus regarding the underlying mechanisms, a holistic influence of biological, psychological and social-cultural factors is suggested. Despite having described some alterations in cellular pain processing among different races, there is an evidence that the *pain treshold* examined under experimental conditions doesn't show significant disparity in individuals of different races and ethnicities in contrast to the *pain tolerance*. The pain tolerance, however, is rather influenced by the environment the patient lives in than native, intrinsic factors. The complex interactions of those factors can be comprised in the so-called biopsycho-sociocultural model of pain.
As to the phaco-pain (PhP) that is the pain caused by PhE, the reduced wound size and the almost constant intraoperative cameral pressure faded the request of preoperative intraocular hypotony such topical anaesthesia (TA) became the most widely applied method of anaesthesia for PhE generally resulting in a far acceptable pain experience for patients. Nevertheless, most ophthalmic surgeons encounter patients reporting on more unpleasantness and pain for the second eye operation. The relating literature seems to be of controversy as to the pain for sequential cataract surgeries. While several authors reported on higher pain scores among the patients undergoing surgery for their second eyes, others did not find correlation between the level of pain perception and the sequence of operation.

Beyond the intraoperative pain, the postoperative irritation, tearing and foreign body sensation are significant factors for the patients' perioperative discomfort. The underlying cause of these symptoms is the impaired tear film quality and tear production which is thought to be the consequence of the transection of corneal nerves that will reduce CS and compromise the afferentation of the lacrimal functional unit. The bigger the surgical incision the more serious dry eye problems are expected. This can be of significance by performing opposite site clear corneal incision (OCCI) to reduce the preoperative corneal astigmatism. In my practice, OCCI is routinely used in PhEs where the toric IOL implantation can not be carried out for any reason. Concerning surgical trauma caused by PhE, we conducted three studies with the following objectives:

**Study 1.:** To investigate the difference in patients' pain perception measured by visual analogue pain scale (VAPS) during consecutive PhEs under TA with the maximal standardization of the PhP influencing factors discovered so far.

**Study 2.:** To find out if there is a difference in perceived pain measured by VAPS during standardized PhE between patients living in the United Kingdom and Hungary.

**Study 3.:** To examine the additional impact of OCCI on CS and tear production in the early postoperative period of PhE compared to that of the single clear corneal incision (SCCI).

**Patients and methods**

**Study 1:** From 200 consecutive patients requiring bilateral cataract removals and admitted to an ophthalmic day surgery centre in London, UK between February and May 2010, 187 were enrolled into this prospective, observational study. Twenty patients were excluded since they met at least one of the following exclusion criteria: need for any other type of anaesthesia than included in our protocol, previous surgery on the eye, intraoperative complications requiring additional procedures, language barrier or mental conditions limiting the proper use of the pain scale. Patients having postoperative complications which can negatively influence their satisfaction at the post-op check (prolonged corneal oedema, inflammation, increased intraocular pressure) as well as those who omitted the scheduled visits and/or did not have all data to be recorded, were also excluded. All procedures were done by the same surgeon, in the same way: clear corneal, 2,75 mm incision, hydrodissection with balanced solution containing 20 mg preservative free lidocaine, "stop and chop" technique, Tecnis ZA9003 foldable lens insertion. In each case included in the study, the same course of topical anaesthetic drops was used as follows: four times a drop of 0,5% proximetacaine (Proxymetacaine Minims®) into the conjunctival cul-de-sac of the eye to be operated on, with 10 minutes intervals on the day ward then another drop into both eyes, in the anaesthetic room, just before entering the operating theatre. To rate the intraoperative pain in a standardized way we used a VAPS with both numeric (extending from 0 to 10) and written indices to help the patients with the pain assessment. In order to prevent patients from being influenced by the presence of the surgeon, the pain scores were being collected by the nursing staff. Each patient was asked to rate the intraoperative pain for his/her each procedure on two occasions: first immediately after the surgery (T1, T2), still in the operating theatre then at the two-weeks follow-up check (C1, C2), consequently, four numbers were collected from each patient. Data were pooled (T1, C1 and T2, C2 referring to the first and the second eyes, respectively) and the four groups were compared statistically (SigmaStat 3.5).

**Study 2:** The same surgeon (HKA) have operated on 80 eyes of consecutive 70 patients with senile cataract (Group E) in the North East London NHS Treatment Center (Ilford, United Kingdom) and two years later, on 85 eyes of 80 Hungarian patients (Group H) at the Department of Ophthalmology of the University of Szeged, (Szeged, Hungary). Concerning the patients'

inclusion- and exclusion criteria and the methods we refer to those written in the „Patients and Methods" section of the *Study 1*.

