OPHTHALMOLOGICAL ASPECTS OF THE EFFECT OF SELECTED PHYSICAL, CHEMICAL AND BIOLOGICAL AGENTS

PhD Thesis

András Hári-Kovács MD

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András Hári-Kovács MD

Department of Ophthalmology, University of Szeged

University of Szeged, Faculty of Medicine

Clinical Medical Sciences Doctoral School

PhD Program:

Clinical and Experimental Research for Reconstructive and Organ-sparing Surgery

Program director: Prof György Lázár MD, PhD

Supervisors: Prof Andrea Facskó MD, PhD / Mihály Végh MD, PhD

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PUBLICATIONS DIRECTLY RELATED TO SUBJECT OF THE THESIS

I. ***Hári-Kovács A,*** Szénási Zs, Tiszlavitz L, Kolozsvári L, Pampiglione S, Letizia MF. Ophthalmo-filarioidosis újabb esete Magyarországon. (A new case of ophthalmo-filariasis in Hungary). *Szemészet (Ophthalmologia Hungarica)* 2002; 139. 109-112.

II. Zsuzsanna Szénási, ***András Hári-Kovács***, Silvio Pampiglione, Maria Letizia Fioravanti, István Kucsera, Balázs Táncos, László Tiszlavitz. Human dirofilariosis in Hungary: an emerging zoonozis in central Europe. Wiener Klinische Wochenschrift 2008; 120: 96-102. **(IF: 0,857)**

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VII. Végh M, ***Hári-Kovács A,*** Roth HW, Facskó A. A kanyaró szemészeti tünetei és kezelése (Ophthalmological symptoms of measles and their treatment). *Orv. Hetil. (Hungarian Medical Journal),* 2017; 158(39): 1523-1527. **(IF/2016: 0,349)**

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.

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II. ***Hári-Kovács A*****,** Janáky M. Giant drusen and persistent hyaloid artery in a patient with retinitis pigmentosa. *Klin. Monatsbl. Augenheilk.* 1997; 211 Suppl. 5. 5.

III. ***Hári-Kovács A,*** Szabó Á, Gyetvai T, Kolozsvári L. A Weill-Marchesani syndromáról-Esetismertetés (Weill-Marchesani syndrome-case report). *Szemészet (Ophthalmologia Hungarica)* 2001; 138: 155-159.

IV. ***Hári-Kovács A***, Gyetvai T, Lovas P, Kolozsvári L. Ultrasound biomicroscopy and peripheral retina. *Clinical & Experimental Ophthalmology* Vol:30, Supplement, April 2002 p.: A356.

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VI. ***Hári-Kovács A***, Horpácsy B, Szabó Á. Eyeball traumas treated in the University of Szeged Department of Ophthalmology between 1998-2003: Retrospective study. *Szemészet (Ophthalmologia Hungarica)* 2006; 143:53-56.

VII. ***Hári-Kovács A***, Skribek Á, Tóth-Molnár E, Kolozsvári L. Three cases of ocular filariasis in Hungary In.: Joint Congress of SOE/AAO. Vienna, 2007; June 9-12. Abstract book: p. 213.

VIII. ***Hári-Kovács A***, Brassai Cs, Kolozsvári L. Childhood eyeball injuries in the University of Szeged Department of Ophthalmology between 1998-2006: Retrospective study. *Szemészet (Ophthalmologia Hungarica*) 2007; 144:9-12.

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X. T. Gyetvai, Á. Skribek, ***A. Hári Kovács,*** L. Kolozsvári. Ultrasound biomicroscopical examination of the tumors of the iris and ciliary body. Ophthalmic Echography Nyctalus, ed.: János Németh, Béla Csákány, György Barcsay Bp., 2006. p. 23-26. ISBN 963-85636-5-6

ABBREVIATIONS
(in alphabetical order)

ACD: anterior chamber depth
AOD: angle opening distance
BCVA: best corrected visual acuity
BE: both eyes
BUT: break up time
CBCA: ciliary body cornea angle
CBT2: ciliary body thickness 2
CES: cilio-choroidal effusioon syndrome
CS: corneal sensitivity
DRep: Dirofilaria repens
ESR: erythrocyte sedimentation rate
IOL: intraocular lens
IOP: intraocular pressure
LE: left eye
OCCI: opposite clear corneal incision
PhE: phacoemulsification
PhP: phaco-pain
RE: right eye
SCCI: single clear corneal incision
ST: Schirmer test
SuD: supha-drug
TA: topical anaesthesia
UBM: ultrasound biomicroscopy
VA: visual acuity
VAPS: visual analogue pain sclale

LIST OF CONTENT

1. INTRODUCTION

The human eye detects majority of the information from the environment that are essential from our point of you and being conveyed as an encoded visual signal towards the central nervous system. At the same time, 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 investigated variables were the intraoperative pain perception and the central corneal sensitivity (CS).

CHEMICAL AGENT: The ciliochoroidal effusion syndrome as an *ophthalmic idiosyncrasy* caused by orally administered sulfonamid-derived medication.

BIOLOGICAL AGENT: Ophthalmo-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.

2. SURGICAL TRAUMA DURING PhE

2.1. Objectives

- To investigate the difference in patients' pain perception measured by (visual analogue pain scale) VAPS during consecutive PhEs with topical anesthesia.
- To find out if there is a difference in perceived pain during standardized PhE between patients living in the United Kingdom and Hungary.
- To examine the additional impact of opposite clear corneal incision (OCCI) on the CS compared to the single clear corneal incision (SCCI) during PhE.

2.2. Anatomical background

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 changes are greately related to the injuriy of the corneal innervation due to the surgery.

2.2.1. Corneal innervation and sensitivity

In human, around 60 nerve bundles originating from the long ciliary nerves enter radially the corneal stroma, and branch immediately. The distal branches anastomose extensively, forming the *anterior stromal nerve plexus* laying in the anterior stroma. In contrast, the posterior half of the human stroma and the corneal endothelium lack sensory nerve fibers. In addition to stromal nerve innervation, a small number of small nerve fascicles originating at the *limbal plexus* and at the conjunctiva superficially enter the peripheral cornea to innervate the perilimbal and peripheral corneal zones. The most superficial, anterior layer of the stromal nerve plexus immediately beneath Bowman's membrane, is referred to as the *subepithelial nerve plexus*, its nerve density generally higher in the peripheral than in the central cornea.

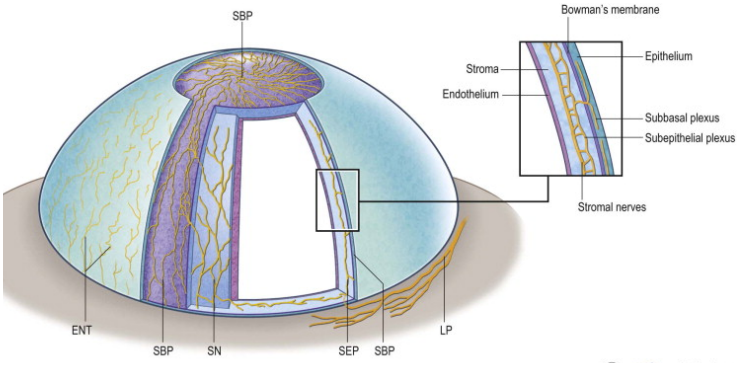


Figure 1. LP=limbal plexus; SBP=sub-basal nerve plexus; SEP= subepithelial nerve plexus; SN=stromal nerves
Adler's physiology of the eye (2011), 11th ed.

Its curvilinear bundles that vertically penetrate Bowman's membrane mainly in the peripheral and intermediate cornea, divide, each into 2–20 thinner nerve fascicles that continue into the corneal epithelium as the *sub-basal nerve plexus*. A relatively low number of stromal nerves penetrate Bowman's membrane in the *central cornea*, which receives most of its innervation from long sub-basal nerves that enter the peripheral cornea directly *from the limbal plexus*.
The sub-basal nerve axons may travel up to 6 mm, roughly parallel to one another in a unique neuroanatomical structure termed an epithelial leash. Epithelial leashes are constituted by up to

40 individual unmyelinated straight and beaded nerve fibers. Nerve fibers in adjacent leashes interconnect repeatedly forming a relatively homogeneous plexus with a whorl-like, spiral pattern, the center of which is called the "vortex" (Fig 1.). In humans, it is located 2–3 millimeters inferior and nasal to the corneal apex. The mechanisms that govern the formation and maintenance of this spiral pattern remain unknown. However, the basal corneal epithelial cells derived from limbal stem cells migrate centripetally in the same whorl-like fashion towards the corneal apex. Most stromal and subepithelial nerve bundles pass uninterrupted through the stroma, but a small proportion of corneal nerve fibers travels downwards to terminate in the stroma as free nerve endings. From the sub-basal nerves single fibers split off and turn 90° vertically ascending between the epithelial cells (Figure 2.), often with a modest amount of additional branching, up to the most superficial layers of the corneal epithelium.

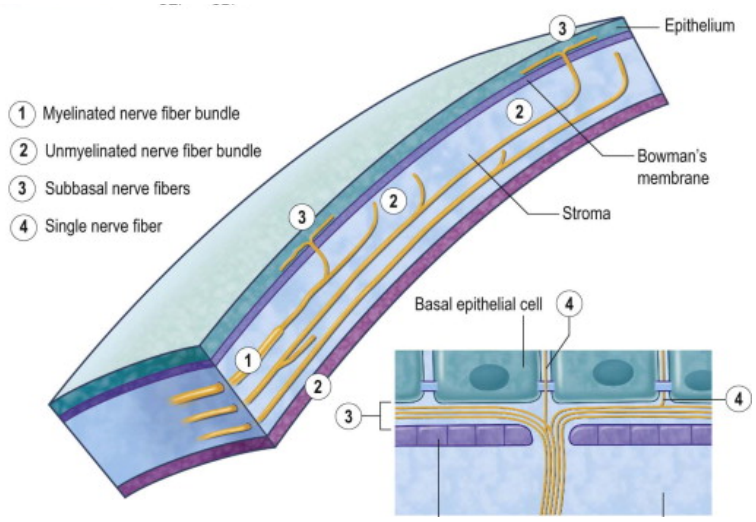


Figure 2. Sensory corneal innervation (1)

Intraepithelial fibers end as free nerve endings, appearing appear morphologically homogeneous, though immunocytochemical staining reveals differences in the expression of neuropeptides and other neurotransmitters. They also contribute to local *inflammation* through the antidromic release of peptide transmitters stored in dense-cored vesicles of their peripheral endings ("neurogenic inflammation"). Occasionally, epithelial cell membranes facing the nerve terminals show invaginations that may eventually completely surround the nerve ending. This intimate relationship allows nerve endings to detect changes in epithelial cell shape or volume, such as those produced by ocular surface desiccation or swelling. The innervation density of the corneal epithelium is the highest of any surface epithelium containing 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. Nerve terminal density, and thus, corneal sensitivity, decrease progressively towards the periphery, and similarly does as a function of age and in several ocular pathologies such as herpetic keratitis, some types of corneal trauma and post-infectious conditions, certain hereditary corneal dystrophies and anterior segment or vitreo-retinal surgery, especially scleral buckling operations.

