Prof. Alon Harris:
"130 years ago von Graefe[1] [von Graefe 1857, 1861] was the first man to **describe glaucoma without increased intraocular pressure**. He called it "blindness with cupping". In present times we know that in certain populations normal pressure glaucoma (NPG) constitutes a major proportion of all cases of glaucoma. Nevertheless, Graefe's idea did not receive support in the world of science of that time. **Having been deeply criticised, von Graefe departed from his theory of glaucoma without increased intraocular pressure and this pressure was once again recognized as the dominant factor in the pathogenesis of glaucomatous damage and atrophy of the anterior optic nerve**. **However there still remain questions about the aetiology of glaucoma without increased intraocular pressure if such a disease does actually exist**." ("Ocular Blood Flow Assessment in Glaucoma"; Górnicki Wydawnictwo Medyczne, Wroclaw 2002)

Prof. Maria Hanna Niżankowska:
"The overwhelming majority of cases of the disease [glaucoma] is a mysterious in its genesis primary open-angle glaucoma. The hidden course of the disease does not provide the patient with signals of progressive loss of vision for a long time and **no increased intraocular pressure, which happens in nearly 30% of cases,** makes the diagnosis difficult for the physician. What is more, also the **pharmacological reduction of pressure within the limits of physiological standards in very many cases does not hamper the disease process. Where is the cause** of these facts well-known to all of us? Is it in a genetic predisposition of the optic nerve to this type of damage? It clearly is, but does it happen in all cases? Clinical observations undoubtedly indicate the significant role of abnormalities in blood supply to the optic nerve in the process of its glaucomatous destruction. [...] This is also evidenced by glaucoma occurring more frequently in persons with vascular dystonia, **which involves migraine headaches or a tendency to have cold hands or cold feet.** [...] This publication should actually contribute to the facilitation of the choice of an appropriate treatment of glaucoma made by each of us, ophthalmologists, facing this difficult challenge every day." ("Ocular Blood Flow Assessment in Glaucoma" by Alon Harris, Preface by Prof. Maria Hanna Niżankowska, Górnicki Wydawnictwo Medyczne, Wrocław 2002)

Prof. Marta Misiuk-Hojło:
"Recent years **have brought no ultimate solution to the problem of progressing**, despite treatment, **glaucomatous damage to the optic nerve.** And so it is still **unknown what the possible prevention is and what the only appropriate procedure is to protect our patients from blindness due to glaucoma**." ("Current views on glaucoma: vascular risk factors" by Alon Harris, Adam Moss, Deepam Rusia, Marta Misiuk-Hojło, Introduction to the Polish edition, Wroclaw 2010)

"Pupillary block and the reason for constructing a tonometer of posterior chamber and vitreous humour of a human eye."

My discovery and description of the migraine mechanism that is dependent on an increased pupillary block with subsequent increased pressure in the posterior chamber and vitreous humour, often with the accompanying pressure drop in the anterior chamber, has made me reflect on the problem of diagnostic capabilities of measuring pressure in the eyeball. Both in the diagnostics of migraine and glaucoma, i.e. diseases the co-occurrence of which has been observed and statistically proved in medicine for a long time. Looking at the abovementioned quotations from works of authorities in glaucomatology (a field of ophthalmology dealing with glaucoma), it can be noted that in the vast majority of cases primary open-angle glaucoma has been almost as puzzling a disease as migraine invariably for more than 150 years. While analysing the physiological mechanisms governing the aqueous humour outflow from the eye and focusing on the issue of the ease of the pupillary flow (this problem is virtually nonexistent in the literature and overlooked in ophthalmological practice for open angle glaucoma[2]), I set myself a goal to construct a tonometer that would non-invasively measure the pressure in the place where it is characteristic for the glaucomatous damage of optic nerve and the compression of intraocular vessels, i.e. behind the lens and iris. I managed to design Nogal's non-invasive tonometer for the anterior chamber and vitreous humour already patented at WIPO in Geneva. The tonometer that is likely to help us to unravel the mystery of multiple failures in the diagnostics and treatment of glaucoma, migraine and many other "idiopathic" eye disorders.

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[1] The bust of Albrecht von Graefe, one of the founders of ophthalmology, stands on a desk in the office of the Head of the Clinic Ophthalmology at Wroclaw Medical University currently managed by Professor Marta Misiuk-Hojło, President of Glaucoma Section of the Polish Society of Ophthalmology.

[2] So far pupil has been treated in open angle glaucoma as an empty space through which aqueous humour flows easily. In the literature related to this type of glaucoma both the phenomenon of aqueous humour secretion by the ciliary body in the posterior chamber of the eye and the problem of the humour outflow through the trabecular meshwork in the iridocorneal angle are widely raised, whereas **variable pupillary flow, which after all determines the variable pressure in both chambers of the eye, remains almost completely beyond suspicion in terms of being the causal factor**. It is evidenced even only by the classification of open angle glaucomas, developed by the world glaucomatological authorities, according to (only iridocorneal angle-related) mechanisms which induce them, into: pre-trabecular (associated with membranes outgrowth in the iridocorneal angle), trabecular (involving "primary" open-angle glaucoma, but it is not known why; if it is primary, then the logical question from me is: why is it here?) and post-trabecular (see **Patrycja Krzyżanowska-Berkowska, MD, PhD**, Chapter 1: Classification and treatment purpose of glaucoma in "Pharmacotherapy of glaucoma" by Marta Misiuk-Hojło, Dorota Szumny, Joanna Jurowska-Liput, Patrycja Krzyżanowska-Berkowska; Górnicki Wydawnictwo Medyczne, Wrocław 2008). This classification has drawn our attention away from inhibiting the flow through the pupil in the pupillary block for many decades!!!

I am asked whether it is necessary to create a new device if in ophthalmology there are already so many accurate and constantly improved apparatuses for measuring the pressure in the eye. I reply that it actually is because the existing tonometers measure pressure in the anterior chamber of the eye in the cornea[3], which in physiological conditions, and all the more so those related to the increase in the pupillary block, is according to my assumption always lower than in the posterior chamber of the eye. Therefore, proving this thesis and measuring pressure in the posterior chamber and the vitreous humour may not only be a milestone, but even a turning point in ophthalmology in terms of a change in attitude towards the diagnostics and treatment of "low"[4] intraocular pressure glaucoma, for which in the absence of data on the increased pressure in the eyeball the "theory of vascular damage" is assumed as the leading one in the process of optic nerve loss. The best answer to the question about the reason for creating a posterior chamber tonometer will be the presentation of this publication.

Thesis to prove:

"In physiological conditions and those related to the increase in the pupillary block, the intraocular pressure in the anterior chamber of the eye (total for a given period of time [5]) is always lower than the one in the posterior chamber of the eye and the vitreous humour chamber".

Piotr Nogal

To prove my thesis I asked myself questions:

1. ***do measurements using the existing tonometers give us objective results in terms of determining the pressure in the entire eyeball?***
2. ***are measurements using these devices useful diagnostically in glaucoma and in other clinical situations related to the increase in the pupillary block?***

and finally:

3. ***is there evidence that intraocular pressure measured so far in the cornea is often inadequate to the most important risk factor of glaucoma, which is the increased pressure in the posterior chamber of the eye and the vitreous humour?***
4. ***how to find increased intraocular pressure in "normal" pressure glaucoma?***

In order to allow Readers of this paper to consider the issue as independently as possible, they must be familiarised with the basics of anatomy and physiology of the human eye. To this end I prepared the following 4 illustrations showing the schematic cross section of the human eyeball.