**Study 3:** In this prospective, non blinded study, two cohorts of patients underwent an uncomplicated, co-axial PhE either with a routine single clear corneal or with doubled opposite clear corneal incisions: Group SCCI and Group OCCI, respectively were compared. OCCI was considered in cases of higher than 1,50 D preoperative corneal astigmatism and a toric artificial lens insertion didn't come into question for any reason. Patients with history of ocular surgeries (apart from eyelid surgeries), injuries including laceration, erosion and chemical injuries, herpetic or other serious keratitis and with existing significant filiform keratitis or corneal haze and scar were excluded. Complications leading to conversion into extracapsular cataract extraction were not included either. Single plane corneal incisions were made by 2,75-2,8 mm clear cut knives 1-2 mms centrally from the limbus, possibly in the steep axis of the cornea determined by keratometry with Zeiss IOL Master in Group SCCI, and exclusively at the steep axis for Group OCCI. The steep axis was marked preoperatively at the slit lamp in the sitting postion of the patients. The side port was made by 15° knife approximately at 90° from the primary incision; at the end of the surgery, the incisions were secured by hydration. In each case, combined topical tetracaine or oxibuprocaine and intracameral 1% preservative-free lidocaine anaesthesia was employed. The following data were captured from both eyes pre- and postoperatively: the central CS threshold, tear film break up time (BUT) and basal tear production. CS was measured with a Cochet–Bonnet aesthesiometer (Luneau Ophthalmologie, Chartres, France) in such way that nylon filament was brought to the central area of the cornea perpendicularly to the surface. Contact was detected by the slight bend of the nylon; CS was taken as the length of the filament in millimetres that gave a 50% positive response from a minimum of 4 stimuli applications. To examine BUT, the tear film was stained by fluorscein, and the mean of three consecutive measurements was registered. To measure the tear secretion Schirmer II test (ST1, ST5) was employed. Pre-and postoperative data were pooled and compared, for the statistical analysis, Prisma for Windows version 6.01software was employed.

**Results**

**Study 1:** We enrolled 187 patients, 99 females and 88 males aged from 57 to 96 years (mean: 76,5 years). Thirteen patients were excluded due to the need for anaesthesia different from the above protocol (6 patients) or because of post-operative corneal oedema (2 patients), missing data (4 patients) and lack of the capacity to properly use the VAPS (1 patient). The interval between the two surgeries ranged from 9 to 15 weeks (mean: 13,02 ± 3,03). The average follow-up period was 2,43 weeks (2-4 wks) On examination of the pain scores distribution among the cases, regardless of the time of questioning, quite similar patterns could be seen for both the first and second eyes, suggesting no obvious difference between the two groups. Although, more erratically for the second eyes, the percentages are inclining towards the higher pain scores for both eyes. Regardless of which eye was operated on, just above two thirds of the patients considered the surgery less than annoying (having given 0 – 1) and none of the them gave 9 or 10 in the study. Data did not show a normal distribution in either group. The median pain score was 1 for both T1 and T2; 1 and 0 for C1 and C2, respectively. To compare the four data sets ANOVA Pairwise Multiple Comparison Procedure (Dunn's Method) was employed. There was not any difference between the first and second eyes if we compared the scores recorded just after the surgery (1,50 vs 1,51). However, weeks after the surgery, second procedures appeared to have higher scores (1,10 vs 0,71), but the difference was not significant. It is also remarkable, that C values are lower than T values for either eye, indicating that patients

recalled much less pain couple of weeks after the surgery than that they indicated on the day of the procedure (0,71 vs 1,50 and 1,10 vs 1,51 for the first and second eyes, respectively).
**Study 2:** Seven patients were excluded from Group E becuase of additional (subTenon) anesthesia (3 patients), complicated surgery (1 patient) or the insufficient co-operation in using VAPS (2 patients). From Group H, 2 patients were excluded due to previous pars plana vitrectomies on the particular eyes in question. Although, the Group E consisted of slightly older patients than Group H, the difference was not statistically significant. The difference was bigger in VAPS scores, the Hungarian patients felt the surgery less painful, but it was not significant either. The distribution of patients giving a certain pain sore was quite similar in the two groups, the most striking difference can be observed in the number of the absolute painless surgeries, i.e. VAPS 0: it was much lower in Group E. There was no patient in either group to give the highest scores of 9 or 10.
**Study 3:** Thirteen and 33 patients were assigned to group OCCI and SCCI, respectively; neither the demographic data of the enrolled patients nor the measured variables showed difference preopertively. No difference could be found between the groups in the four parameters measured on the 1-3 postoperative days postoperatively with $p<0,05$ being considered significant. To analyze the data Student t-test and Mann-Whitney test were employed.

**Discussion**

In *Study 1*, the PhE was conducted under steady and standardized circumstances concerning the pain-influencing factors which we think to be one of the main advantages of our investigation compared to the related ones. All of the enrolled patients underwent bilateral surgeries which were done by the same surgeon and - to exclude any possible influence by the surgical method - the same ("stop and chop") technique was used. Data always were obtained from each patient's both eyes procedures (otherwise excluded) consequently, the compared groups did not differ in either age, gender, education level, psychological characteristics or racial distribution. Similar studies, in contrast, compared independent groups of patients undergoing the first and second eye PhEs, moreover the procedures were done by different surgeons. Taking into consideration, that a patient complaining about more pain or unpleasantness by the second eye surgery, actually he or she compares the recently perceived pain with the remembered pain of the first procedure, we decided to try to estimate the remembered pain of the procedures as well. Therefore, patients were asked for rating the pain they felt during the particular operation not just once but on two occasions: first perioperatively then 2-3 weeks later: expediently, at the routine postoperative checking. A study from Ursea et al. have a very similar design to ours: surgeries were done by the same surgeon, each subject's pain scores from the first and second cataract extractions were paired controlling for the individual variations in pain perception furthermore, the pain scores (the median! not the average) were registered twice: first immediately after the procedure, then at the first postoperative day. Patients added higher scores for the second eyes on the day of the surgery, but difference faded for the next day. Authors think that the amnestic effect of the intravenously administered midazolam may be responsible for the difference. As intravenous sedation was not applied in our practice, the hardly predictable amnestic effect of midazolam on the pain assessment could entirely be avoided. Although, psychic factors such as preoperative anxiety, fear (of the unknown), increased awareness of the procedure, education level etc. can undoubtly influence the pain perception, to measure these parameters remains quite difficult and the correlation between them and the experienced pain is of contradiction. Therefore, the above factors remained out of the scope of our investigation. Neither the perioperative scores nor the remembered pain scores showed significant difference between the first and second eye operations (C1 vs C2 and T1 vs T2) i.e. patients rated the second eye procedures just as painful as the first eye operations. However, a