An individual stromal axon entering at the corneoscleral limbus after repetitive branching may have a receptive field as much as 50 mm^2 with significant overlapping with other receptive fields.

2.2.2. Regeneration of the corneal nerve fibers

The sensory denervation of the cornea caused by either local (herpetic keratitis, chemical injuries, surgical procedures etc.) or central (tumors, vascular abnormalities, surgeries affecting the trigeminal ganglion or its nuclei in the brainstem) pathologic conditions not only results in corneal an/hypesthesia but often are associated with damage of the corneal epithelium. The underlying mechanism includes increased epithelial layer permeability as a result of decreased cellular adhesion, impaired wound healing with failed re-epithelization, decreased epithelial cell migration and mitosis (2). After a mechanical injury, the reinnervation process of the cornea is shaped by parallel degeneration and regeneration of neurites in and around the wound. As to the wound location, two substantially different pattern of the reinnervation can be distinguished. When the lesion leaves the main nerve *supply around the limbus intact* (central abrasions, radial or circular keratotomies) the process have two phases. In the first phase, the axon degeneration proceeds rapidly from the injured intraepithelial terminals towards the epithelial plexus: at 1 week no leashes are seen within the wounded area. During the same time, *collateral sprouts* grow from intraepithelial axons proximal to the wound orienting perpendicular to the edge of it and ramifying terminals primarily in the repairing epithelium within the wound. The second phase begins around 7 days after injury and extends for 2 to 3 weeks. An additional sprouting in the subepithelial plexus gives rise to a second wave of wound oriented neurites which are arranged obliquely as is normally seen in an intact cornea. During the same time the neurits formed in the first phase degenerate and disappear by 3 weeks. By 4 weeks, a normal innervation pattern is reestablished but the neural density is less than normal. *Perilimbal* lesions cutting the main ciliary nerve bundles are also followed by degeneration and regeneration but the collateral sprouting from intact axons is much more limited. Reinnervation mostly proceeds

from regrowing stromal stumps that pass through the limbal scar tissue such taking a much longer time (more than 60 days), and the density of innervation remains lower than normal.

2.2.3. Central projections of corneal nerve fibers

Ocular sensory fibers are functionally heterogeneous and include mechanoreceptor (Aδ), polymodal nociceptor (C-fibers), and thermoreceptors, however not all parts of the eye encompass the full range of somatosensory perceptions. The somatic innervation of the cornea, conjunctiva, iris and sclera, unlike other parts of the body, conveys principally the sensations of *pain or irritation*. After repeated noxious stimulation or tissue injury, ocular polymodal nociceptors become *sensitized* and cause sustained pain and *hyperalgesia*.

Sensory information from the eye is carried by the primary sensory neurons of the *trigeminal ganglion* to the ventral portion of the ipsilateral trigeminal brainstem nuclear complex containing the *principal nucleus* in the pons that is the major relay for all the tactile sensations from the head, including the eye to the cortex, preserving the somatotopic organization throughout the pathway. The other part of the complex is the *nucleus of the spinal tract* which receives a broader spectrum of inputs including pain and temperature, and have projections to the reticular formation, and through that connections with the vegetative spinal and brainstem nuclei responsible for the vegetative reactions following pain such as tachycardia, nausea, faintness, perspiration etc. as well as for the oculocardiac reflex. Further projections to the superior salivatory nucleus and facial motor nucleus contribute to the afferentation of the *lacrimal functional unit* (Fig. 3). Neurons receiving corneal information have been identified in the thalamic posterior nucleus. These thalamic neurons project in turn to the postcentral gyrus, the primary and secondary somatosensory cortical areas responsible for pain sensations (sensory-discriminative aspects). Projections to the *insula* (affective-motivational aspects) and to the *prefrontal* and *cingulate cortex* (cognitive-evaluative aspects) provide the neural substrate for the reactions and the affective and cognitive components of sensations evoked by eye stimulation. The first realistic explanation for the central, conscious control of pain sensation was provided in 1965 by Melzack and Wall's gate control theory of pain (Fig. 4) which-with mild modifications-has been proved in many ways (Melzack).

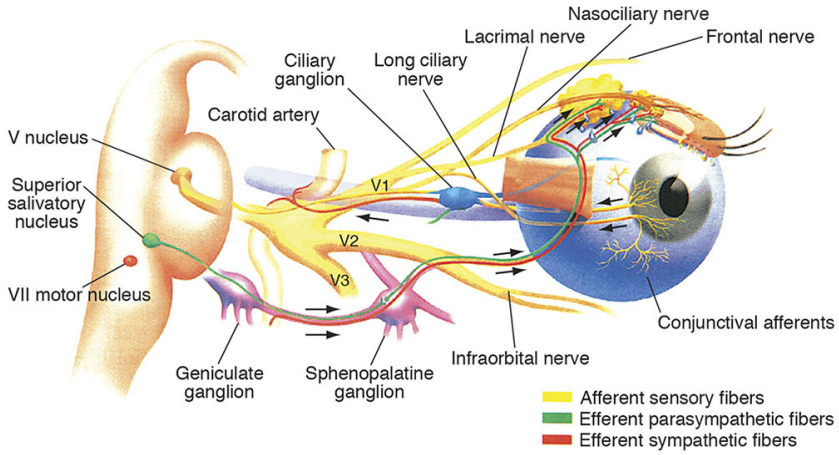


Figure 3. The LFU unifies the complex reflex network responsible for the regulation, production and health of the tear film. The afferent component originates from the nociceptors in the cornea ocular surface and through the trigeminal nerve synapse in the brainstem with efferent autonomic and motor nerves. The formers innervate the lacrimal gland, Meibomian glands and conjunctival goblet cells. The latter ones innervate the orbicularis muscle for blinking (3).

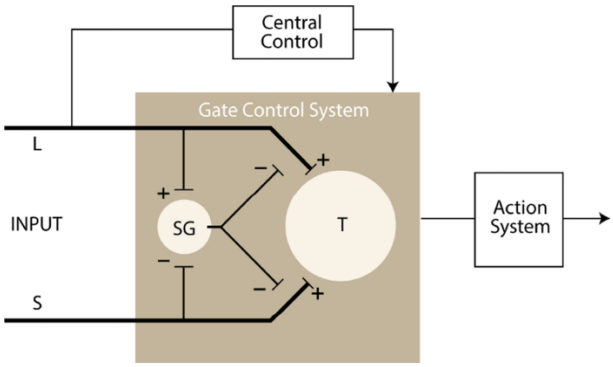


Figure 4. Schematic diagram of Gate Control Theory by *Melzack&Wall 1965* (4). The theory proposes that both large, A-fibers (L) and small, C-fibers (S) synapse onto cells in the substantia gelatinosa (SG) and the first central transmission cells (T). The inhibitory effect exerted by SG cells onto the primary afferent fiber terminals at the T cells is increased by activity in A-fibers and decreased by activity in C-fibers. The central control trigger is represented by a line running from the A-fiber system to the central control mechanisms, these mechanisms, in turn, project back to the Gate Control system giving the anatomical substrate of the *counscious feedback* on the pain experience.

2.3. Factors influencing pain perception

Due to the various aspects of the pain experience and the ampel methods available, the examination of pain in human can pose a challenging and complex problem for the examiner. The investigation may focus on either acute or chronic-, clinical pain or experimental pain of different modalities such as cold, heat, pressure, electricity or ischemia. A bunch of the pain related factors such as pain threshold, pain tolerance, reported unpleasentness of pain,

emotional response to pain, pain-related disability, and the fear of pain etc. can be examined. Morover, the experience of pain is characterized by an immense inter-individual and group variability with numerous contributing factor such as age, gender, previous experiences, anticipated pain for a procedure, race, ethnicity etc. Although there is no consensus regarding the underlying mechanisms, a holistic influence of biological, socio-cultural, and psychological factors is suggested. The complex interactions of those factors can be comprised in the so-called *bio-psycho-socio-cultural model* of pain (5).

2.3.1. Age

There seems to be a consensus about the role of age in the literature. The pain threshold is proved to be lower in younger individuals compared to the oldsters. Besides the learned socio-cultural differences in the background, physiological changes during aging also account for the decreasing pain sensitivity. In the cornea, for example the number of receptors is proved to be declining with the age. Clinical studies on phaco pain are in line with the above experimental results (6-9)

2.3.2. Gender

In studies on experimentally induced pain, women have demonstrated lower tolerance for and diminished thresholds to a broad assortment of noxious stimuli relative to men. (10,11) In addition, epidemiologic studies suggest that women report more negative responses to pain and more numerous pain experiences than men (12) A number of studies have attributed the gender differences in pain experiences to biologic differences, namely the less effective endogenous pain inhibitory systems. The importance of biologic factors is mirrored by the observation that menstrual cycle affects the pain threshold in women: luteinizing hormone may desensitize the opioid receptor, increasing pain sensitivity in women during the ovulatory and luteal phases (13). At the same time, the argument supporting psychological and social factors has also grown considerably. Female gender norms are being structured so that the expression of pain is more acceptable in females than in males (14). Contrary to the above unequivocal experimental findings about the difference between the genders, just a part of the clinical studies on phaco-pain (PhP) - for practical reason, I will term the pain induced by PhE - supported the lower pain threshold in women (6,7), others didn't find significant difference between the genders (9,15,16).

2.3.3. Anxiety

Strong interaction between psychological factors and pain sensitivity and tolerance is well established, moreover the structural substrate of this connection in the brain has also been described. Depression, negative mood negatively, positive psychological factors, namely hope, pain acceptance, and optimism, positively affect the adjustment to persistent pain.