Abbreviations used:

IOP - intraocular pressure, **AC IOP** - "anterior" pressure in the anterior chamber, **PC IOP** - pressure in the posterior chamber, **PS IOP** - "posterior" pressure in the "posterior segment", **AC** - anterior chamber of the eye, **PC** - posterior chamber of the eye, **VHC**; vitreous humour chamber, **PS** -
"posterior segment of the eye" (the space behind the lens and the iris; PC+VHC).

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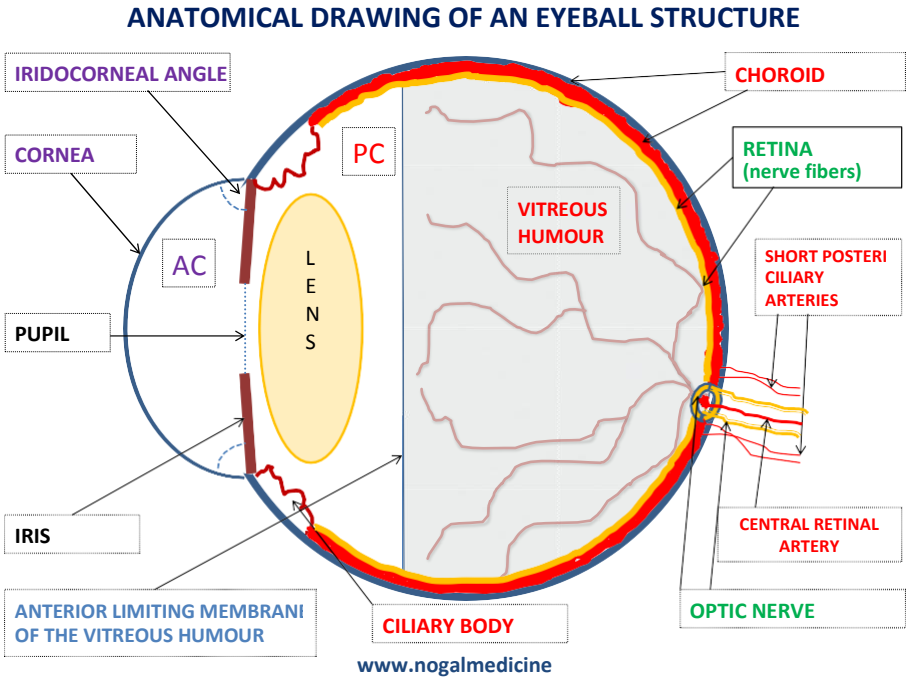
[3] There is one interesting tonometer that measures pressure in the eyeball in a very interesting way through the eyelid. However, this is apparently done in a not fully controlled way since it is difficult to define precisely both the measurement volume projecting on the eyeball wall that is obscured by the eyelid, and the objectivity of such a measurement considering different instantaneous and individually variable stiffness of the eyelid through which the measurement is being taken. The accuracy must also be influenced to some extent by varied flexibility of the eyeball wall within the cornea (the thicker edge from the centre) or the sclera rearwards from the edge (the degree of ciliary muscle tension does after all change the stiffness of the wall on which the muscle projects itself).

[4] Personally, I reject the existence of glaucoma without clinically significant intraocular overpressure and therefore I put the word "low" between quotation marks. I hereby support the "theory of mechanical damage to the optic nerve" (which holds that the overriding aetiological factor is the compression on the optic nerve in the eyeball caused by the intraocular overpressure), just as the Founders of modern Ophthalmology have been doing for over 150 years, criticising sharply the abovementioned von Graefe's theory of glaucoma without increased intraocular pressure. The "theory of vascular damage to the optic nerve" in the eyeball assumes that the overriding causal factor is nerve ischaemia. In one of the following articles I will describe a hydraulic pathophysiological model of fluids circulation in the eyeball, giving evidence that indirectly also supporters of the vascular theory are right, although in my view the direct causal factor is the "relative intraocular overpressure", which I can easily prove in any discussion based on medical arguments.

[5] The pressure gradient may be temporarily reversed between the chambers of the eye, which is associated with a temporary phenomenon of compression of the anterior chamber forced externally in relation to the eyeball (e.g. dynamic gonioscopy or strong eyelid clamping in the presence of contraction of the circular muscle of the eye with eyelids compressing the cornea and episcleral venous vessels).

SLIDE No. 1: Static drawing of a human eyeball structure



On the first slide I marked only the most important structures of the eye in order to keep the drawing readable. The lens has been intentionally offset rearwards from the iris in order to show the condition without pupillary block with free flow from PC to AC, which, as a matter of fact, never takes place in the eye[6]. The posterior chamber (PC) has been abnormally enlarged in order to more easily present the phenomena taking place in the eye behind the lens and iris; normally PC is a gap-like space (bordered with the iris, lens, ciliary body and vitreous humour), into which aqueous humour is secreted by the ciliary body, and the gel-like vitreous humour separated from PC and lens only by a thin and flexible anterior limiting membrane of the vitreous humour (the blue line)[7] fills almost completely the "posterior segment" of the eyeball. Anatomical structures have been included in the drawing, which are the ones adjusting the intraocular pressure (IOP) in the eye by a variable production and outflow of aqueous humour from the eye, those affected directly by the process of glaucoma: retina with nerve fibers and the optic nerve, which in glaucoma under intraocular overpressure are subject to irreversible retroactive changes determining secondary blindness, as well as blood vessels supplying them.

The anatomical parts of the eye observed in glaucoma have been highlighted using colours and divided due to their location in the eye into those found only in the anterior chamber of the eye: **the iridocorneal angle** and **cornea**[8], on the border of two eye segments: **the iris with pupil and the lens** and structures of the "posterior segment" of the eye (PS), involved in the glaucomatous process and affected by it according to both theories of optic nerve damage: **the ciliary body** (secreting aqueous humour into the posterior chamber and increasing pressure in the eyeball), **the vitreous humour** (carrying this pressure to the bottom of the eye), **vessels of the retina** and **choroid**, determining blood supply to the structures of the posterior part (they supply blood to the eye carrying arterial pressure "from the back" towards the posterior segment and applying pressure on the retina and the optic nerve) and above all **retinal nerve fibers** and the **optic nerve** head[9], the damage of which constitutes by definition glaucoma of any type.

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[6] In my opinion, pupillary block is always a mechanism which is active in varying degrees and which governs many processes related to the eye and indirectly to the whole body. The lens always physiologically blocks to some extent the pupil, "leaning" from the back against the iris and impeding the flow of the aqueous humour not only from PC to AC, but above all blocking the backflow from the AC to PC!; to me this is a kind of penstock that I call a “pupillary valve”.