great and significant difference could be found between T and C values for each eye procedure: the remembered pain practically was by around 50%: (1,50 vs 0,71) and 30% (1,51 vs 1,10) less for both eyes than the perioperative pain level. It is in line with the common experience that the longer the time passes by after a painful event the less pain can be recalled and with studies demonstrating the people's tendency to remember aversive experiences as less unpleasant than they actually were. Above results seem to suggest that the consecutive procedures, in fact, do not differ in the perceived pain, nevertheless, patients may find the latter surgery more painful because they compare it with the obviously lower level of the remembered pain of the first procedure.

In *Study 2*, the Hungarian patients reported lower intraoperative pain, but the difference was not statistically significant. It was speculated that living in and belonging to a country could represent the resultant of the varied, immensely investigated factors that are influenced by the subject's socio- educational, ethno- cultural background and relation to the healthcare system or provider. Some circumstances favoured the comparison of Group E and H. Like in Study 1, we did not need to count with the influence of the surgeon's personality and experience as influencing factors, since each surgery was performed by the same surgeon, by the same technique. The interval between the surgeries of the two groups was almost two years, but the surgeon operated on the patients of Group E with more than 12 years surgical experience in phacoemulsification such the impact of the time interval on the learning curve can be disregarded. Morover, females and younger patients have been reported to have lower pain treshold, but the groups did not show significant difference neither in age or in gender proportion. One could concern about the patients in both groups who underwent sequential cataract extractions and both eyes' data were registered and included in the study. Albeit, some examiners concluded that second eye surgeries would be more painful, others including us have could not find difference in the intaoperative pain between the consecutive surgeries for a patient. There is another circumstance –apart from the nationalities- which did not match in the groups: as topical anesthetic, proxymetacaine was used in Group E and oxybuprocaine in Group H. Study to directly compare the agents' effect could not be found in the literure. The department in Hungary is the healthcare provider of three counties mostly involved in agriculture, consequently lot of patients are referred to us from rural environment that of course is not the case for a hospital located in London. Patients living at rural places are showed to have higher pain sensitivity but this factor deemed to be not strong enough to neutralize or overcome other, antagonistic factors related to the different biopsychosocio-cultural background of English patients. The different ethnical composition of Group E is the gratest drawback of the study design. Though, the majority of the patients were white Caucasian, a significant proportion included patients themselves or their ancestors originating from India, Pakistan and much less but some from Africa and East-Asia. The unrecorded ethnical composition obviously makes the investigation hardly repeatable and comparable with forthcoming similar studies. Nevertheless, Grop-E like Group H can be regarded as a representative sample of English and Hungarian ophthalmic patients such giving relevance to our findings.

*Study 3* aimed to look into the impact of PhE on CS, tear production and tear film stability in the early postoperative period. These parameters have been investigated by several authors but the wound size (2,8-4,1 mm) and location (corneal, sceral) vary in these sudies.

BUT was found to be reduced in both groups at each time of measuring but both CS and ST lowered only in the dry eye group! In contrast with the the majority of the related publications, we couldn't find significant CS lowering in either of the investigated groups. It was especially surprising in Group-OCCI where the cumulative wound size equals to (2x2,8=) 5,6 mm. Since the CS were perfomed by three different examiners, even mild differences in the way of using the aesthesiometer may result in measurement errors. The 8 cases where the CS was even grater

after than before the surgery could bear out the above explanation. However, some of the authors found increased tear production measured by ST I on the first postoperative day. They explained the transient increase in ST values with the inflammatory process stimulated by the irritation presenting immediately after the surgery. Perhaps, our measurements were performed without significant errors, and the inflammation persisting right after the surgical trauma can rather cause a transient sensitisation of nerve endings, reminding one the well known phenomena of both the increased sensitivity for painful stimuli and the difficulty of inducing anaesthesia of the inflamed organs and tissues. On the other hand, it is also established that after repeated noxious stimulation or tissue injury (which basically occurs during PhE), ocular polymodal nociceptors become sensitized and cause sustained pain and hyperalgesia. Former papers gave significance to the position of the wound presuming more serious damage to the sensory afferentation with temporal than with upper or upper-temporal incisions, as the corneal nerve plexus was thought to be originated from the rami of the long ciliary nerves which are running at 3 and 9 o'clock positions. However, the more recent morphological studies revealed, that around 60 nerve bundles originating from the long ciliary nerves enter radially the corneal stroma, and branch immediately such their multiple anastomoses can bypass the peripheral injury preserving the afferentation of the central cornea. Due to the low number enrolled of patients and the lack of masking, we consider the above investigation a pilot study. Results are planned to be clarified in the future by increasing the sample size, employing a blinded method and forming different groups for the patients with and without former dry eye disease. In summary, with the above number of cases, our hypothesis that the additional cornal incision during PhE would decrease more the central CS as well as the tear film quality and quantity causing more serious dry eye symptoms than a single clear corneal incision was not justified.