Anxiety is one of the most important central modulator of the pain experience. The higher the anxiety the higher the pain scores are expected. For anxiety assessment, the STAI (State-Trait Anxiety Inventory) has been introduced and widely accepted. The form has 2 subscales, one to measure the state of anxiety and another one to measure the anxiety trait. Studies performed in different countries in connection with dental interventions have shown that women, in general, report higher anxiety compared to men. (17-19). However, clinical studies addressing the interplay of anxiety and PhP show a great diversity. Ursea et al looked at the pain and anxiety for sequential PhEs and found second eye surgeries to have a higher pain and lower anxiety level, i.e. an inverse ratio between them (20). Sharma, in contrary could not reveal any difference in the anxiety either between the first and second eyes or between the genders (21). Khezri's work did not justify any influence of the reduced anxiety on the intraoperative PP (22), furthermore Gombos questioned the usefulness of STAI results in the age group of cataract patients (9).

2.3.4. Socio-cultural background

Despite having described some alterations in cellular pain processing among different races (23), there is an evidence that the *pain threshold* examined under experimental conditions doesn't show significant disparity in individuals of different races and thnicities in contrast to the *pain tolerance*. The pain tolerance, however, is rather influenced by the environment the patient lives in than native, intrinsic factors. There are many ways in which the environment can determine the individual's pain experience. The severity of pain assessment and the emotional response to pain follows parental patterns and is imprinted in the very early childhood. These first impressions can hardly be modified later in adulthood. The parental model mirrors the socialisation which can be influenced by plenty environmental factors from geographical locus and country through common beliefs and religion to ethnicity and ethnical identity (24). For example, evidence exists for African Americans and Hispanic Whites demonstrating greater severity of both clinical and experimental pain and higher levels of pain-related disability compared to non-Hispanic Whites (25-28). Other studies (23) have included a broader range of study participants such as African Americans, Caucasians, Indian, Asians

and Hispanics. Still other investigators have examined group differences among Danish Whites and South Indians (29); across Chinese, Malay and Indians (30); and among Alaskan Indian, Eskimo and non-Hispanic Whites (31), and between Nepalese porters and Occidentals (32). Concerning PhP, there are several reports addressing the socio-cultural or ethnical background of patients as well. For instance, Omulecki and co-workers demonstrated that the co-operation was lower and the level of the pain perception was higher during PhE among the patients living in rural environment than that among the citizens. However, the level of the education did not have an impact on the level of the intraoperative pain (7). Ursea et al registered higher median, Tan et al higher mean of PhP scores among Hispanic and non—Chinese patients compared with Caucasians and Chinese patients, respectively (20,33).

2.4. Steps of PhE as potential sources of the intraoperative pain

The ocular structures, the PhP can originate from are as follows: eyelids, conjunctiva, cornea, iris, ciliary body. The *lens* is likely to be without surface sensitivity but seems to have what might be called position sensibility with receptors in the ciliary body. The eyelid (the skin) usually is not involved but accidentally by an inadvertent touch with scissors or forceps, and the removal of the strongly adherent isolation material can cause significant unpleasantness at the end of the surgery. Most of the authors agree that patient discomfort is predominantly resulted from direct iris manipulation or movement of the iris diaphragm due to rapid hydrodynamic changes, and at IOL insertion (34). In contrast, Gombos (9) stated that the iris was not touched, the anterior chamber depth was stable and the pupil wasn't narrowing when the patients reported pain, consequently the intraoperative pain of cataract surgery usually doesn't originate from the receptors located in the iris or the ciliary body.

Of 1068 cases (610 females/458 males; 75,1±8,8 years), underwent PhEs performed by myself during a 1-year period – from January 1 to December 31, 2010, 125 reported more or less pain during the surgery prompting the team to administer additional anesthesia. Only two of the patients indicating intraoperative pain required additional proximetacaine drops for gaining complete analgesia. Intriguingly, there was no correlation between the reported pain and adverse events during the surgery: from the 131 "complicated cases" only 27 patients (21%) complained about pain or discomfort (Table 1., own unpublished data). This proportion is comparable with that published by Westborg and Mönestam: among their patients, 24% of the complicated cases required additional anesthesia (16). To our experience, iris touching or pushing towards the iris root during mechanical synechiolysis or using iris hooks are less, while pulling it centripetally is more likely to cause pain. Most frequently: in 47% of cases with

reported pain, the causing maneuver included the insertion/removal or repositioning of the eyelid speculum. It was followed by the hydrodissection and IOL implantation (Table 1). In a similar study by Hou and co-workers (34), the step of „infusion of cortex aspiration" induced pain the most often (20,7%), followed by the „infusion of phaco sculpting" (11,3%).

Table 1. PCR=posterior capsule rupture, CTR=capsular tension ring, ECCE=extracapsular cataract extraction

Reported pain related to routine manipulations and maneuvers for complications n (%)		
Non complicated cases n=98	*Eyelid speculum related*	*62 (47)*
	Hydrodissection	38 (31)
	Infusion for cortex removal	25 (20)
	IOL insertion	28 (23)
	Water jet behind IOL	11 (9)
Complicated cases/complicated cases with reported pain n=27	Iris hooks	6/1 (0,8)
	Manual synechiolysis and/or iris stretching	9/2 (1,6)
	Iris prolapsus	4/1 (0,8)
	Iris engaged by pahco-or I/A tip	11/9
	Subconjunctival infusion	61/2 (1,6)
	PCR with vitrectomy	3/2 (1,6)
	PCR without vitrectomy	6/0 (0)
	Zonulolysis	8/3 (2,4)
	CTR	8/2 (1,6)
	Conversion to ECCE	3/2 (1,6)
	IOL to the sulcus	6/2 (1,6)
	Corneal erosion	6/1 (0,8)
	TOTAL	**131**/27

2.5. Further aspects of phaco-pain

As the reduced wound size and the almost constant intraoperative cameral pressure faded the request of preoperative intraocular hypotony, the TA became the most widely applied method during the introduction and headway of PhE (35-38). Although, the pain scores registered with TA are slightly higher than those with periocular injections (9,39,40), still are far acceptable, and the higher patient comfort and safety during administration and the better cost-effectiveness overweighs that drawback. Though, patients' satisfaction is based on the highly favorable visual outcome, it can negatively be influenced by pain or discomfort experienced during the procedure. Some of the pain related, factors such as age, gender, anxiety, ethnicity have already been discussed in the sections above. The most of the 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 (6,20) others did not find correlation between the level of pain perception and the sequence of

operation (7,16,21). To look into the problem in another way, we conducted a single centre, single surgeon prospective study (*Study 1*.) where the remembered pain registered two weeks after the first eye surgery was additionally taken into account as an influencing factor. *Study 2.* aimed to compare groups of different nationalities (living in different countries) regarding the intraoperative pain they experienced during PhEs performed by the same surgeon (HKA). 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 by several authors to be the consequence of the transection of corneal nerves by the clear corneal incision during PhE (41, 42, 43, 44). Demaging the corneal sensory nerves will compromise the afferentation of the lacrimal functional unit (3) which is basically responsible for the normal production and homeostatis of the tear film. The bigger the surgical incision the more serious dry eye problems are expected. This can be of significance by performing OCCI to reduce the preoperative corneal astigmatism. That was invented by Lever and Dahan (45) and resulted in an average of 2,0D reduction of astigmatism with a 3,5mm wound size. Further publications reported on reduction varied between 0,5-1,5 diopters (46, 47, 48) depending on the the wound size, the incision site as well as whether the preoperative astigmatism is with- or against-the-rule (49). In my practice, OCCI is routinely used to decrease postoperative astigmatism in cases where the toric IOL implantation can not be carried out for any reason such I wanted to find out if a phacoemulsification combined with OCCI induces more severe dry eye symptoms than without it (*Sudy 3*.).

2.6. Patients and methods

2.6.1. Study 1.

The study design was reviewed and approved by the Institutional Review Board and adhered to Declaration of Helsinki. From 200 consecutive patients requiring bilateral cataract removals and admitted to our ophthalmic day surgery centre in London, UK between February and May 2010, 187 were enrolled into this prospective, observational study. The participation was voluntary and none of the patients refused the co-operation. After presenting the aims of the study, verbal consent was obtained. 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. If it was not contraindicated, routinely, 10 mg per os temazepam was administered on the day ward. To rate the intraoperative pain in a standardized way we used a VAPS with both numeric (extending from 0 to 10) and written indices (Figure 5.) 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. The patients were not told at the first time that they would be asked again during the follow-up period or at the time of the second eye procedure. After explaining how to use the VAPS, each patient was asked to rate the intraoperative pain for his/her each procedure on two occasions: first immediately after the surgery (primary endpoint), still in the operating theatre then at the two-weeks follow-up check (secondary endpoint), 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) in order to determine if there is any difference between the first and second eyes in terms of the intraoperative pain.

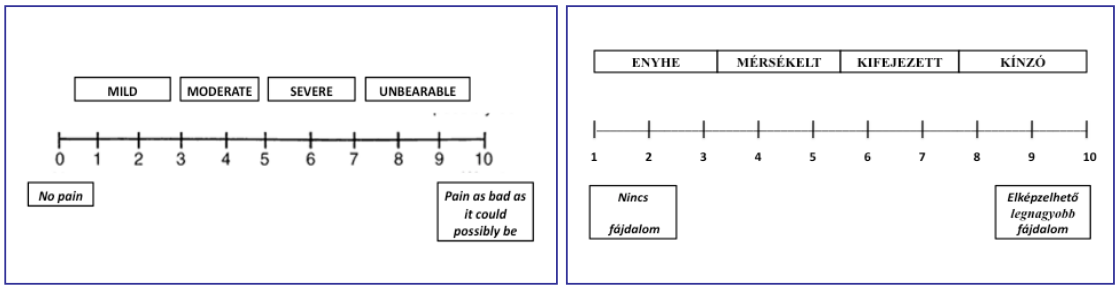


Figure 5.
Ten-point VAPS with both numeric and descriptive indicis in English (left) and in Hungarian (right)**.**

2.6.2. 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). The study plans were proved by the local ethical commities and the conduction was adherent to the tenets of the Declaration of Helsinki. The participation was voluntary and none of the patients refused the co-operation. Concerning the patients' inclusion- and exclusion criteria and the methods, apart from two alterations, we refer to those written in the „Patients and Methods" section of the Study I/A. First, logically, the VAPS descriptions were written in Hungarian for the Group H (Figure 5.); secondly, the topical anesthetics employed preoperatively were different: in Group A proxymethacaine 0,5% while in Group H oxibuprocaine was used.