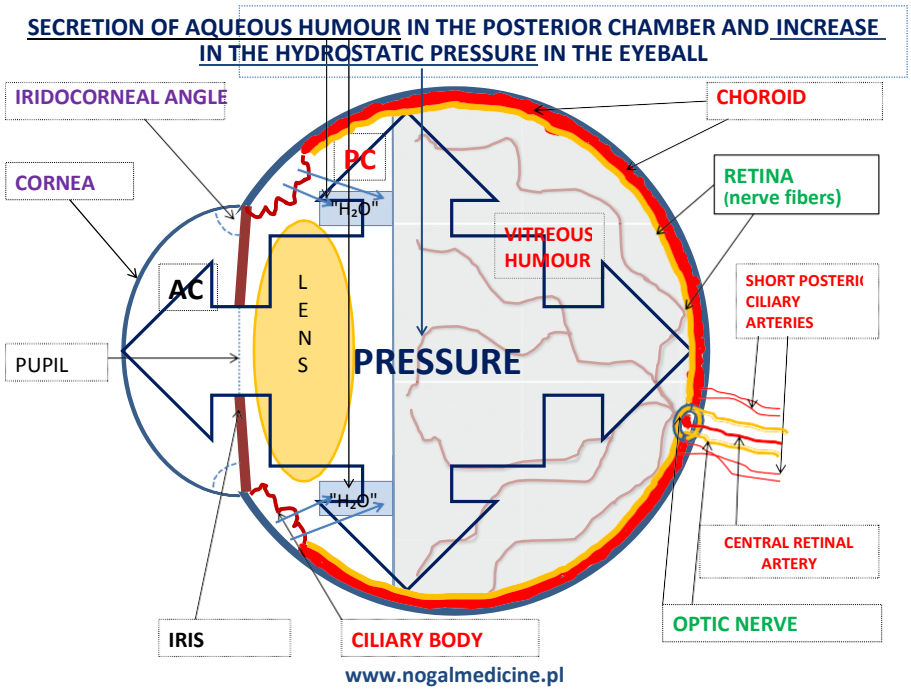
[7] The separation of the posterior chamber from the vitreous humour chamber only with a thin and flexible membrane entitles me to treat in hydraulic respects these two centres closed in the posterior section of the eyeball as a common "posterior segment of the eye", which allowed me to analyse this segment in terms of the assessment of the highest IOP in the posterior section of the eye as a globally clinically important segment, to create a tonometer for this segment and to facilitate further description.

[8] E.g. Haab’s striae, a drop in the number of endothelial cells in mm², Krukenberg’s spindle in pigmentary glaucoma, or corneal pachymetry and the still prevailing measurement of intraocular pressure on the cornea; Schiötz, an applanate, "puff", etc. …

[9] In German glaucoma is called "der grűner Star", which is "a green starling"; in the meaning of "green blindness" (in Polish everyday speech there is a saying “ślepy jak szpak” [*in English literally: “blind as a starling”*], apart from a more frequent one in Polish: “ślepy jak kret” [*English: “blind as a mole”*]).

The mechanisms indicated above show that the eyeball may not be treated statically when attempting to analyse processes occurring in it. The eye is a very dynamically[10] changing organ, with the most important role being played by both hemodynamic parameters of the circulatory system and the vegetative nervous system.

SLIDE No. 2: Abnormally equal hydraulic conditions in both chambers of the eye



On slide no. 2 I marked the most important parameter that regulates the flow of aqueous humour in the eyeball, of axoplasm within the axons of retinal nerve fibers and of blood through the intraocular vessels; **intraocular pressure (IOP)**. The pressure marked with a quadruple arrow increases with the secretion of the aqueous humour into PC by the ciliary body, and on the above drawing it applies in the same way to the entire eyeball: the "anterior segment" (AC) and the "posterior segment" (PC and VHC). It should be noted that only in an unnatural offset of the lens rearwards from the iris and ignoring differences in hydrostatic pressure it has the right to be alike in both segments of the eye and to influence on the entire eyeball with a similar force according to Pascal's law, which causes that the ease of the outflow from AC through the iridocorneal angle outside the eyeball has the right to regulate the IOP throughout the eyeball. Meanwhile, in different segments of the eye this pressure depends on the varied physico-chemical characteristics of the fluids that fill all the chambers of the eye, i.e. on the specific weight of the vitreous body (gel, more dense than water; heavier than water), sometimes on different densities (weights) of the aqueous humour in AC and PC and on the amount of aqueous humour secreted by the ciliary body into PC, on its individually variable viscosity, and therefore on the ease of its outflow through the pupil into AC and next from AC into the system of extraocular veins, and further from the orbit into the cavernous sinuses, into the venous system of the brain, into the internal cartoid vein, into the subclavian vein and further...[11] However, let us focus on the pupillary block, which, in my opinion, is the most common cause of the clinically significant increase in the intraocular pressure (IOP), which I believe is the hidden increased PS IOP (posterior segment intraocular pressure)[12].

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[10] E.g. during response to adrenaline in splits of seconds! : mydriasis, eyelids retraction, exophthalmos (thus in everyday speech there is a saying "strach ma wielkie oczy" [*in English literally: "fear has big eyes"*]) and sudden increase in the secretion of the aqueous humour by the ciliary body due to the response of multiple β-receptors contained in it.

[11] Increased venous pressure on any of the sections of the venous outflow of the aqueous humour from the eye may obviously result in the increased IOP because of the extraocular block of the outflow from the eyeball, e.g. in case of arteriovenous fistula in the cavernous sinus, or even due to neck compression caused by a too tight collar of a shirt and a tie (see: "Basic and clinical science course, Section 10; Glaucoma" / 1st Polish edition edited by Prof. Maria Hanna Niżankowska; Tables 2-3, p. 32)

[12] So far measuring IOP on the cornea, that is in AC as the one related to it anatomically and physiologically, we subscribed to the view that IOP in AC and in PC is almost always equal, which provided that in physiological conditions we could recognize the trabecular meshwork in the iridocorneal angle, or a narrower angle as well, as the point of the largest resistance for the outflow of the aqueous humour from the eye. However, my research, treatment and analysis of patients with closed angle glaucoma and migraine and my full description of the mechanism of the aqueous humour outflow from the eye (the paper "POLAND"; publication coming soon) all require me to recognize this point to be the "pupillary valve" (the meeting edge of the iris and the lens), which significantly separates PC from AC, reduces the humour flow into AC and accumulates the pressure in PS (PC and VHC).

Only the eyeball presented in this way (with an idealised communication between AC and PC not blocked by the lens) provides that the IOP measurement taken so far on the cornea could be prominent and almost objective for the entire eye. But even in such ideal outflow conditions a difference in pressure occurs between PC and AC because of the secretion of the aqueous humour into PC and its outflow into AC through the pupil, which is determined by a simple outflow mechanism, since when two limited segments of a particular pressure are combined, liquid can outflow only from a centre of a higher pressure into a centre of a lower pressure[13]. In the eye we are dealing with a situation in which the flow from PC to AC through the pupil is not only forced by a pressure gradient between the chambers, but also it is regulated, inter alia, by a variable intensity of pupillary block, always limiting this flow to some extent, and by filling intraocular vessels, which raises the pressure behind the lens and iris even further, increasing the gradient between the chambers of the eye. On the above slides you will not see all the values of the variables regulating pressure in the eyeball (e.g. the arterial pressure, the degree of choroid filling, the individually variable consistency of the aqueous humour in the posterior chamber, or the resistance in the outflow in venous vessels outside the eyeball). The most important local variable in the analysis of the problem in question is IOP shown in both segments of the eye, the anterior and the posterior ones, which fluctuates depending on such intraocular factors as:

1 the difference in density of the vitreous humour and the aqueous humour, which determines variable hydrostatic pressure in the posterior segment of the eye,
2 individually variable viscosity of the aqueous humour, which determines variable hydrostatic pressure in PC, variable ease in the outflow from PC to AC and variable hydrodynamic pressure of the aqueous humour in the pupil[14],
3 varied physico-chemical characteristics of the aqueous humour in AC and PC[15],
4 variable production rate of the aqueous humour in PC,
5 variable ease in the flow of the aqueous humour from PC to AC through the pupil, which is determined by the degree of intensity of the pupillary block and the viscosity parameters of the aqueous humour,
6 variable shape of the lens[16], which determines the variable intensity of pupil blocking,
7 variable ease in the outflow of the aqueous humour from AC through the trabecular meshwork outside the eyeball, which determines pressure in the anterior chamber and diversifies the AC ≠ PC gradient from the front.