## II., OPHTHALMIC IDIOSYNCHRASY DUE TO SYSTEMIC SUD ADMINISTRATION

Several drugs, especially sulphonamide-derived medications, so called sulpha–drugs (SuD) are widely recognised to cause visual disturbancies, most often acut onset and transient myopia (pseudomyopia). Besides other medicines such as morphin–derivates, hydrastine and the digitalis group, SuDs since the 19th century have been known to cause spasm of accomodation of the ciliary body, which will finally lead to transient (pseudo)myopia. Lately, there are reports on sulphonamide-induced ciliary body oedema and supraciliary effusion always presenting with acut myopia and acute angle closure glaucoma (ACG) which has been referred to as ciliochoroidal effusion syndrome (CES) since 2006. There are theories, but the pathophysiology of the SuD-induced ophthalmic disorders has not been fully discovered yet. Three potential contributors have been suggested, namely osmotic disturbancies of the lens leading to thickening and changing its refractive index; secondly the ciliary body oedema and finally, the accomodative spasm of the ciliary muscles. Both of these can result in the anterior displacement of the iris-lens diaphragm with decreased ACD and narrowing of the irido-corneal angle, occasionally with ACG. Having encountered *three cases* with unusual ocular side-effects of two different SuDs, we had the opportunity to conduct both qualitative and quantitative studies to highlight the morphological changes of the anterior segment and the ciliary body, decisively by means of UBM. Study 4 below aims to report on our results of the investigation of SuD-related ocular idiosynchrasy.

## Methods

Beyond the basic ophthalmic examinations the further instruments were used in the investigation. For gonioscopy Goldmann's triple-mirror contact lens was used after instillation topical anaesthetic. Fundus photographs were taken by the fundus photo mode of OCT (Topcon 3D OCT-2000, Topcon Corporation, Tokyo, Japan). Conventional B-scan ophthalmic echography was performed by10 MHz transducer, cristalline lens thickness was measured by A-scan contact mode. UBM (VuMax 35-50 MHz, Sonomed Escalon Inc., NY, USA) saggital scans were recorded and the measurements were performed in four quadrants of each eye and the average of the values was taken into consideration for comparing the examinations of different visits. Care was taken to hold the transducer's scanning plane perpendicular to the structure having been examined. The AOD measured between the inner aspect of the cornea and the anterior surface of the iris at a 500 microns distance from the scleral spure. ACD between the endothelial aspect of the cornea and the anterior surface of the (pseudo)lens, CBCA was determined as an angle between the anterior aspect of the ciliary body and the inner aspect of the cornea; ciliary body thickness (CBT2) was introduced by us, and was defined as a line between the outer and inner aspects of the ciliary body at 2 mm distance from the scleral spur.

**Case 1:** A 39 years old female patient was referred to our out-patient clinic for consultation due to headache and sudden bilateral visual impairment. For hypertension, twice a day medazepam 10 mg, twice a day bisoprolol 2,5mg and once a day indapamide 1,5mg (PRETANIX ret® , Les Laboratoires Servier) tablets were prescribed. In particular, she was complaining about the loss of distant vision and having blunt pain in the outer corners of the eyes on attempted reading while the near vision was preserved. BCVA was 0,08–6,0 Dsph=1,0 and 0,06-6,0 Dsph=1,0 and IOP measured 25mmHg and 24 mmHg in the RE and LE, respectively. Normal versions and convergence, slight esophoria for near and orthophoria for the distance were seen. Mid-dilated, equal pupils with normal direct and consensual light reflexes, shallower anterior chamber, clear medias, and unremarkable fundi could be observed. On gonioscopy, narrow and moderately open parts (Shaffer Grade 1, 2) of the angle could be seen. After instilling a drop of cyclopentolate hydrochloride 0,5% into both eyes, the refractive error decreased to – 5,0 D in both eyes. According to the above findings, accommodative spasm resulting in (pseudo) myopia was diagnosed, however, the central origin could not be entirely ruled out. The next day, her headache diminished, other complaints were substantially unchanged. The VA was 0,08–7,0 Dsph=1,0 / 0,06-7,0 Dsph=1,0; IOP 24/26 mmHg. An optical biometry revealed shallower anterior chamber but normal lens thickness in BE. By UBM, the ciliary body, throughout its "visible" extent was markedly thickened, the suprachoroidal space showed a very low reflectivity with a few more reflective membrans suggesting ciliary body-choroidal detachment and effusion. The anterior aspect of the ciliary body moved forward which could be demonstrated by the decrease of the CBCA with 25°, on the average. The ciliary processes rotated remarkably forward, occasionally attaching the posterior aspect of the iris and angle opening distance (AOD500) was markedly reduced. After putting 3-3 drops of cyclopentolate hydrochloride 0,5% into both eyes, with 15 minutes intervals, the refraction decreased to -0,75/-0,50 Dsph. Two days later, at her next follow-up appointmet, the patient denied the symptoms she had been complaining about. The uncorrected VA was again 1,0/1,0; IOP 13/17 mmHg, the anterior chamber deep and clean. Ciliary body edema and detachment disappeared, both of CBCA and AOD500 returned to the normal. The patient admitted that she had discontinued taking PRETANIX ret® two days before on her own, as she thought her blood pressure had lowered too much. During her two years follow-up her full vision was maintained in BE.