2.6.3. Study 3

Both the study design and conduction complied to the Declaration of Helsinki (1975) and its Revision in 1983. In this prospective, non-blinded study, two cohorts of patients underwent an uncomplicated, co-axial Phaco either with a routine single clear corneal or with doubled opposite clear corneal incisions: Group SCCI and OCCI, respectively were compared. OCCI was considered in cases of higher than 1,50 D preoperative corneal astigmatism where 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. The 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 position 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 corneal sensitivity (CS) threshold, tear film break up time (BUT) and basal tear production.

CS was measured with a Cochet–Bonnet aesthesiometer (Luneau Ophthalmologie, Chartres, France), which consists of a nylon filament with the diameter of 0,12 mm that can vary in length from 0 to 60 mm. The nylon filament was brought to the central, area of the cornea smoothly and perpendicularly to the surface (Fig 7). Contact was detected by the slight bend of the nylon; sensitivity was taken as the length of the filament in millimetres that gave a 50% positive response from a minimum of 4 stimuli applications.

Figure 7. Cochet–Bonnet esthesiometer in use.

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 (ST) was employed. The test paper was inserted to the lateral third of the lower lid and the length of the soaked area of the test paper in millimetres was registered 1 (ST1) and 5 (ST5) minutes after the insertion of the test stripe. Patients were asked to keep eyes gently closed during the measurement. In order to find out if there is any difference between the groups concerning the measured parameters, the pre-and postoperative data were pooled and compared between the groups. For the statistical analysis of the data, Prisma for Windows version 6.01software was employed, and statistical significance was considered if $p<0,05$.

2.7. Results

2.7.1. 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 being different from the above protocol (6 patients) or because of postoperative 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. (Figure 8.)

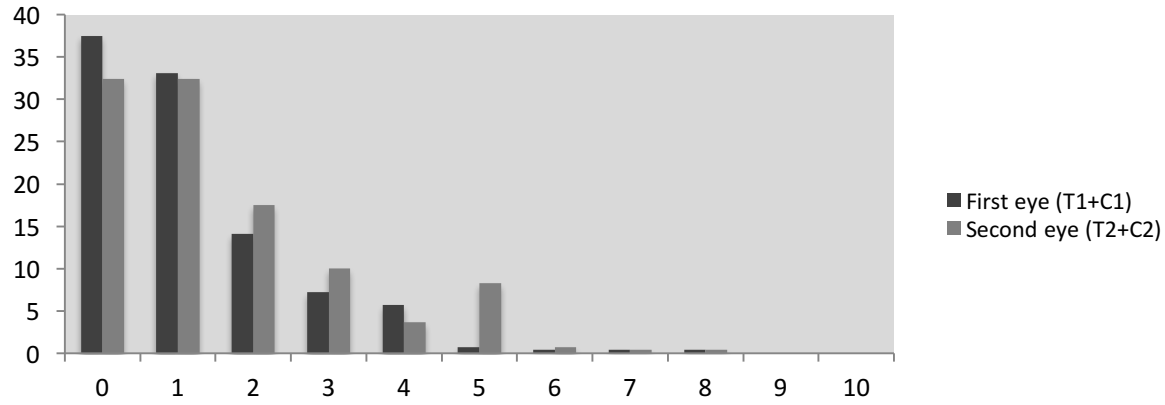


Figure 8. Percentage of recorded pain scores.
Bars represent for each eye the sum of scores recorded perioperatively (T) and at the follow-up clinic (C).

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. (Table 2.) 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).

Table 2. Means of pain scores (± SD) recorded in the theatre, immediately after the surgery (T), and at the follow-up check (C).

	1st eye	**2nd eye**	
T	1,50 ± 1,43	1,51 ± 1,36	**NO**
C	0,71 ± 1,21	1,10 ± 1,41	**NO**
	YES	**YES**	significance (<0,05)

2.7.2. Study 2

None of the patients refused to participate in the investigation. 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 VAS (2 patients). From Group H, 2 patients were excluded due to previous pars plana vitrectomies on the particular eyes in question. Our results are summarized in Table 3.

Table 3. Demographic data and the mean of the measured VAS values in the two groups. (± standard deviation; E=Group E, H=Group H)

	E	**H**	***p***
Case number	80	85	
Age (yrs)	76.5±11.4	71.2 ±9.3	**0,11**
Gender (male/female)	33/37	31/49	
Mean VAS score	1.50±1.40	1.26±1.42	**0,07**

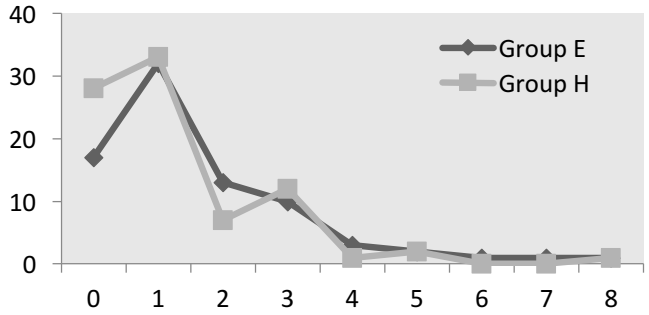


Figure 7. The distribution of patient numbers in the two groups as a function of the given pain scores.

Although, the Group A consisted of older patients than Group H, the difference was not 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 groups, the most striking difference can be observed in the number

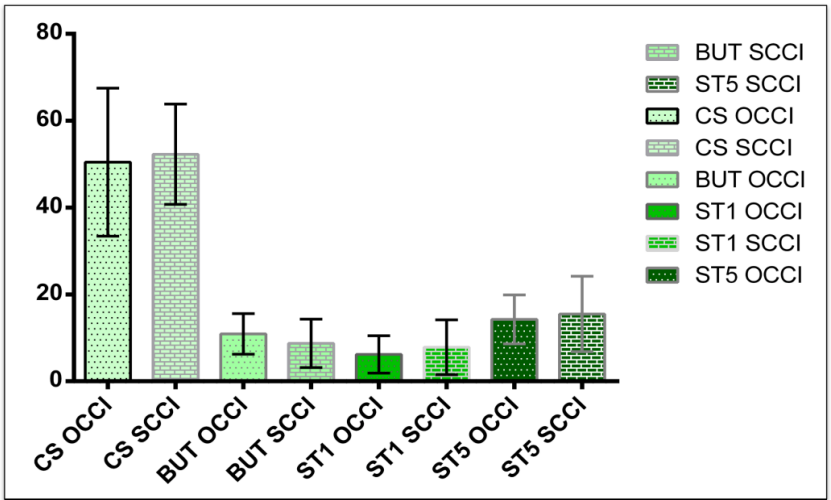
of the absolute painless surgeries, i.e. VAS 0: it was much lower in Group E. There was no patient in either group to give the procedure the highest scores of 9 or 10 (Fig 7).

2.7.3. Study 3

Thirteen and 33 patients were assigned to group OCCI and SCCI, respectively; the demographic data of the enrolled patients and the preoperatively measured parameters are summarized in Table 4. We could not find difference between the groups in any respect with $p<0,05$ being considered significant. The means of the parameters measured at the first follow-up visit taking place on the 1-3 postoperative days are shown in Figure 8. In neither variable could find a sigificant diffrence between the groups. To analyze the data Student t-test and Mann-Whitney test were employed.

Table 4. The preoperative data of the groups. (mean±SEM). T-test (*), Mann-Whitney test (**)

	CASE Number	AGE (years)	GENDER (m/f)	CS (mm)	BUT (sec)	ST1 (mm)	ST5 (mm)
SCCI	33	68,5±2,6	10/23	53,2±2,7	8,3±1,2	8,6±1,7	14,9±1,8
OCCI	13	70,1±2,0	4/9	50,6±8,2	11,0±2,0	4,1±0,9	9,9±1,4
p		0,59*		0,57*	0,24**	0,15**	0,12*



	CS± SEM	BUT± SEM	ST1± SEM	ST5± SEM
SCCI	52,3± 2,2	8,7± 1,0	7,8± 1,2	15,5± 1,7
OCCI	50,5± 4,7	10,9± 1,4	6,2± 1,2	14,3± 1,6
p	0,76	0,24	0,73	0,99

Figure 8. The top diagram of the figure illustrates the postoperative results of the two groups. The means (± standard error of means) of the measured parameters and the level of the significance are shown by the bottom chart.

2.8.Discussion

In *Study 1*, there was no difference between the first and second eye PhEs in terms of pain if the patients were questioned immediately after the surgery, however 2-3 weeks later the second procedures were reported to be more painful. Since in our institution PhEs are performed in a big volume and are strictly complying with the protocols, the study was conducted under steady and standardized circumstances which we think to be one of the main advantages of our investigation. All of the 187 patients we enrolled to the investigation underwent bilateral surgeries which were done by the same surgeon and - to exclude any possible influence by the surgical method (50)- 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 (6, 16, 21) 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 our study: 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 (20). 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 undoubtedly influence the pain perception, to measure these parameters remains quite difficult and the correlation between them and the experienced pain is of contradiction (2, 8, 9, 20, 51). Ursea, for example registered lower anxiety level among the patients having given higher scores found the second eye surgery which would suggest the opposite of the usually

experienced effect of anxiety on the pain perception. Therefore, the above factors remained out of the scope of our investigation. Neither the perioperative scores (T1, T2) nor the remembered pain scores (C1, C2) showed significant difference between the first and second eye operations 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 (52). 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. Remembered pain probably plays a more important role in the patients' pain evaluation for sequential phacoemulsifications than other presumed factors. In our view, the obvious contradictories of different studies on this topic should even more emphasize the importance of a proper and meticulous patient consultation.