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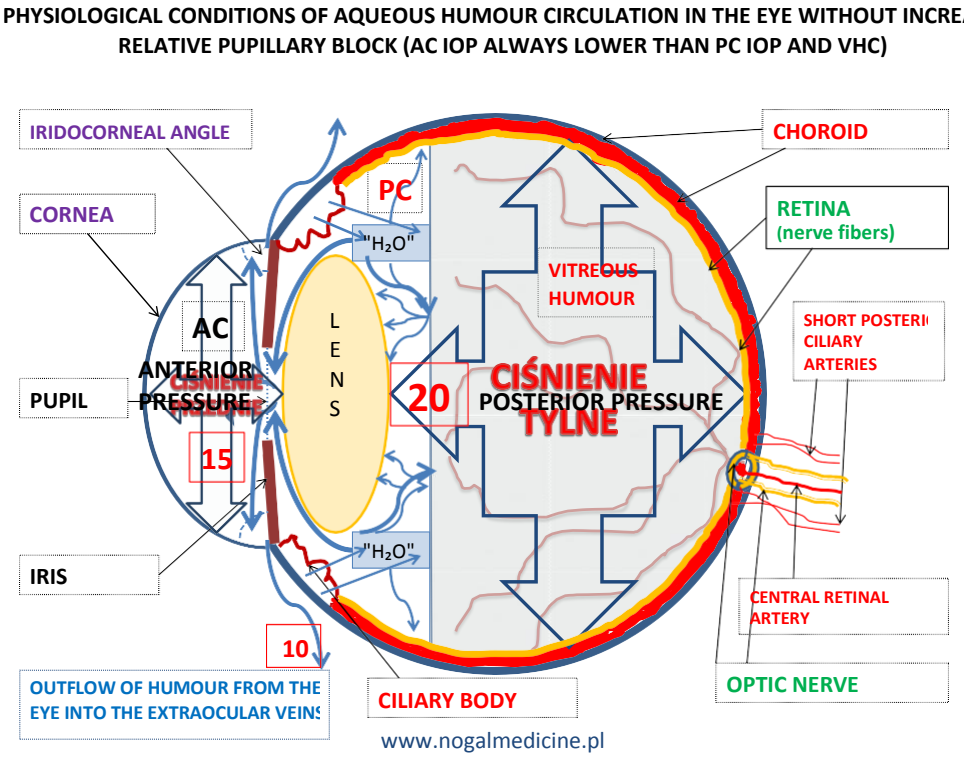
13 I am writing here about a passive outflow, which I mention to stay ahead of the speculations of "physicists", the discussion with whom would have to bring a compromise that the humour may, for example, be actively transferred despite the pressure gradient, which, all in all, consists in producing an increased pressure, e.g. by a pump, in the centre of an initially lower or equal pressure and exercises the simple law of physics I mentioned here that can be observed e.g. on a punctured ball with an unblocked hole from which air escapes outside until the pressure inside it equals the atmospheric pressure. When inflating a sealed ball, pumping air inside is possible only if pressure in the pump is higher than the one inside the ball.

14 During laser iridotomy different density and viscosity of aqueous humour is observed; sometimes the aqueous humour flows with difficulty through the hole in the iris into AC and looks more like transparent glue or frog spawn rather than water (gel-like fluid with suspended pigment from the iris pigment epithelium; author's observation and term). My attention to this long-observed but not noticed by us problem was drawn by one of the leading and, according to many of us, including myself, most progressive glaucomatologists in the world - Professor Marek Rękas from the Ophthalmological Clinic at WIM in Warsaw during a symposium in Ossa near Warsaw organized by him and the medical team of the Ophthalmological Clinic at the Military Institute of Medicine in September 2013. During a lecture he told about the examination of aqueous humour collected intraoperatively from glaucomatous patients, which was significantly individually varied in terms of physico-chemical properties.

15 If aqueous humour always had the same consistency in both chambers of the eye, during blasting a hole in the iris with laser in iridotomy we would not be able to observe the thick stream or thick blister of aqueous humour in the less frequent aqueous humour of the anterior chamber. When properties of the aqueous humour in AC and PC are similar, we only observe pigment discharged into AC, which immediately begins to spread in AC and is not suspended in the gel near the hole in the iris!

16 A human lens is the only anatomical element in the skull that grows physiologically throughout the life (next layer every 6 months; similar to the growth of rings of a tree trunk), which with age aggravates the risk of the increased pupillary block complicated by e.g. a "primary" closed angle glaucoma attack.

SLIDE No. 3: Division of intraocular pressure into "anterior" (in the anterior chamber of the eye) and "posterior" (in the posterior chamber of the eye)



The arguments developed above, based on the basic laws of physics related to the flow of fluids, eye anatomy and the physiology of production and outflow of the aqueous humour from the eyeball, entitle me to divide intraocular pressure into the anterior (for AC) and posterior (for PS: PC and VHC) ones[17]. Therefore, on slide no. 3 I marked two different intraocular pressures, i.e. "anterior pressure" (symbolic 15mmHg) and "posterior pressure" (symbolic 20 mmHg), even though on the drawing between the lens and the iris I maintained a clear space in order to show the direction of the aqueous humour flow. However, this space is actually never clear. The lens always adheres from the back to the iris and the humour must get through to AC between them, which further increases the gradient value of the pressures between the chambers of the eye. By the way, it is worth mentioning that it is physiologically correct that the aqueous humour outflows from the PC into AC variably easily[18] both in the eyeball position through the cornea and through the bottom of the eye downwards (the head is positioned face down or up)[19]. The same happens with the outflow from AC into episcleral veins in which pressure must be lower than in AC (on the slide it is 10 mmHg).