**Case 2:** A 69 years old man was referred to our department with presumed bilateral retinal detachment. Couple of days before his referral, he underwent YAG-laser capsulotomy for his LE due to posterior capsular opacification and due to the following IOP elevation (30 mmHg) on his LE he was given 2x250 mg acetazolamide (Huma-Zolamide® , TEVA) per os. Shortly after that, normal IOP was measured for BE, but later on, he noticed darker, reticulated areas in the nasal part of his RE's and in the lower part of his LE's visual field. On his first ophthalmic examination at our department, he had full vision (VA: 1,0/0,8 -1,75Dsph -1,0Dcyl 90'=1,0), and normal IOP (11/11 Hgmm) on both sides, but the ophthalmoscopy as well as ultrasonography discovered bilateral circumferential choroidal detachment, that approached the posterior pole in the RE. Although neither myopic shift nor IOP elevation was found, having recalled Case 1, UBM was employed which revealed that the choroidal effusion in both eyes invaded the supraciliary space, too: the mean of CBT2 was 840μ in the RE. The iris-(pseudo) lens diaphragma moderately moved forward resulting in mild shallowing of the anterior chamber (ACD 3 mm) an dnarrowing of the iridocorneal angle (350μ). Interestingly, by measuring the CBCA, a significant forward movement of the anterior aspect of the ciliary body i.e. ciliary muscle spasm could not be detected: the mean of CBCA was 127° in the RE (the LE scans were not of quality good enough to measure CBCA precisely. Observation was opted, and two weeks later, his BCVA was full and IOP within the normal limits in BE. Neither ophthalmoscopy nor echography including UBM could detect chorioidal effusion in the eyes.

**Case 3:** An 82 years old man underwent a combined phacoemulsification with posterior chamber IOL insertion and pars plana vitrectomy with injection of 20% $SF^6$ due to his RE rhegmatogenous retinal detachment. In the first postoperative day, the right eye's IOP raised markedly (39 mmHg) the left eye was normal, therefore 500 mg acetazolamide tablets per os and brinzolamide eyedrops topically in the right eye were administered. By the evening of the same day, RE's IOP returned to normal and remained so. The second day, the other eye routine funduscopy with dilated pupil discovered a circumferencial bulging of the peripheral retina. B-scan echography revealed 360° peripheral choroidal detachment of his LE, which caused no visual deterioration such it was completely unnoticable for the patient, and certainly not present on his admittance to our department. UBM showed the characteristic picture of the supraciliary effusion with the following parameters: CBCA = 112°, CBT2 = 1 mm, AOD = 300μ. When he was emitted BCVA was 0,15 and 1,0; IOP was 19 and 16 mmHg of the RE and LE, respectively. Eight weeks later, neither funduscopy nor ultrasound examination showed choroidal detachment of either eye. Unfortunately, for technical reasons, the control UBM study is not available. He had no complaint and full vision for his LE.

**Discussion**

In the literature, there are only two articles on indapamide caused transient myopia as a rare adverse event, but none of them used UBM for the examination of the anterior segment changes. Apart from our papers, there are six publications employing UBM to investigate the SuD - related morphological changes. There seems to be a consensus about the limited role of the lens in the observed refractive changes and IOP elevation. Although, some increase of the lens thickness can always be observed, the thickening itself can not explain either the anterior chamber shallowing or the myopic shift. Our Case 1 supports the above statement since the average thickening of the lens was 0,2/0,3 mm while the anterior chamber flattening was around 1,4/1,2 mm in the RE and LE, respectively. The observation that both transient myopia and ACG can occur in pseudophakic patients, also undermines the significance of the lens tickness changes in the pathomechanism. The marked discomfort during close work and the fact that cyclopentolate significantly improved her pain as well as the refractive errors indicate rather a