Since I happened to have the opportunity to perform cataract extractions both in England and in Hungary with a short interval of time, I aimed to ascertain if there is any difference in the intraopertaive pain perception during a routine PhE done by the same surgeon between the groups of patients of the above nationalities (i.e. Group E and H). It was speculated that living in and belonging to a country could represent the resultant of the varied, immensely investigated factors that are related to the subject's socio-educational, ethno-cultural background (53) and relation to the healthcare system or provider (54) and certainly affecting the clinical pain perception in human. The following circumstances favoured the comparison of Group E and H. We did not need to count with the influence of the surgeon's personality and experience (9, 55, 56) 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 PhE such the impact of the time interval on the learning curve can be disregarded. Moreover, females and younger patients have been reported to have lower pain threshold and the expressed pain is higher (2, 6, 8, 9), but the groups did not show significant difference neither in age or in gender proportion. One can concern about the first and second eye surgeries in the same patient. There were 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 (6, 20), others including us have could not find difference in the intaoperative pain between the consecutive surgeries for a patient (2, 15, 16, 21). As the length (and complexity) of the procedure is of no influence on the pain sensitivity (55, 57), the duration of the surgeries was not recorded. 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 to agents' effect could not be found in the literature. 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 biopsycho-sociocultural background of English patients. The different ethnical composition of Group E is the greatest 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, Group E like Group H can be regarded as a representative sample of English and Hungarian ophthalmic patients such giving relevance to our findings. In summary, the Hungarian patients reported lower intraoperative pain, but the difference was not statistically significant. To our knowledge, the current study is the first to compare the intraoperative PhP in patients of different nationalities.

The impact of the cataract surgery on tear production and tear film stability have been investigated by several authors but the wound size and location vary in these studies.

Sitompul et al compared two groups of 15/15 patients who underwent PhE through 5,5 mm corneal wound with PMMA IOL insertion and és 15 extracapsular cataract extraction through a scleral wound, respectively. Decreased CS was found in the PhE group on the first postoperative day as well as one and two weeks after the surgery; ST- surprisingly- was elevated on day one in both groups then returned to the preoperative level (44). Khanal and co-worker reported on lower CS measured in the centre of the cornea during the postoperative period between the third day and third months of PhEs with 4,1 mm corneal incision in 18 patients (41). The same wound size and the similar design of the studies by Oh and al from 2012 (58) and by Park et al from 2016 (59) renders the results more comparable with ours. The former study revealed significantly decreased CS and BUT in the 48 eyes of 30 patients on first postoperative day but 2 months after the surgery both parameters improved, almost to the

preoperative level, while ST taken at any time during the follow-up period hadn't been change! In the latter one 48 eyes of 34 patients were studied, but the patients were devided into two groups as to whether they had (18 patients) or hadn't been diagnosed (16 ptients) preoperatively with dry eye disease. 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 the investigated groups. Taking Khanal's results, one could consider the bigger, 4,1 mm wound size causative for lower CS, but in our Group-OCCI where the cumulative wound size equals to (2x2,8=) 5,6 mm, the postoperatively unchanged CS remains without explanation. Since the CS were performed 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 greater after the surgery than before can bear out the above explanation. However, Sitompul unlike other authors found increased tear production measured by ST I. (without putting anaesthetic drops in the eye before measurement) 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 sensitization 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. 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 (2, 49) revealed, that the subepithelial and subbasal plexus of the cornea is rather characterized by a homogenous, whorl-like pattern of nerve fibers than a horizontal orientation, and their multiple branching and 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 corneal incision during PhE would decrease more the central corneal sensitivity as well as the tear film quality and quantity causing more serious dry eye symptoms than a single clear corneal incision was not justified. Adding it to the above, that performing OCCI doesn't require extra instruments, skills or expertise from the

surgeons, we deem OCCI a safe and useful procedure to reduce the postoperative corneal astigmia.

3. OPHTHALMIC IDIOSYNCRASY DUE TO SYSTEMIC SuD ADMINISTRATION

3.1. Introduction

Several drugs, especially sulphonamide-derived medications, so called sulpha–drugs (SuD) which are widely used as anticonvulsants (topiramate), diuretics (acetazolamide, methazolamide), antibiotics (sulphacetamide, sulphadiazine), chemotherapeutics (sulphamethoxazole), antidiabetics (glibenclamide), antihypertensives (indapamide) as well as synthetic hormones (spironolactone, bromocriptine) are widely recognized to cause visual disturbances, most often acute 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 (60), which will finally lead to transient (pseudo)myopia. Lately, there are several reports on sulphonamide-induced ciliary body oedema and supraciliary effusion always presenting with acut myopia (61-64) frequently associated with acute ACG. (65-78) There are theories (65,75,79,80), but the pathophysiology of the SUD-induced ophthalmic disorders has not been fully discovered yet. To explain the exact mechanism of drug-induced refractive changes three potential contributors have been suggested, namely the osmotic disturbances 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 anterior chamber depth and narrowing of the irido-corneal angle, occasionally with ACG. Having encountered three cases with unusual ocular side-effects of two 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 (64,81). Study 4 below aims to report on our results of the investigation of SUD-related ocular idiosyncrasy.

3.2. Methods

VA was assessed by Kettesy's decimal visual chart, IOP was measured by either Goldmann or iCare applanation tonometers, slit lamp (Haag-Streit; Liebfeld-Bern, Switzerland) biomicroscopy for the anterior and posterior segment examination, latter one with Volk 90 D

aspheric lens. 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, crystalline lens thickness was measured by A-scan contact mode. UBM (VuMax 35-50 MHz, Sonomed Escalon Inc., NY, USA) sagittal 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 (82); ciliary body thickness (CBT2) was introduced by us, and was determined as aline connecting the outer and inner aspects of the ciliary body at 2 mm distance from the scleral spur.

3.3. Patients

3.3.1. Case 1

A 39 years old female patient (Patient 1) was referred to our out-patient clinic for consultation due to headache and sudden bilateral visual impairment. Neurological assessment and cranial CT scans were unremarkable. 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. Neither of the the drugs' package insert listed myopia as potential side-effect. 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. Her eyes have otherwise been known normal and she has never worn spectacles. On her general ophthalmic evaluation, VA 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 right and the left eye, 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 BE, the refractive error decreased to – 5,0 D in BE. According to the above findings, accommodative spasm resulting in (pseudo) myopia was

diagnosed by the ophthalmologist, however, the central origin could not be entirely ruled out. On returning to the neurology, cranial MRI was performed and blood and cerebro-spinal fluid were taken from the patient: the MRI scans as well as both samples proved to be normal, therefore, the patient was discharged. The next day, her headache diminished, other complaints were substantially unchanged, 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 both eyes. To obtain more information about the morphological background of the acute myopia, UBM was employed. The ciliary body, throughout its "visible" extent was markedly thickened, the suprachoroidal space showed a very low reflectivity with a few more reflective membranes suggesting ciliary body-choroidal detachment and effusion (Fig 9). The anterior aspect of the ciliary body moved forward which could be demonstrated by the change of the CBCA (Fig 10). The ciliary processes rotated remarkably forward, occasionally attaching the posterior aspect of the iris.

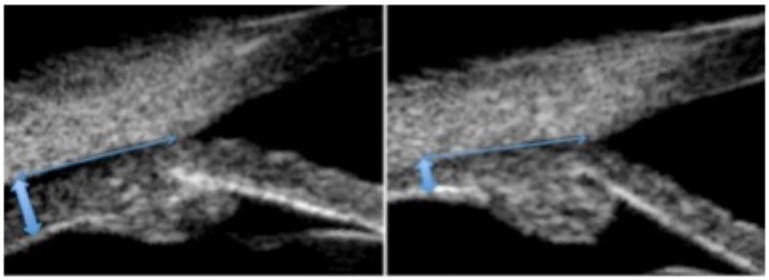


Figure 9; Ciliary body thickness during the acute fase phase and the convalescence
The CBT2 (thick double arrows), measured at a 2,0 mm distance (thin double arrows) from the scleral spure, was doubled during the acute phase (left side) compared to the normal value (right side).

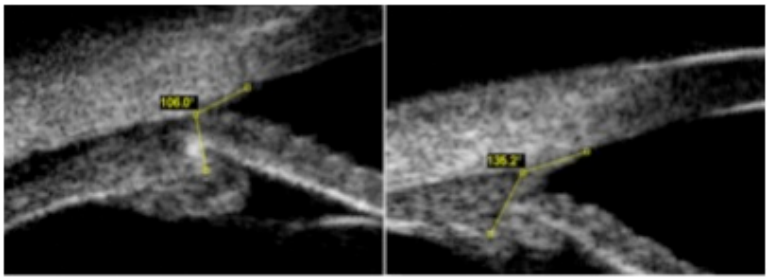


Figure 10; CBCA during the acute phase (left side) and the convalescence (right side)
The angle between the anterior aspect of the ciliary body and the inner surface of the cornea reflects the forward movement of the ciliary body. Several days after discontinuation of taking indapamide, the ciliary body-cornea angle increased by approximately 25 degrees compared to the acute fase (left side).

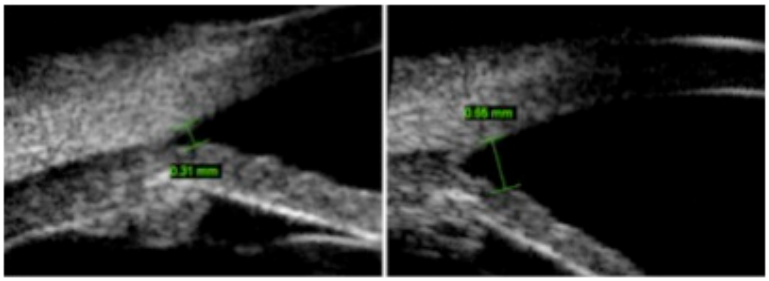


Figure 11; AOD changes displayed on the saggital UBM-scans.
During the acute phase (left side), AOD markedly decreased compared to that of during convalescence (right side).

AOD was markedly decreased (Fig 11). After putting 3-3 drops of cyclopentolate hydrochloride 0,5% into both eyes, with 15 minutes intervals, the refraction measured -0,75/-0,50 Dsph. Two days later, at her next follow-up appointment, 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 increased. (Table 5.) 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.

Table 5. Biometric data of the anterior segments of the right/left eyes during acute phase and convalescence of Patient 1.