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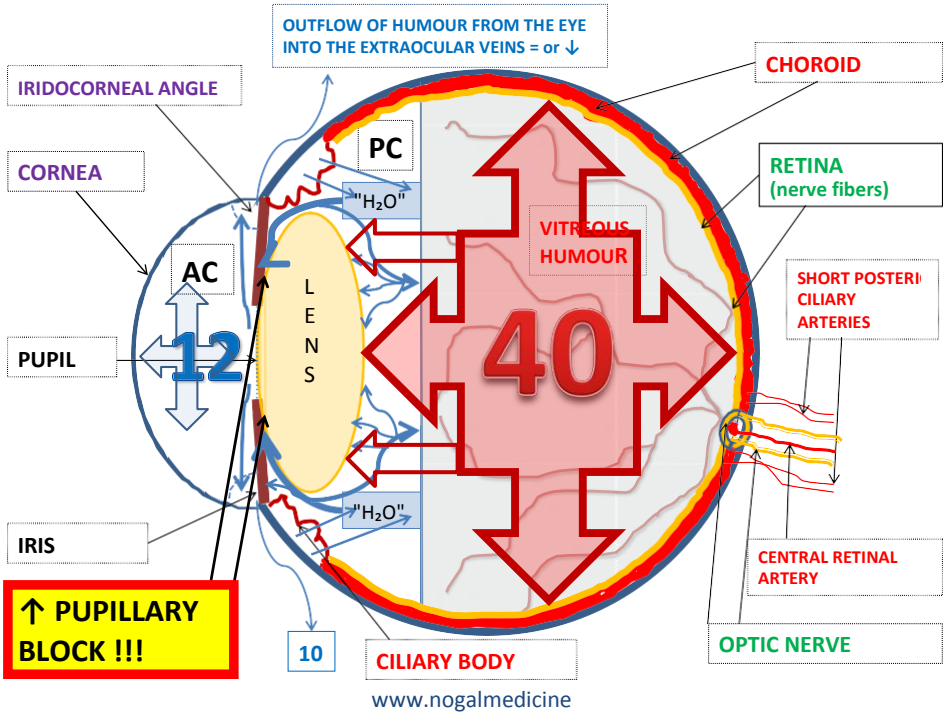
[17] The impermeability of the lens-iris diaphragm and pressure differences between the two segments of the eye (anterior-AC, posterior-PC and VHC) can be seen in many situations in ophthalmology, e.g. during dynamic gonioscopy. The cornea, when pressed with a Zeiss gonioscope, causes the compression of aqueous humour in AC, which forces the lens-iris diaphragm backwards because of the speed limitation of the outflow through the trabecular meshwork; especially the juxtacanalicular meshwork, not unsealing the pupil, though. Most energy of the backward pressure wave in AC triggered by the excessive gonioscope pressure on the cornea distorts the previously convex iris, allowing us to see the place of its attachment. This is because the lens pressed from the back by posterior pressure higher than in AC does not make the diaphragm unsealed, effectively blocking the pupil from the back.

[18] If the eyeball is positioned with cornea down, the pupil is blocked from the top much more by the lens that is forced from the back (in this position from the top) with its own weight and the weight of the vitreous humour, just like a "bathtub drain stopper by water filling the bathtub; it is not easy to push the stopper out of the bathtub when it is filled with water... and the eye is filled at the back with a much heavier gel..." the hydrostatic pressure of the vitreous humour! With this head position (face-down) my migraine patients demonstrate immediate headache and migraine symptoms intensity, which proves the migraine mechanism described by me! Paradoxically, it is more difficult for the aqueous humour to outflow when the anterior chamber is positioned lower than the posterior chamber, which is not unreasonable in the eye and proves the excellence and not the blemishes of nature; I will explain why it is so soon (author's observation and comparison).

[19] The mechanism of the aqueous humour outflow from the eye ("POLAND") described by me explains how it happens that any eye position does not block the outflow of the aqueous humour from it despite the changing gravitational loads forced by different eyeball and body positions, which after all determine variable values of both static and dynamic pressure concerning both blood and aqueous humour.

SLIDE No. 4: Pupillary block; pressure drop-AC and pressure increase-PS



To advocate my thesis that the place of the greatest resistance for the aqueous humour in the eye in physiological conditions and in conditions related to primary open-angle glaucoma is actually the "meeting edge of the iris and the lens" (the lens-iris diaphragm; "pupillary valve") even only in relative pupillary block, but not trabecular meshwork in the iridocorneal angle, as it has been maintained so far, I marked such a block with its intensity on **slide no. 4**. This phenomenon leads to a reduction in the flow of aqueous humour from PC through the pupil into AC (thick blue arrows do not pass through the pupil into AC), which causes a drop in AC IOP (sometimes down to the value of pressure in the veins draining water from AC outside the eyeball; normally 5-12 mmHg (symbolic "12") and an increase in PC IOP due to the compression of aqueous humour in it, which is produced continuously by the ciliary body, with the transfer of this pressure onto the vitreous humour that presses the bottom of the eye (symbolic "40"). This in turn causes an increased pressure on the lens, which is forced by PS overpressure (PC and VHC) into the pupil from the back (small blue arrows of the aqueous humour pressure and red transparent vitreous humour pressure)[20], additional intensity of pupillary block and increased pressure on the vitreous body, transferred through it, as if it was through an oil piston, to the bottom of the eye, including on the layer of retinal nerve fibers, on the optic nerve head and on the intraocular vessels (the central retinal artery and vein and the choroid). In such a situation we often measure low IOP on the cornea using existing tonometers, not being aware that behind the lens and iris there remains a hidden intraocular overpressure[21].

On slide 4 you can also see reduced venous outflow from AC into episcleral veins (thin arrows and number 10 expressing pressure in extraocular veins (in mmHg), into which aqueous humour escapes).

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[20] The aqueous humour pressure spreads in the posterior chamber according to Pascal's law equally in all directions and with the same force it presses all PC limitations (the ciliary body, iris, lens and vitreous humour; on slide 4 an illustration of this phenomenon was intentionally omitted so as not to make the diagram blurred), and additional red transparent arrows indicate the increased direction of pressure of the vitreous humour having the hydrostatic pressure increased by the aqueous humour, which encounters resistance of the rigid bottom of the eye when pressing backwards and sideways. This causes a stronger impact on a more flexible lens-iris diaphragm with tension of the iris and Zinn's ciliary zonule and even stronger "forcing the lens from the back into the pupil", i.e. The increase in the pupillary block, which further raises the pressure in the posterior chamber and vitreous humour ("vicious circle").

[21] Observation of migraine patients and patients with "normal" pressure glaucoma and with primary closed angle glaucoma helped me to describe the mechanism of migraine, dependent on the pupillary block, which leads to an increase in IOP in the posterior segment of the eye and IOP being equal to the low blood pressure in the choroid, which leads to even greater intensity of the pupillary block with even greater increase in IOP in PC and VHC ("vicious circle"). It is the increased IOP that is, in my opinion, the only triggering and direct stimulus of glaucoma and the migraine mechanism described by me in the presence of intensified pressure on the bottom of the eye with its nerve fibers (loss of optic nerve) and blood vessels (periodic arterial and venous hypertension in the skull; so far the "idiopathic intracranial hypertension"- IIH, with numerous nervovascular conflicts; definition of Migraine by Nogal: **MIGRAINE** - **M**ultiple **I**ndisposition **G**enerated **R**apidly **A**gainst **I**ntraocular pressure increase to **N**eurological **E**mergency).

This situation means that measurements of IOP on the cornea should make us ask ourselves a question about the point in having monitoring of glaucoma treatment based on such a measurement and in case of "normal" pressure glaucoma (with pressure so far being measured on the cornea, i.e. concerning AC and not PC) they should keep us alert and force us to **seek increased IOP in the posterior segment of the eye (PC and VHC), which is actually where the increased IOP is the main pathogen of the glaucomatous process because there are nerve fibers located out there, which in glaucoma undergo atrophy**. In such a situation measuring low AC IOP of a value close to the normal venous pressure in veins, to which the aqueous humour outflows from AC, with progressing damage of the optic nerve and often palpably hard eyeball in my opinion tells us to maximize the glaucoma treatment in order to reduce the "posterior pressure" in the eyeball (PS IOP) regardless of the measurements on the cornea. Pressure reduction in AC down to a value less than 12 mmHg with simultaneous progression of glaucoma actually constitutes, in my view, at least a suspicion, if not a proof, of the increased "relative"[22] pupillary block with limitation of the aqueous humour flow into AC and IOP accumulation behind the lens and iris with increased pressure on the bottom of the eye and all of its structures. Especially in a situation where minor haemorrhages can be observed on the optic nerve disc, which are, in my opinion, the evident effect of a blood vessel compression due to increased IOP and blood pressure cracks due to increased blood pressure.

Question 1:
Do measurements using the existing tonometers give us objective results in terms of determining the pressure in the entire eyeball?