spasmic component in the pathomechanism. Furthermore, exclusively in our study, the drug-induced forward movement of the ciliary body has also been measured by adopting the method of Croft and co-workers'. Their studies on rhesus monkeys proved that the forward movement of the ciliary body achieved by the contractions of the longitudinal parts of the ciliary muscle plays a paramount role in the physiologic process of accomodation. In the middle aged group of monkeys they could registrate the average of 27,9° forward ciliary body movement as the difference between the CBCA meaasured during nonaccomodated and maximally accomodated states of the ciliary muscles. We also have found a significant forward movement in Case 1 reflected by an average of 30° lessening in CBCA suggesting that the accomodative spasm of the ciliary muscle, additionally to its edema, also contributed to the development of the symptoms. The third presumed factor contributing to the myopic shift, ciliary body engorgement with forward movement could convincingly be demonstrated by UBM. The centripetal circumferential thickening of the ciliary body, predominantly caused by the supraciliary effusion, was registered and expressed by the increase of the CBT2 wich parameter was invented by us. The associated forward rotation was registered as well as expressed by the decrease of CBCA. The anterior segment changes detailed above may give rise to ACG. If it occurs, the therapy should consist of prompt discontinuation of taking the causative drug and instilling cycloplegic drops. It is of interest, that neither of the so far reported three cases of indapamide induced acute myopia, included ours, nor Case 2 and 3 developed angle closure glaucoma. The combination of the above symptoms (iris-lens-ciliary body complex forward movement, shallow anterior chamber, myopic shift, ACG, choroidal effusion) resulting from the idiosyncratic effect of SUDs on the uvea was proposed to term as CES in 2002 by Ikeda. The bilateral involvement and the spontaneous recovery after cessation the causative drug undoubtly assign the cases of Study 4 to the ciliochoroidal effusion syndrome. However, Case 2 and Case 3 need to be considered unique and exceptional among the acetazolamide caused ocular adverse reactions have been reported till today, since these patients – contrary to all the other cases in the literature - developed neither transitory myopia nor ACG. Although in both cases, in addition to the choroidal detachment showed by the conventional echography the supraciliary effusion occured, and was confirmed by the UBM, refractive changes couldn't be measured, and full vision has been preserved all the time. The male gender of Patient 2 and 3 might be of significance because the majority of the SuD idiosyncrasy cases occurs in femals. Perhaps, the different hormone status favours the milder forms of idiosynchrasy to be manifested. The question arises: do our cases represent a *rarely occuring*, newly discovered form or rather a milder therefore *rarely detected* form of the acetazolamide-related CES. Considering the characteristics and erratic nature of drug idiosyncrasy, the letter is held to be more likely. By reviewing our cases as well as the related literature, we considering it being proved that the SuD-related ocular idiosyncrasia represents a continous spectrum of the changes within the uveal tract extending from the silent forms of supraciliary and choroidal effusions through the mild-to-severe acute myopia up to the acute ACG.

Finally, it might be worth to discuss practical issues concerning the administration of the above-mentioned SuDs.

a. In the package insert of PRETANIX ret®, there is not any ocular side-effect listed (84).
b. One of the main indications for systemic use of acetazolamide is the glaucoma (85). In cases of bilateral IOP elevation with anterior chamber flattening or ACG, one needs to consider idiosynrasy otherwise the further administration of the drug can result worsening in the patient's condition.
c. Only the „transient visual disturbance" as not frequent (1000/1 - 100/1 cases) possible ocular side effect is listed by the package leflet of Huma-Zolamide® 250 mg tablet. The „transient" myopia, however can be associated with angle closure which, if left untreated, may lead to irreversible damage to the eye. Since the acetazolamide can be administered

with other than ophthalmic indications as well, the practicioners of other specialities should be warned to refer their acetazolamide taking patients with visual complaints to an ophthalmologist.

## III., HUMAN DIROFILARIA REPENS INFECTION

Recently, the climate change is one of the most concerning global issues. It is estimated that a total increase of 1.1°C to 6.4°C in temperature all over the world will be effected by the end of this century. It seems so that global warming can affect the human health in at least three ways: directly, for example by the heat wave which in Europe in 2003 caused about 70,000 deaths principally from cardiovascular diseases; indirectly through declining air, food, water quality and quantity, and through socio-economic factors such as appearing new pathogens and vectors by migration or international trade. A relevant example for the latter is how Aedes albopictus was introduced from China into Europe accidentally by the commercial tire trade through tires harboring mosquito larvae. Now it is spreading rapidly and becoming established in regions of Europe where dirofilariasis is endemic, and the stable presence of this vector increases the risk of infections because its diurnal activity adds to the nocturnal activity of indigenous mosquito species. Six out of 40 species of dirofilaria known to cause diseases in humans, most frequently the DRep. Its vectors are mosquitoes (Culex pipiens, Anopheles maculipennis, Aedes vexans and recently Aedes albopictus). It has been recognised an endemic parasite in the tropical and mediterranean countries. In human infections, normally, a single worm can be found in a single nodule, but multiplex cases have also been described. In periocular forms, the nodule is generally situated either in the subconjunctival space or in the subcutis of the eyelid causing itching and mild irritation, however ocular infections involving the retrobulbar space, lacrimal gland, anterior chamber and as an exceptional case vitreous cavity were also described. In subconjunctival localization, a reactive cyst envelops the nematode, another time, it can freely move in the subconjunctival space. The diagnosis is decisively based on the (immune-) histological examination of the removed granuloma or, most favourably of the intact nematode. It is a generally accepted paradigm that because of man being an imperfect, accidental host, the parasite can't reach its sexual maturity, what in habitual hosts normally takes 5-9 months. However, that finding can also be resulted from the earlier discovery and surgical removal of the parasite interrupting its normal growth; furthermore, there are reports on cases where the filaria can survive for years inside the nodule or can wander in the subcutaneous tissue over large distances. In human cases eosinophilia is a rarity and mirofilaremia almost never occurs.