	Acute phase	Convalescence
ACD	2,32/2,49 mm	3,68/3,66mm
L	4,02/4,09 mm	3,78/3,81mm
AOD500	300/314 μ	630/644 μ
CBT2	720/700 μ	340/350 μ
CBCA	108/114°	140/134°

ACD=anterior chamber depth, L=lens thickness, AOD500=angle opening distance, CBT2=ciliary body withs, CBCA=ciliary body-cornea angle

3.3.2. Case 2

A 69 years old man (Patient 2) was referred to our department with presumed bilateral retinal detachment. His BE were pseudophacic, and couple of days before his referral, he underwent YAG-laser capsulotomy for his LE due to posterior capsular opacification. The following day he returned with elevated IOP (30 mmHg) of his LE therefore he was given 2x250 mg acetazolamide (Huma-Zolamide® , TEVA) per os and topical levubonolol. Shortly after that, normal IOP was measured for both eyes, 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 fields. 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. (Figure 12). Although neither myopic shift nor IOP elevation was found, having recalled the idiosyncratic case of Patient 1, UBM was employed to discover the possibly occuring morphological alterations of the ciliary body. By means of the UBM it was revealed, that the choroidal effusion in both eyes invaded the supraciliary space, too. The iris-(pseudo) lens diaphragm moderately moved forward resulting in mild shallowing of the anterior chamber (Figure 5). 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 (Figure 13).

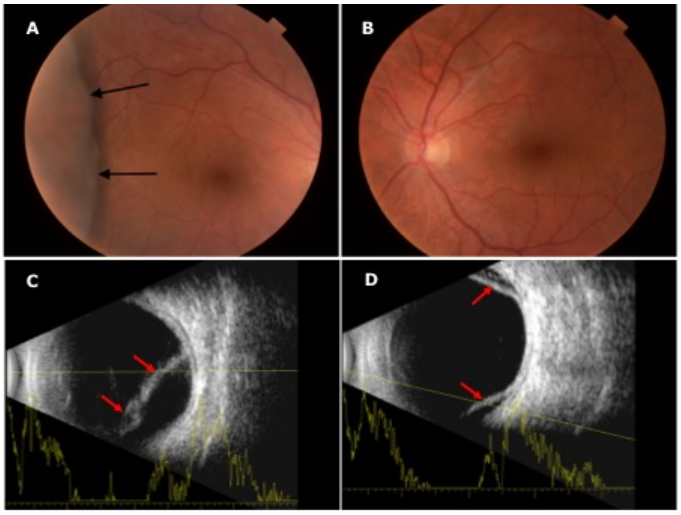


Figure 12; Fundus photographs and ultrasound B-scans taken of the eyes of Patient 2.
Picture A: black arrows show the central border of the temporal choroidal effusion in the RE. Picture B: in the LE the the very shallow and peripheral lesion could not be displayed by the OCT camera (question mark). In picture C and D, the red arrows are pointing at the highly reflective membranes corresponding to the inner aspects of the RE's higher and the LE's shallower choroidal detachments. Retinal detachment did not presented in either eye.

Topical glaucoma drops were stopped and we decided to observe the patient. Two weeks later, his VA was full and IOP within the normal limits in BE. Neither ophthalmoscopy nor echography could detect the former choroidal effusion in the eyes (Figure 7, Table 6).

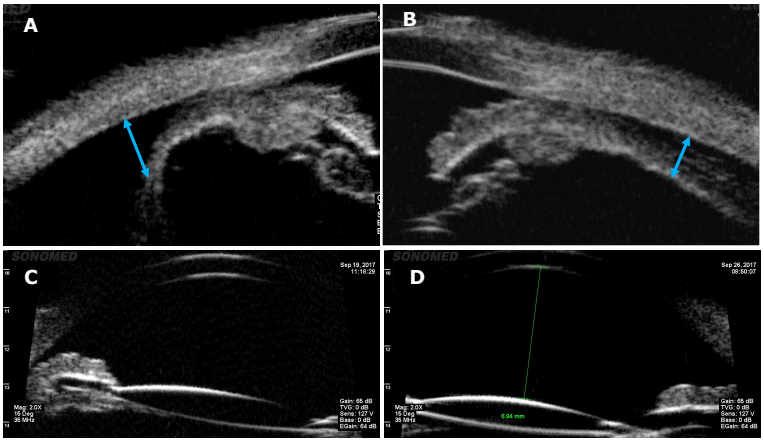
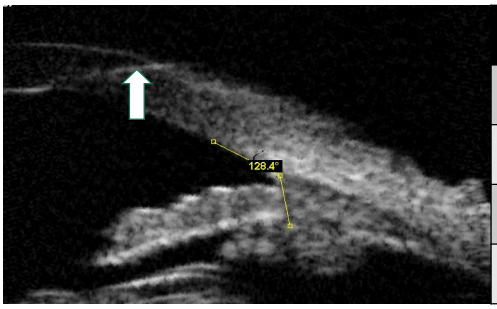


Figure 13. Radiaer UBM-scans of Patient 2.
The top two pictures represent the RE choroidal and supraciliary effusion. The detachment was much higher in the temporal (A) than in the nasal (B) site. The bottom same-sized images illustrate the moderate difference in the ACD between the acute stage (C) and the recovery (D).



	ACUT	RECOVERY
AOD 500	350 µ	550 µ
ACD	3,0 mm	3,5 mm
CBCA	127°	122°
CBT2	840 µ	400 µ

Figure 14.
On the left side the RE's UBM scan can be seen, CBCA is confined by the yellow lines, the reflective, nearly horisontal line with the white arrow indicates the former corneal incision made during PhE. In the table, the biometric data of the anterior segments of the RE during acute and convalescent phase are shown.

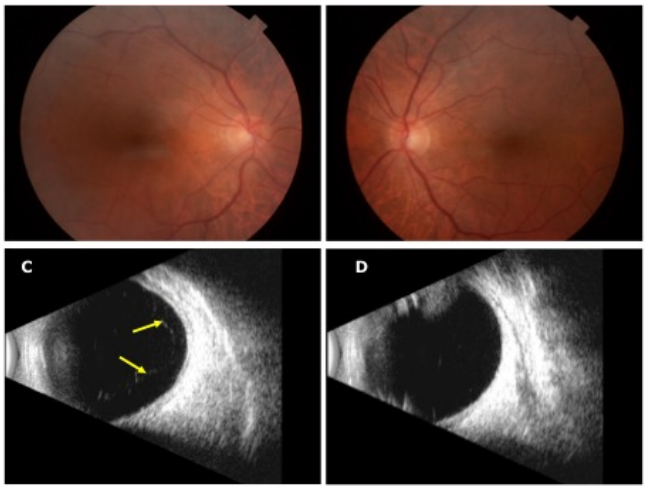


Figure 15; Fundus photographs and ultrasound B-scans taken of the eyes of Patient 2 *two weeks later*
Both the funduscopy and the echography showed the complete resorption of the choroidal effusions in the eyes. The membrane of medium reflectivity in the Picture 3 corresponds to the detached posterior vitreous membrane (yellow arrow).

3.3.3. Case 3

An 82 years old man (Patient 3) underwent a combined phacoemulsification with posterior chamber intraocular lens insertion and pars plana vitrectomy with injection of 20% SF^6 due to his right eye 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 acetazolamid tablets per os and brinzolamide eyedrops topically in the right eye were administered. By the evening of the same day, right eye's IOP returned to normal and remained so. The second postoperative day, the other eye routine funduscopy with dilated pupil discovered a circumferential bulging of the peripheral retina. The adjunctive B-scan echography revealed 360° peripheral choroidal detachment of his LE, which caused no visual deterioration such it was completely unnoticeable 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 (Figure 16).

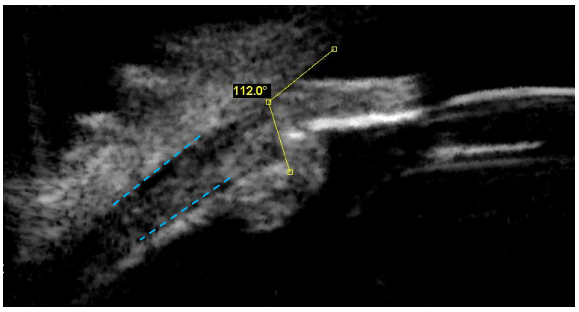


Figure 16; Left eye saggital UBM-scan in Patient 3.
The inner and outer surfaces (blue dashed lines) of the ciliary body are almost parallel instead of the normal acute angle. CBCA is confined by the yellow lines.

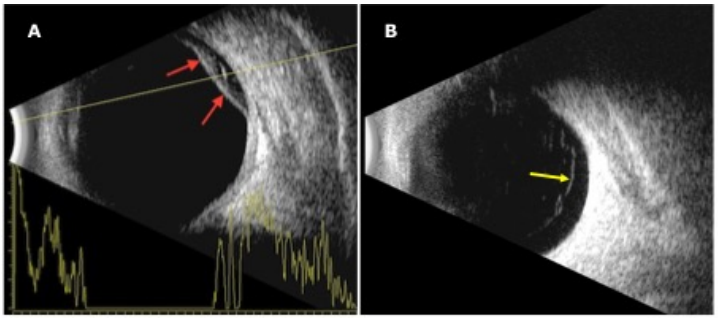


Figure 17; Left eye B-scan echograms of Patient 3.
A; The highly reflective convexity of the posterior eyewall (red arrows) corresponds to the peripheral choroidal detachment. B; Control examination showed the complete resolution of the choroidal effusion. The membrane of medium reflectivity corresponds to the partially detached posterior vitreous membrane (yellow arrow).

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. (Figure 7). Unfortunately, for technical reasons, the control UBM study is not available. He had no complaint and full vision for his LE.