NO! So far existing tonometers have been measuring intraocular pressure (IOP) on the cornea, which always refers to IOP of the anterior chamber of the eye (AC) and only, **if necessary**,[23] IOP behind the lens and iris, i.e. in the posterior chamber (PC) and vitreous humour (VHC). Nota bene, it is, in the "posterior segment of the eye" (PS), where nerve fibers are located at the bottom of the eye, damaged in glaucoma according to the "theory of mechanical atrophy of the optic nerve" due to the most important risk factor of this disease, which is increased IOP. This is where blood vessels are located, which are associated with glaucoma according to the "vascular theory of optic nerve damage"[24]. However, in cases of an increased relative or absolute pupillary block (occasionally in such situations as iris and ciliary body inflammation complicated with peripheral posterior synechia or in rare cases of closed angle glaucoma clamp attack with an impermeable separation of the pupil in low IOP in PC) IOP becomes substantially reduced in PC with a clinically significant pressure increase behind the lens and iris, i.e. in the "posterior segment" (PS), as I named PC and VHC altogether[25].

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[22] I put the word "relative" for pupillary block between quotation marks because during observation of migraine and glaucoma patients it turns out that only the relative intensity of this block can be clinically absolute for a suffering person. In the current ophthalmological nomenclature there is a division of pupillary block into relative, which does not completely block the pupil, and absolute, which causes the separation from the pupil, i.e. a total block of the flow through it. In my opinion, in case of an eye with a lens and a correct iris we always deal with a relative pupillary block, which may be increased either moderately or extremely till reaching the absolute pupillary block.

[23] This does not happen in physiologically functional eye; the lens always remains in contact with the iris, blocking to some extent the flow of the aqueous humour through the pupil, and the differences in pressure values between the chambers prove the direction of the humour flow through the pupil; from the back to the front, which means the pressure at the back is always higher than at the front. This happens even in the event of a patent iridotomy and iridectomy, although in this case the pressure gradient may not be large.

[24] Personally, I agree on both theories, because like other ophthalmologists, I believe that both mechanisms contribute to the glaucomatous loss of optic nerve, except that **I am quite certain that low arterial pressure has only an indirect effect on the loss of optic nerve**. The mechanism of migraine (the paper "MIGRAINE") and the mechanism of the aqueous humour outflow from the eye (the paper "POLAND") described by me prove that low arterial pressure, very often (almost always in migraine) along with increased intraocular pressure, due to the mechanism of equalisation of intraocular pressure and blood pressure in the choroid and in intraocular arteries, bring a "vicious circle" response, which results in the increase in intraocular pressure clinically significant for both glaucoma and migraine. And it is the **increased IOP in PC and VHC that is, in my opinion, the most important, direct pathogen of glaucoma!** Both the retinal nerve fibers and the optic nerve head undergo, in my opinion, reverse changes under the influence of too high PS IOP that is equal or higher than the pressure in the choroid, which is facilitated by the originally low arterial pressure.

[25] In my view, we can treat these two centres closed in the posterior segment of the eye (the posterior chamber, filled with aqueous humour, and the vitreous humour, separated from the posterior chamber with a very thin and flexible anterior limiting membrane, not constituting **a clinically significant physical barrier for the pressure gradient between these centres** when IOP is compressed in PC, equalling PC pressure with originally higher pressure of the vitreous humour, and then exceeding it with pressures of both these centres growing along together) as one centre during intraocular pressure measurements in order to determine the maximum residual pressure in this common segment separated with the lens and iris from the front, with the ciliary body from one side and with the bottom of the eye from the back. The vitreous humour, being a centre of a much greater density than the aqueous humour, may be characterised, according to hydraulic principles, with pressure greater than or equal to the pressure of the aqueous humour in PC, both in a situation without and with increased pupillary block. At the same time this means that the measurement of the highest pressure in the posterior chamber can be taken indirectly along with the measurement

This is due to the aqueous humour outflow through the pupil being blocked by the lens from where it is produced, i.e. from PC to AC. While discovering and describing the mechanism of migraine, I noticed that even only the relative pupillary block, i.e. partially restricted flow of aqueous humour from PC to AC, may cause a clinically significant pressure increase in the posterior chamber of the eye (PC) when normal pressure is measured in AC. So we are dealing with a situation in which IOP measured in AC (on the cornea) using existing tonometers has probably nothing to do with IOP in the posterior segment of the eye, which makes this measurement non-objective. This is because we measure the pressure in the segment (AC) having completely different physical parameters from the "posterior segment of the eye" (PC and VHC), which is directly related to the most important risk factor of these disorders, i.e. the increased intraocular pressure behind the pupil. A device that measures this parameter is the first in the world Non-Invasive Tonometer for the Anterior Chamber and/or the Vitreous Humour of the Eye designed by me.

Question 2:

Are measurements using these devices useful diagnostically in glaucoma and in other clinical situations related to the increase in the pupillary block?

Of course they are! To me there are, however, not many situations in the treatment of glaucoma when these measurements give us almost objective information on the residual pressure in the entire eyeball. They include e.g. the condition after iridotomy surgery (a hole in the iris that facilitates the flow of the aqueous humour from PC to AC) when its patency is maintained (not always![26]), the complete angle closure in a standard glaucoma attack, or synechiae in the angle with subsequent equalisation of pressures in both chambers. There are also situations that, due to extremely low pressure measured on the cornea (refers to AC) and clinical indirect evidence for the existence of pupillary block (e.g. hard eyeball with low pressure measured using an applanate in rare cases of a primary closed angle glaucoma attack), make us suspect the increased pupillary block. But we have to be aware that until a tonometer measuring IOP "at the back" is created all measurements on the cornea, i.e. those related to AC, bear signs of highly probable subjectivity and lack of relevance to the residual pressure in PC.

I also managed to develop a non-invasive method of checking the individual inclination to an increase in the pupillary block based on measurements taken using an applanate, i.e. a tonometer measuring the anterior pressure of the eye (AC IOP)[27].

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of the pressure in the vitreous humour chamber. In my view, in clinical aspects the most important parameter in the diagnostics of glaucoma is not IOP in the posterior chamber..! but the vitreous body pressing the bottom of the eye, intensified by the increased PC pressure, and expressed in the hydrostatic pressure of the vitreous body (the important thing is the compression of the structures of the bottom of the eye caused by pressure; see the "mechanical theory" of glaucoma). The vitreous body acts as an oil piston, which transfers the variable pressure created by the aqueous humour in the slit-shaped PC to the bottom of the eye with its structures (retinal and choroidal vessels, retinal nerve fibers and the optic nerve). Owing to the low compressibility of the gel-like vitreous body (just like oil in hydraulic installations), even minimal and very quick changes in pressure in the slit-shaped posterior chamber are transferred immediately to the bottom of the eye, which is compensated only to a minimum extent and for a short time by the variable capacity of PC dependent on the flexibility of the iris and the sclera in the PC and VHC projection on the wall of the eyeball and on the stretchability of the Zinn's ciliary zonule ligaments. The two centres (PC and VHC) of different density closed in one posterior segment of the eye with dynamically regulated pressure in one of them (the PC pressure regulates the total PS pressure due to changes in the production rate of the aqueous humour, its varied consistency and ease of its outflow into AC) constitute a mechanism similar to a hydropneumatic sphere of a genius motor vehicle suspension system designed by an engineer from Citroen and his team (there, by contrast, the total pressure inside the sphere is regulated by the varying pressure of the oil, i.e. the centre of a density greater than the compressed nitrogen locked together with it).