### Case report on the first autochthonous human dirofilariasis in Hungary

In 2000, a 56-year-old man was referred to the Department of Ophthalmology at Szeged University Hospital with the diagnosis of "conjunctival tumor". He had experienced a mild itching and burning sensation in his right eye for two or three days, but without severe pain, visual loss or other vision related symptoms. The man was a farmer living in close proximity to dogs, cats, pigs and also to stagnant water where mosquitoes occurred in great number during hot weather. *He had not travelled abroad*, except for a short trip to Vienna ten years before. He did not have any history of visual disorder or complaints regarding his vision. During examination, the nasal area of the conjunctiva of the right eye was injected, and a subconjunctival nodule of approximately 4 x 3 x 2 mm in size was found in which a slow moving, whitish, thread-like worm was discerned. Brighter illumination resulted in more intense movements of the worm. Ophthalmoscopy and ultrasonography showed no remarkable alteration. Laboratory investigations: ESR and blood cell count were normal, withoute

eosinophilia. No microfilariae were detected using the Knott concentration technique on blood samples taken and tested in the morning, at noon and in the evening. However, it's worth noting that the detectability can also be hindered by the nocturnal periodicity of microfilariae: the highest number in the peripheral blood is found between 10 p.m. and 3 a.m and the minimum between 11 a.m. and 3 p.m. Emitting microfilaria into the bloodstream assumes preceding fertilization of the nematode i.e. the co-existence of a matured female and male worm within the same host, which is very unlikely partly because human is less exposed to the mosquito's bite than habitual hosts; on the other hand, the man's more intense immune defence is likely to prevent microfilariae to enter the bloodstream. Nonetheless, there is a report on microfilaremia in an immune-compromised patient suffered from malignancy, and another one on a young girl treated with corticosteroids due to systemic lupus erythematosus. The subconjunctival nodule was surgically excised under local anesthesia with cocaine. The living, moving helminth was removed intact and put first into physiological saline to make macroscopic observations and then into 70% ethyl alcohol. The wound was washed with povidone iodine and closed with 8/0 sutures. Wound healing was uneventful and perfect. According several authors' experience, including myself neither atropine nor pilocarpine or anaesthetic drops paralyze the nematode therefore the double forceps approach is strongly recommended during the surgery: while the worm is being fixed with forceps through the conjunctiva it can be opened and with another forceps the filaria removed. Macroscopic examination revealed an intact, living, whitish, thread-like worm, 45 mm in length, with a maximum thickness of 390 μm. The body was cylindrical with conoid ends and a corkscrew-like tail. The specimen was made transparent with lactophenol. Microscopic examination revealed that the cuticle had external *longitudinal ridges* over the entire length of the body which is one of the most characteristic features of DRep and could also be seen in the transverse sections of the helminth stained with periodic acid Schiff stain and Masson–Goldner trichromic stain, respectively. On the basis of the above data, it can be stated with certainty that a *living* immature male DRep specimen was found in the subconjunctival nodule of our patient.
Within three years two further cases of subconjunctival DRep were detected. I think, it is worth mentioning for three reasons: **1,** In the third patient, ultrasound biomicroscopy was additionally performed resulting the first report in the literatue on using this device to in vivo describe the morphology of DRep and to aid making diagnosis preoperatively. The biometric data of the nematode obtained by UBM were congruent with the measurements performed on the histological sections. **2,** For personal reasons, this patient presented for the surgery only the following day. To our greatest surprise, the filaria couldn't be seen either subconjunctivally or in other intraocular location. MRI of the orbits performed on the same day didn't show pathologic alteration. Patient was emitted with therapy of per os 200 mg albendazole (Zentel®) twice a day for two weeks. The patient had been strictly followed up for 3 months, neither signs nor symptoms presented during that period and the patient didn't re-appeared since then. At this point, it is worth mentioning that the adult filaria's response to the direct light remains unclear. Probably, it rather avoids the bright light as it was suggested in formerly published case where the subconjunctival DRep crawled away before it could have been removed. Two days later, the patient was kept under dark conditions until opening the conjunctiva. **3,** Above two new cases with verified autochthonous origin within couple of years after the first reported case in Hungary suggested that human dirofilariasis in 2004 was about to become endemic.

**Human dirifilariasis in Hungary and Europe**

According to current scientific literature, Addario's "*Filaria conjunctivae"* from 1885 is considered to be the first report on DRep, at least in the Old World. However, we may suppose that the helminth described as "*Filaria peritonei hominis"* by Babes in Budapest from 1879