3.4. Discussion

In the literature, there are only two articles on indapamide caused transient myopia (62,63) 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 (65,72-77) 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 (see Table 1). The observation that both transient myopia and ACG can occur in pseudophakic patients (72), also undermines the significance of the lens thickness changes in the pathomechanism. Ramos-Esteban at al. stated that the spasm of accomodation is the most unlikely mechanism in the SuD-caused transient myopia as instillation of cycloplegic drops almost never abolishes the refractive change (65). Both Krieg's (75) and our case are rather contrary to the above statement since both reported patients had a marked discomfort during close work indicating a spasmic component over and above, cyclopentolate significantly improved her pain as well as the refractive errors. 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 measured during nonaccomodated and maximally accomodated states of the ciliary muscles (82). We also have found a significant forward movement in Patient 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 which 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 angle closure glaucoma. If it occurs, the therapy should consist of prompt discontinuation of taking the causative drug and instilling cycloplegic drops. YAG-iridotomy is of no effect and pilocarpine is contraindicated (65,74)! It is of interest, that neither of the reported cases of indapamide induced acute myopia, included ours, developed ACG. Beyond the ciliochoroidal detachment, Blain and co-workers noticed diffuse choroidal thickening at the posterior pole and scattered islands of delayed fluorescein filling at the early and midstage fluorescein angiography suggesting transient lobular choriocapillary hypoperfusion (63), presumably, related to choroidal thickening. In our case, the posterior pole was normal, choroidal thickening or effusion was excluded by ultrasound, and full vision was all the time preserved. The combination of the above symptoms (iris-lens-ciliary body complex forward movement, shallow anterior chamber, myopic shift, angle closure glaucoma, choroidal effusion) resulting from the idiosyncratic effect of SUDs on the uvea was proposed to term as ciliochoroidal effusion syndrome in 2002 (83). The bilateral involvement and the spontaneous recovery after cessation the causative drug undoubtly assign our three cases to the CES. Comparing Case 2 and Case 3 to the other, acetazolamide related idiosyncratic ocular adverse reactions have been reported till today, they need to be considered unique and exceptional, since Patients 2 and 3 – 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 females (78). Perhaps, the different hormone status favours the milder forms of idiosyncrasy to be manifested. The question arises: do our cases represent a *rarely occurring*, 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. Idiosyncrasy refers to adverse reactions to drugs that are typically unrelated to the drug's pharmacologic effect, occur in small fraction of patients and have no obvious relationship to dose or timing and duration of therapy. The liver is the most common target of drug idiosyncrasy. There are theories about the underlying mechanisms, conventionally, it is thougt to have a metabolic basis involving drug metabolism polymorphisms or to arise from a specific immune response to the drug or its

metabolits. Above several recently emerged hypothesis such as drug disposition, adaptive immunity, mitochondrial dysfunction etc., Roth and co-workers proposed inflammatory stress hypothesis (79) which is of special interest for us. It postulates, that the modest inflammatory episodes during drug therapy may render an individual susceptible to a toxic reaction that would not otherwise occur. Conditions associated with inflammation include arthritis, atherosclerosis asthma, bacterial infections with special regards to the exposure to endotoxins from Gram-negative bacteria. Endotoxemia is a normal but episodic occurence in people, and numerous conditions such as alterations in diet, alcohol consumption, gastrointestinal distress, anaesthesia, surgical trauma etc, can enhance endotoxin concentration in the plasma (80). The authors reviewed published clinical reports for evidence of underlying inflammation in association with idiosyncratic episodes. In 68% of chlorpromazine cases, prodromal signs consistent with inflammation or endotoxin exposure (fever, diarrhea, vomiting, etc.) could be found! Krieg and co-workers publication (75) analysing two cases of drug-induced myopia seems to be consistent with the inflammation theory. In the first case, the symptoms presented during pregnancy after ingestion of chlorthalidone, in the second one, acetazolamide administration following PhE caused flattened anterior chamber, myosis with marked spastic component in a patient with aspirin-sensitive asthma. Taking into consideration, that in both conditions the disturbance in eicosanoid metabolism is present resulting in increased levels of prostaglandins and leucotriens, they might be responsible for the miosis and, through the vasodilatation and increased permeability of the capillaries, for the ciliary body oedema (prostaglandins) and for the ciliary body spasm (leucotriens). 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 angle-closure glaucoma. 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 angle closure, one needs to consider idiosyncrasy 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 leaflet 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 practitioners of other specialities should be warned to refer their acetazolamide taking patients with visual complaints to an ophthalmologist.

d. Catching out the above side-effects is hindered by the dose- independency and great variability of the signs and symptoms in different individuals and for different medicines. Over and above, the same individual can react in a different manner to the same medication in different times of administration. After having proved the existance of the „silent" form of acetazolamide-induced uveal effusion, we believe that a significant part of SuD-related ocular adverse reactions remains undiscovered.

4. HUMAN DIROFILARIA REPENS INFECTION

4.1. Climate changes and infectious diseases

Recently, the climate change is one of the most concerning global issues. Although, its existence has been disputed, there are compelling arguments for it including the global temperature rise, warming oceans, shrinking ice sheets, sea level rise and ocean acidification etc (Fig 18). 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 (87). Despite the growing concern and the rising number of the papers (Fig 19.) about human infectious disease allied with the climate change, predicting the consequences of climate change for infections has been surrounded by controversy. The relating articles published between 1995 and 2014 were analyzed by Liang et al., and demonstrated that there was an increasing number of articles reporting negative or uncertain responses (88). It seems so that discovering the climatic change-infectious disease nexus requires a multidimensional approach regarding that just global warming can affect the human health in at least three ways (89). Directly: According to Robine et al. the heat wave in Europe in 2003 caused about 70,000 deaths principally from cardiovascular diseases (90); indirectly through declining air, food, water quality and quantity, and through socio-economic factors such as appearing new pathogens and vectors by migration (91,92) 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.

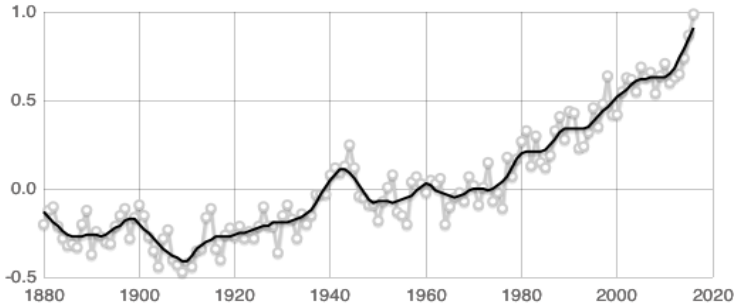


Figure 18. The graph illustrates the change in global surface temperature relative to 1951-1980 average temperatures. Sixteen of the 17 warmest years in the 136-year record all have occurred since 2001, with the exception of 1998. The year 2016 ranks as the warmest on record. (86)

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 (93). In relation to Hungary, the global warming leads to the extension of the Mediterranean climatic belt to the north, giving better opportunity for both vectors and parasites to thrive and spawn infection.

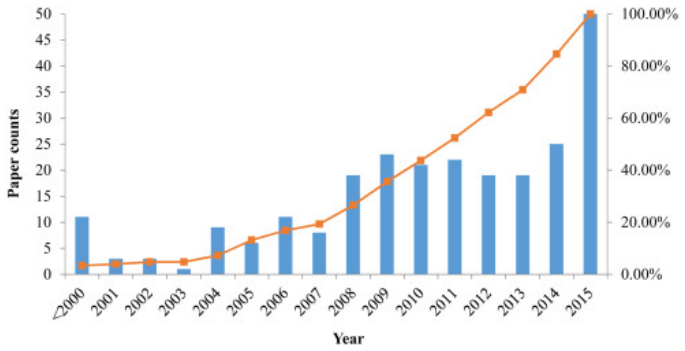


Figure 19. Rising interest in climate change and human health interactions. The blue bars indicate the number of papers published annually. The orange line shows the cumulative amount of papers (87).

4.2. Dirofilaria repens

There are exclusively human pathogen filariae such as Loa loa, Wuchereria bancrofti, Onchocerca volvulus etc., while drofilariae infect humans rather accidentally, their natural hosts are the cats, dogs and wild carnivores. Six out of 40 species of dirofilaria i.e. *D. immitis*, *D. repens*, *D. straita*, *D. tenuis*, *D. ursi* and *D. spectans* are known to cause diseases in humans, most frequently the Dirofilaria/Nochtiella repens' (DRep). Adult worms living in subcutaneous nodules even for 8-10 years releases microfilaria into the bloodstream of the primary host (dogs). Mosquito taking blood meal ingests microfilaria which develops to infective L3 larva over 10-30 days and migrates from mosquito's digestive tract through the Malpighian tubules to the head and proboscis. Infective L3 is transmitted by mosquito's bite to the next host's bloodstream including humans. Then, microfilaria migrates to the subcutaneous tissue and

grows to mature in 5-9 months. 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. The maturation from L1 to L3 is on one hand temperature dependent: the higher the temperature the quicker the larva develops. It has been experimentally demonstrated that the development of infectious L3 larvae requires 8 to 10 days at 28°- 30°C, 11-12 days at 24°C, and 16-20 days at 22°C. Below 14°C, development arrests, although it can be restarted when the temperature increases above this threshold. Of interest, other studies suggested that a bacterium, the intracellular *Wolbachia* developed a symbiotic relationship with DRep, in which the bacteria support the molting and embryogenesis of filariae, whereas filariae contribute amino acids for bacterial growth (94). On macroscopic examination, the adult filaria has got a whitish cylindrical body with lateral chords being of triangular or trapezoid shapes, and rounded ends. The mouth terminal small and circular, without lips, with cephalic papillae sometimes visible; the posterior end is thinner and sharper having two papillae in females, and sexual tubules in males: a longer and a shorter spiculum. Length varying from 48-70 mm in males and 100-170 mm in females with the diameter of 370-450 microns and 460-650 microns, respectively. Length of the oesophagus is 915-1080 microns, the cuticle 8-40 microns thick with longitudinal ridges prominent 1-6 microns and present over the entire length of the body being one of the most characteristic morphological feature of the DRep species making easy to distinguish from Dirofilaria immitis. In human infections, the more frequent superficial and the visceral manifestations can be distinguished, the former ones, due to the phototropia of the worm, tend to involve (in approximately 75% of cases) the head-and neck region. The less frequent visceral infection reportedly may involve the lungs, gastrosplenic ligament, peritoneal cavity, mesocolon, pancreas, perirectal region, scrotum, spermatic cord etc. The pulmonary lesion easily can be misdiagnosed as malignant lesion! In subcutaneous localization, a granulomatous chronic inflammatory reaction similar to that caused by a foreign body occurs. Normally, a single worm can be found in a single nodule, but multiplex cases have also been described (Pampiglione 1995). In the human 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 (96), anterior chamber (97,98) and as an exceptional case vitreous cavity (99) were also described. In subconjunctival localization, a reactive cyst sometimes forms which 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. 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 Doczi et al suggested in a case where the subconjunctival DRep crawled away before it could have been removed (100). Two days later, the patient was kept under dark conditions until opening the conjunctiva. I also encountered a case where the worm abandoned the subconjunctival space and disappeared before the planned removal (101). 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 (102). 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 several years inside the reactive nodule or can wander in the subcutaneous tissue over large distances (100). In human cases eosinophilia is a rarity and mirofilaremia almost never occurs. The detectability of the latter one 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. (103). 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 (104), and another one on a young girl treated with corticosteroids due to systemic lupus erythematosus (105). Morover, microfilariae were observed in the parasite's uterus in some cases (103), and Sulekova et al. as well as Damle et al reported on a case in whom microfilariae were detected in fine-needle aspirate of subcutaneous node, without evidence of microfilaraemia, confirming that complete development and fertilization of Drep worms in human hosts may occur (106, 107).