[26] While performing laser iridotomy surgery currently does not constitute a problem for us by technical means (I have also performed dozens of surgeries in patients with very difficult irises; Afro-Americans, Asians and patients with light-shaded irises, the stroma of which resembles transverse optical fibers that reflect the laser light), maintaining the iridotomy hole patent is always a challenge for us. I have noticed that despite intensive steroidal treatment applied prophylactically even before YAG-iridotomy, the iridotomy hole becomes very often overgrown with a thin "cellophane" film even within several dozen minutes after the surgery... This phenomenon perfectly corresponds to the question raised a few years ago in public at the ophthalmological symposium by Professor K. Pecold. She asked Professor M.H. Niżankowska if she "didn't think that the traditional treatment of glaucoma using surgical iridectomy many times turned out to be a lot more effective than the YAG-iridotomy (laser) treatment, as it was indicated by her observations related to hindering the progression of loss in the visual field after the operation, which is often unattainable when using a laser". (I heard that question many years ago; if my memory serves me well, it was during the 1st Silesian Retina Meeting 2010 in Katowice and so I may not quote exactly, but when recalling that situation I tried neither to commit an abuse nor to provide Professor Pecold's utterance in a way that diverges from the meaning of the question).

[27] I invented 2 non-invasive methods of indirect assessment of the inclination to pupillary block and the place of the greatest block of the outflow of the aqueous humour in the eye, which I hope to present during one of the next ophthalmological symposia (LNT - "Light Nogal Tonometry", based on the measurement of pressure in the eyeball using an applanate, and FNG - "Flash Nogal Gonioscopie").

In terms of obtaining an objective IOP measurement in glaucoma, we must not forget about the anatomy and physiology of the eye. It draws our attention that all structures involved in the glaucomatous process with "normal" IOP ("primary"[28] open-angle glaucoma) are behind the iris and lens, i.e. in the segment related to the posterior chamber and the vitreous humour of the eye. This means an interesting quantitative comparison of the presence of nervous and vascular structures, which determine the process of "manufacturing" intraocular pressure and are involved in the loss of optic nerve between the two segments of the eye, i.e. the anterior chamber and the "posterior segment" (posterior chamber and vitreous humour chamber):

Table 1: Quantitative comparison of the presence of anatomical structures of the eyeball involved in primary open-angle glaucoma with "normal" pressure in both segments of the eyeball.

ANATOMICAL STRUCTURE	ANTERIOR CHAMBER	POSTERIOR CHAMBER AND VITREOUS HUMOUR CHAMBER
RETINAL NERVE FIBERS	0.0	1.0
OPTIC NERVE	0.0	1.0
CHOROID	0.0	1.0
CILIARY BODY	0.0	1.0
CENTRAL RETINAL ARTERY	0.0	1.0
TOTAL	**0.0**	**5.0**

In this comparison AC looks manifestly pale, in which so far we have actually measured the intraocular pressure, which is a direct and most important causal factor of the loss of glaucomatous optic nerve according to the "mechanical theory" of glaucoma, which suggests that retinal nerve fibers and the optic nerve are compressed by intraocular overpressure where they actually are located, i.e. in the posterior segment of the eye, which are after all related to PC and VHC, and separated from PC with variable intensity by a "pupillary valve" (the lens in the pupil). Therefore, it becomes obvious that we should not relate measurements of the intraocular pressure taken on the cornea in AC, which has no structures damaged by pressure, to the pressure in the posterior chamber and vitreous humour chamber, which do have these structures[29].

Meanwhile, the following slide no. 5 shows how to measure IOP using an applanate, which so far has been a "gold standard" in the diagnostics and monitoring of intraocular pressure in glaucoma... in each type of glaucoma... irrespective of the angle status or the suspicion of increased pupillary block. An applanation tonometer, considered by many as the most accurate eye pressure measuring device, measures this pressure on the cornea, which constitutes a wall only for the anterior chamber of the eye. And it would probably remain as such in relation to the entire eyeball, provided that measurements were taken in the condition free from the pupillary block if the assessment of the block was relatively easy and objective. Whereas the non-invasive assessment of the degree of pupillary block is unfortunately neither easy nor objective (see: guidelines of the European Glaucoma Society for laser iridotomy from 2009 and footnote no. 27).

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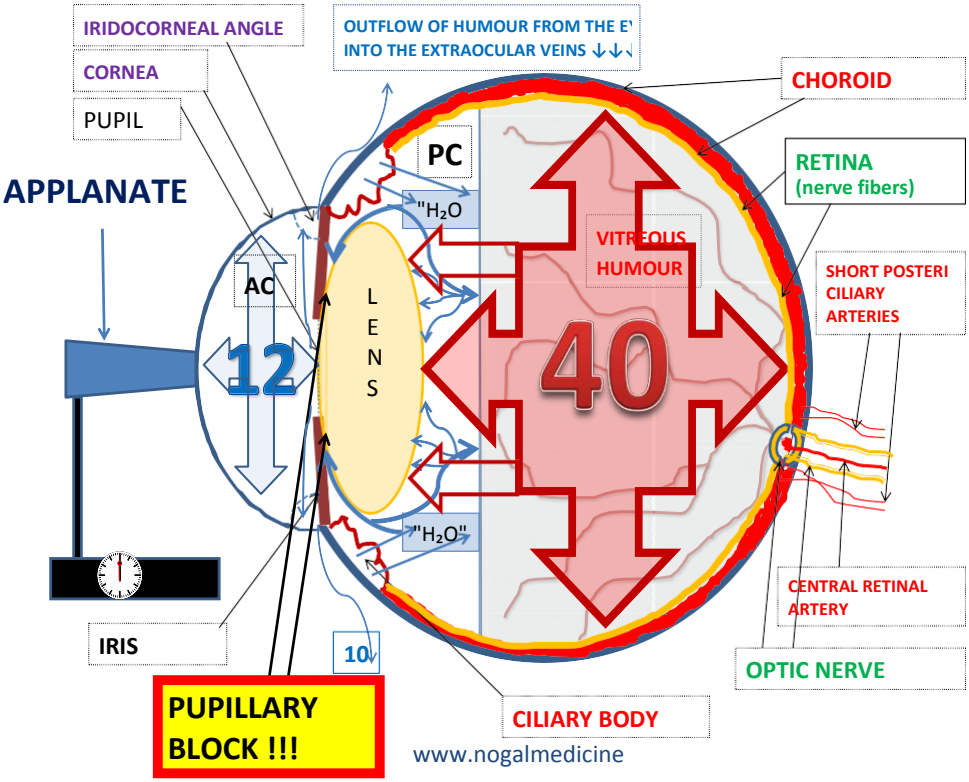
[28] I intentionally put the word "primary" (meaning idiopathic), i.e. out of nowhere, between quotation marks because I do not believe any disorders of a living organism are without an existing cause. Finding increased intraocular pressure in this "primary" glaucoma of "normal" pressure would mean the discovery of the most likely cause of glaucomatous damage and unravelling of another pathophysiological mystery that actually shows how poorly we can deal with advances in medicine, despite the fact that it is totally technologically advanced; tomographic devices, magnetic resonance tomographs, ultrasonography, endoscopes, etc. ... If these devices had fallen into the hands of founders of medicine, who used to invent and describe the potential mechanism first and then build needed measuring devices to prove it, medicine these days would probably be a thoroughly described, boring and unoriginal field, which it definitely has not been so far... Strangely enough, the pupillary block has been known in ophthalmology for over a century and yet so far few institutes have pointed out the need for measuring pressure in the posterior section of the eye...