might also belong to the *Dirofilaria* species. This reasoning can be accepted on the basis of the drawings reported by Babes and on the interpretation of Desportes. Babes' case was reported in 1879 and 1880, and preceded Addario's paper by six years. Thus, we proposed that Babes' findings should be reconsidered and taken as the very first scientific report to document an infection due to DRep in Hungary. To review the Hungarian cases between 1879 and 2015 when the last infections were published, it seems reasonable to divide the period into three intervals. The *first* extends between 1879 when the first Hungarian case was published until 2000 when the first time, a living DRep was surgically removed intact and the autochthony of the infection was undisputable on the basis of the patient's clear statement regarding his travel history. During this period, *13 reports* were published on 6 likely but not confirmed and 7 confirmed DRep infections. The *second*, only 6-year long period comprised *16 cases* (mean age 60 years) diagnosed at the Department of Parasitology, National Center for Epidemiology, Budapest. In eight of 16 cases the eye was affected (7 subconjunctival, 1 upper eyelid), all of the rest but one in a lymphnode with subcutaneous localization. Based on the available epidemiological data, it can be concluded that most of these cases were autochthonous infections. The *third* period embraces 9 years between 2007 and 2015 with further *87 cases* rocketing the overall number to 116 cases in Hungary. All in all, eyes were affected in 45 episodes (38,8%), which is in line with the international data; visceral involvement were found in five patients. The territorial distribution of Hungarian cases favours water sources (rivers, channels, lakes, reservoirs) exist in the areas of all counties. Nonetheless, the occurrence of episodes is lower in Transdanubia (Baranya, Fejér, Somogy, Zala, Vas). There are counties such as Veszprém, Győr-Moson-Sopron, Komárom-Esztergom, Tolna without any reports of dirofilariasis cases. Cases in Vas and Zala counties were diagnosed in 2014 only, that may suggest the spreading of the infection to the western part of Hungary.Epidemiological studies also described an emergence of dirofilariasis in central and northern European countries where canine dirofilariasis was previously not or just sporadically found. The geographical and time distribution of the spreading of the infections can be traced by the countries with publications about the first human infections considered autochthonous. These are in chronological order as follows Hungary 2000, Austria 2006, Slovakia 2008, Romania 2009, Poland 2010, Germany 2014, Czech Republic 2016. Warsaw at the latitude 52° is the northernmost site where an autochthonous case was reported on. The emergence of infections in Europe can mainly be attributed to two factors. *First,* human activities such as the urbanization of wilderness areas at city peripheries by creating microhabitats that favour vector population growth in regions where such habitats do not naturally exist. *Secondly*, global warming - again due to human activities - directly affects host-parasite systems by inducing favourable changes in the development and survival rates of both parasites and vectors. As mentioned above, the higher the temperature the shorter the period the larvae need to mature such increasing the chance for developing infectious filariae within the 30 days lifespan of a mosquito.

## SUMMARY AND CONCLUSIONS

Human body and its environment are acting as dynamically changing systems mutually affecting each other. The same environmental factor may have different effect on different individuals as we could see in relation to drug idiosynchrasy or in PhP while human activities inducing changes in the environment can modify the agents affecting the human body, referring to the climate change-infectious disease relation. Above thesis aimed to investigate this complex interaction by means of five different studies. Respecting surgical trauma as a physical agent, *Study 1*, wished to learn if the second eye PhE is really more painful? We proposed to draw remembered pain under investigation, and managed to justify it's a significant role in the

patients' pain experience for sequential PhEs. According to our results, in order to avoid any disappointment, we would suggest cataract surgeons that warn patients that they are likely to feel more pain and discomfort during the second eye operation. *Study 2* investigating the socio-cultural background-pain nexus, to our knowledge, the first time, intended to compare citizens of two countries as to the PhP; while *Sudy 3*, to our best knoweldge, first in the lieterature, investigated how does OCCI influence central CS and tear production. As performing OCCI wasn't proved to be more harmful to the eye surface than SCCI and doesn't require extra instruments, skills or expertise from the surgeons, we deemed OCCI a safe and useful procedure to reduce the postoperative corneal astigmia. *Study 4* examined variable effect of the same chemical agent, and presented the third published case on transient myopia caused by per os indapamide and the first published cases of acetazolamide-induced uveal effusion *without* coexisting transient myopia and IOP elevation. The letter scenario was referred to as silent form of CES. Mainly by means of UBM, we described and measured the morphologic changes of the ciliary body demonstrating the lack of the spasmic component in the silent forms. *Study 5* looks into the primariliy global warming-related factors that could account for substantial increase in numbers of dirofilarial infections throughout Europe. By having reported on the first, undoubtly approved autochthonous human DRep infection in our country and further indigenous cases discovered by reviewing the literature we confirmed that dirofilariasis became endemic in Hungary.

***In summary*,** conclusions of the studies presented in the thesis are:

I. No difference could be measured by VAPS in patients's pain perception for sequential PhEs. However it was also demonstrated that patients recalled lower pain two weeks after the surgery than in the perioperative periode such they can have more severe pain experience during the second eye PhE since, in fact, a recent pain experience is being compared with a remembered one.

II. Having compared two countries in terms of PhP the first time in the literature, a tendentious difference could be found between English and Hungarian patients which suggests that modifications in anesthetic method should be considered for patients of different countries.

III. We first investigated the effect of OCCI in PhE on the CS and tear production, and demonstrated that OCCI employed with a wound size of 2,8 mm doesn't decrease either the central CS nor the tear secretion in the early postoperative period such it is not likely to cause more serious dry eye complaints than a routine PhE.

IV. To our best knowledge, our publication is the first to report on the asymptomatic: „silent form" of the acetazolamide-induced ciliary body oedema and supraciliary effusion. Therefore, we are suppose that the SuD-related ocular idiosyncrasy represents a continous spectrum of the uveal involvement not essentially including the classical trias of uveal effusion, transient myopia and acute angle-closure glaucoma what CES involves.

V. UBM proved to be suitable and fundamental tool for investigating CES. In the case with transient myopia, decreased CBCA was measured while the unchanged CBCA may suggest the lack of the spasmic component in the silent forms of CES.

VI. We managed to remove the first intact, living specimen of DRep in Hungary. In addition to reliably identifying the specimen, its autochthonous origin was traced and verified therefore our report can be considered a pivotal evident for dirofilariosis to become endemic in Hungary.

VII. Although, surgical removal is likely to result in complete healing of the disease in cases of subconjunctival localisation, we recommend to consider systemic treatment because the scrutinouse review of the related literature suggests that either microfilaremia or multiple nodules can't be excluded with certainty.

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