4.3. The first autochthonous human DRep infection 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 RE 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 what were frequented by mosquitoes 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 of the RE, "red eye" was found without eyelid edema, left eye was normal. The visual acuity of both his eyes was 1.0. Slit-lamp examination revealed a smooth transparent cornea, clear anterior chamber and lens in both eyes. 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 (Fig. 20). Ophthalmoscopy revealed clear transparent vitreous space and normal fundus. Ultrasonography (B scan) also showed clear vitreous space, normal thickness of the ocular wall and normal orbit echogram. Laboratory investigations: ESR and blood cell count were normal (no 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. Radiologic and dermatologic examinations did not reveal other localization of nodules. 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. Macroscopic examination revealed an intact, living, whitish, thread-like worm (Fig. 20), 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. A small apical mouth without lips was observed. Cephalic papillae were not visible. The length of the esophagus was 86 μm. Two unequal spicula, 145 and 450 μm long, were found. Pre- and post-cloacally, outlines of some caudal papillae were visible. The distance from the cloaca to the caudal end was 95 μm (Fig. 20). In transverse sections of the helminth, the big tubule (testicle) and the small tubule (intestine) were stained with periodic acid Schiff stain and Masson–Goldner trichromic stain, respectively. Cuticular ridges and muscle fibers were well evident. The ridges were separated from each other by 3–7 μm. The

thickness of the cuticle was 12–14 µm. Lateral cords were also visible (Fig. 21). 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.

Figure 20. On the left side, a subconjunctival nodule containing a whitish thread-like worm and the injected conjunctiva can be seen. In the middle, the removed living intact whitish worm is shown which survived for 4 days after removal. On the right side, caudal part of *DRep*. Two unequal spicula, caudal alae and cloaca are shown. The distance between the cloaca and the caudal end is 95 microns. (Blue-lactophenol, x 100).

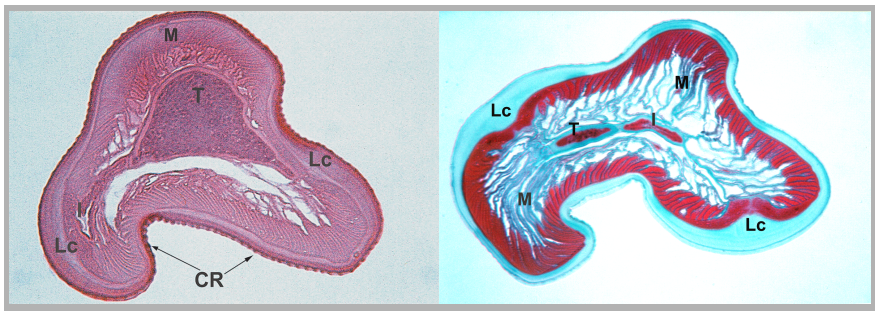


Figure 21. Transverse section of *D. repens*: external cuticular ridges (*CR*), lateral cords (*LC*), muscle fibers (*M*), testicule (*T*) and intestine (*I*) are evident (Left side: Periodic acid Schiff, x 350; right side: Masson-Goldner trichromic stain)

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 (101). The biometric data of the nematode obtained by UBM were congruent with the measurements performed on the histological sections (Fig. 22. D, E). **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 (Fig 22C).

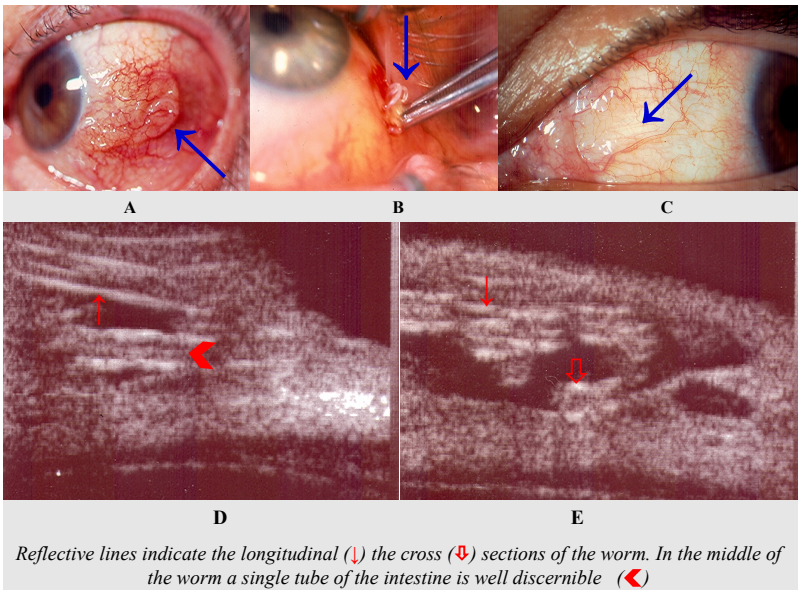


Figure 22. A, B removing the second patient's nematode with forceps **C** the nasal conjunctiva of the third patient's left eye used to contain a DRep on the day of the planned surgery **D, E** On the high-resolution UBM scans reflective, parallel lines in 408-427 μm distance from each other represent the longitudinal sections of the cuticle of the coiled body. In the axis of the body a reflective strand corresponding to the single tube of the digestive system could also be distinguished. The diameter of the reflective circles varied from 411 to 442 μm.

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.

4.4. Review of human dirofilariasis in Hungary

According to current scientific literature, Addario's *Filaria conjunctivae* from 1885 (108) is considered to be *D. repens*, at least in the Old World. However, we may suppose that the helminth described as *Filaria peritonei hominis* by Babes (109) in Budapest 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 (110). 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 *D. repens* in Hungary. To review the Hungarian cases between 1879 and 2015 when the last infections were published (100), 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 morphology of the parasite and 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 presented during the last year, between 1999 and 2000! The mean age of the patients was 55,6 years; as to the localization 6 were subcutaneous, 3 subconjunctival, 2 in the eyelids, 1-1 in gastrosplenic ligament and in spermatic cord. 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 lymph node with subcutaneous localization (111). Knott concentration technique was used for detection of microfilariae in ten cases, and the results were negative. Twelve out of 16 identified *Dirofilariae* were female and 4 were male. This marked prevalence of females corresponds to data in the literature (95). 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 (Fig. 23). All in all, the gender distribution was 59 men and 56 women, the mean age of the patients was 47.4 years. The youngest patient was a 10-year-old girl (112). Subcutaneous dirofilariasis was diagnosed in 66 cases. 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.

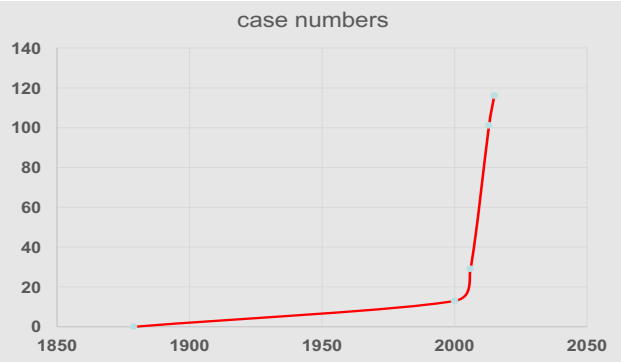


Figure 23. The graph demonstrates the exponential increase in the number of diagnosed dirofilariasis in Hungary between 1879 and 2015. (based on literature review)

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 (100).

4.5. Human dirofilariasis in Europe

Epidemiological studies and recent clinical reports on the expansion and emergence of dirofilariasis described a significant prevalence of autochthonous infections of dogs with DRep in Central and Northern European countries where canine dirofilariasis was previously not reported or where cases were only sporadically found. (93) Wherever canine dirofilariasis exists, there is a risk of human infection. Until 1999, most reported cases originated from Mediterranean countries where DRep is traditionally endemic (Italy, France, Greece, and Spain) with sporadic reports of small outbreaks of mainly subcutaneous and ocular infections in Germany, the Netherlands, the United Kingdom, and Norway. Over the following decades, more cases were reported in Mediterranean countries at the same time, a series of cases was described in Turkey, Serbia, Croatia, Romania and Austria, Hungary (113-120). and sporadic cases occurred in other countries A case report of orbital dirofilariosis from northern France turned to be an imported infection from Senegal (121). The geographical and time distribution of the spreading of the infections in Central Europe can be traced by the countries with the first human infections considered autochthonous. These are in chronological order as follows Hungary 2000 (111), Austria 2006 (122), Slovakia 2008 (117), Romania 2009 (123), Poland 2010 (124), Germany 2014 (125), Czech Republic 2016 (126). Warsaw at the latitude 52° is the northernmost site where autochthonous case was reported on. In conclusion, the emergence of DRep infections in Europe like worldwide can mainly be attributed to two factors. *First,* human activities such as the urbanization of wilderness areas at city peripheries and the construction of irrigation and artificial aqueduct systems also contribute to the spread of dirofilariasis by creating microhabitats that favour vector population growth in regions where such habitats do not naturally exist. Changes in the distribution and prevalence of canine reservoirs are also being influenced by human activity. The presence of infected dogs depends largely on pet management approaches, including the correct diagnosis and application of chemoprophylaxis, trips to and from regions of endemicity. DRep was in a substantial part introduced into Central and eastern Europe by dogs with asymptomatic such undiagnosed, subcutaneous dirofilariasis acquired in southern regions of endemicity (127,128). *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 (129). 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. Above factors together could account for substantial increases in numbers of dirofilarial infections throughout Europe in the near future.

5. 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 idiosyncrasy 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 *Study 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 primarily global warming-related factors that could account for substantial increase in numbers of dirofilarial infections throughout Europe. By having reported on the first, undoubtedly 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 continuous spectrum of the uveal involvement not essentially including the classical trias of uveal effusion, transient myopia and acute ACG 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 scrutinous review of the related literature suggests that either microfilaremia or multiple nodules can't be excluded with certainty.*

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