[29] The author is aware of the number of repetitions of the description of measuring intraocular pressure in AC, and not in PC and VHC, and wilfully allows this stylistic device in order to attract the reader's attention to this amazing fact, which means that subsequent generations of ophthalmologists have wrongly believed in the diagnostic effectiveness of the prevailing measurements of intraocular pressure on the cornea and of the treatment based on this diagnostics, which often proves to be simply inefficient (target pressure after treatment is "perfectly" low, but patients are going blind!; see quotes by Authorities in the introduction to this paper).

SLIDE No. 5: Measurement of intraocular pressure using an applanate in case of increased pupillary block; pressure drop-AC + pressure increase-PS = the result of measurement on the cornea is falsely understated in relation to the increased pressure in the posterior chamber and vitreous humour chamber (measurement irrelevant to the residual pressure in the the eyeball behind the lens and iris!!!)



Therefore, pressure in the anterior chamber of the eye is measured in this way. In view of the eye anatomy and the physiology of the aqueous humour outflow, in a small percentage of cases it probably remains only close to the residual pressure in the most interesting for us, in terms of increased pressure, segment of the eye, that is the "posterior segment", along with its posterior chamber and the vitreous humour chamber and all the structures observed in the eye that are suspected of cause-effect relationship with primary "low" pressure glaucoma. This is both in terms of the "mechanical" (a layer of retinal nerve fibers and the optic nerve) and the "vascular" (nerve + blood vessels) theory of the optic nerve damage.

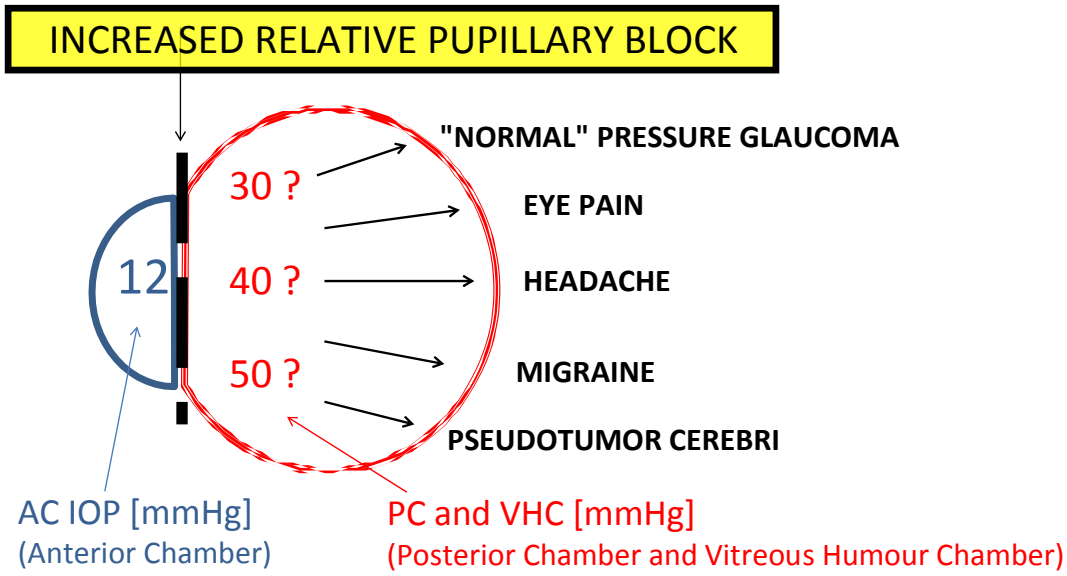
Question 3:
What is the evidence that intraocular pressure measured so far in the cornea is often inadequate to the most important risk factor of glaucoma, which is the increased pressure in the posterior chamber of the eye and the vitreous humour chamber?

The main argument in such an analysis are simple laws of physics that govern the physiology of the aqueous humour flow in the eye from PC through the pupil into AC and further from the eye into the episcleral veins. When segments (AC and PC) are in interaction, the fluid can flow through the pupil only according to the pressure gradient, i.e. from the chamber with higher pressure into the chamber with lower pressure. Whereas if the flow is blocked, pressure in PC must be increased due to continued production of the aqueous humour in it and blocking the outflow from it. Therefore, the analysis of the aqueous humour circulation in the eye is the proof that pressure in the posterior chamber and vitreous humour chamber must remain higher than the pressure in the anterior chamber, both in physiological situations and those related to the increase in the pupillary block.

Unfortunately, the pressure gradient value is unknown and may change depending on the increase in the production rate of the aqueous humour in PC and/or on the intensity of the pupillary block in the outflow of this humour.

Measurement of the pressure difference will probably be enabled by the tonometer of posterior chamber and vitreous humour of the eye biult by me, which in the "puff" version, measuring immediately pressure in AC, will give automatically the value of this gradient, specifying the "ease of pupillary flow" (the parameter proposed by the author). However, we can guess that pressure differences in both chambers are often very big. It is also obvious that it is the increase in the pupillary block that is able to rapidly increase the value of the pressure in PC and VHC (PS - "posterior segment"), as indirectly evidenced by the occurrence of a primary closed angle glaucoma attack in patients undergoing maximum hipotensive treatment for glaucoma, hindering the production of aqueous humour in the eye.

The existence of a huge difference in pressure values in both chambers of the eye is evidenced by how the anterior section of the eye responds in the primary closed angle glaucoma attack, during which, because of the pupillary block, the iris becomes so convex considering being pushed from the back by the residual pressure in PC that it closes the iridocorneal angle. Ophthalmologists know many other proofs observed in daily practice, a part of which I present below, presenting a poster prepared by me.



IOP - intraocular pressure

EVIDENCE OF THE PC IOP GRADIENT >>> PC IOP:

- PHYSIOLOGICAL AQUEOUS HUMOUR OUTFLOW FROM PC INTO AC !!!
- "CONVEX", "NON-PHACOMORFIC" IRIS
- ERUPTION OF THE IRIS PIGMENT AND AQUEOUS HUMOUR FROM THE POSTERIOR CHAMBER INTO THE ANTERIOR CHAMBER DURING YAG-IRIDOTOMY
- FLATTENING OF THE IRIS AFTER YAG-IRIDOTOMY DUE TO THE EQUALISATION OF PRESSURES IN BOTH CHAMBERS OF THE EYE
- TEMPORARY INCREASE IN PRESSURE IN THE ANTERIOR CHAMBER AFTER SUCCESSFUL YAG-IRIDOTOMY, INDEPENDENT OF THE NUMBER OF IMPACTS AND THE APPLIED TOTAL POWER OF THE LASER
- "PUSH" MECHANISM OF THE "PRIMARY" ANGLE CLOSURE IN THE PUPILLARY BLOCK
- LOW PRESSURE IN THE ANTERIOR CHAMBER (measured on the cornea) IN RARE CASES OF CLOSED ANGLE GLAUCOMA ATTACK
- AC IOP "VERTICALLY" (WHEN SITTING) ≠ AC IOP "HORIZONTALLY" (WHEN LYING DOWN)
- PALPABLY HARD EYEBALL AT LOW PRESSURE MEASURED ON THE CORNEA (IN THE ANTERIOR CHAMBER)
- "NORMAL" PRESSURE GLAUCOMA ..?
- ... AND MANY MORE KNOWN BY OPHTHAMOLOGISTS...

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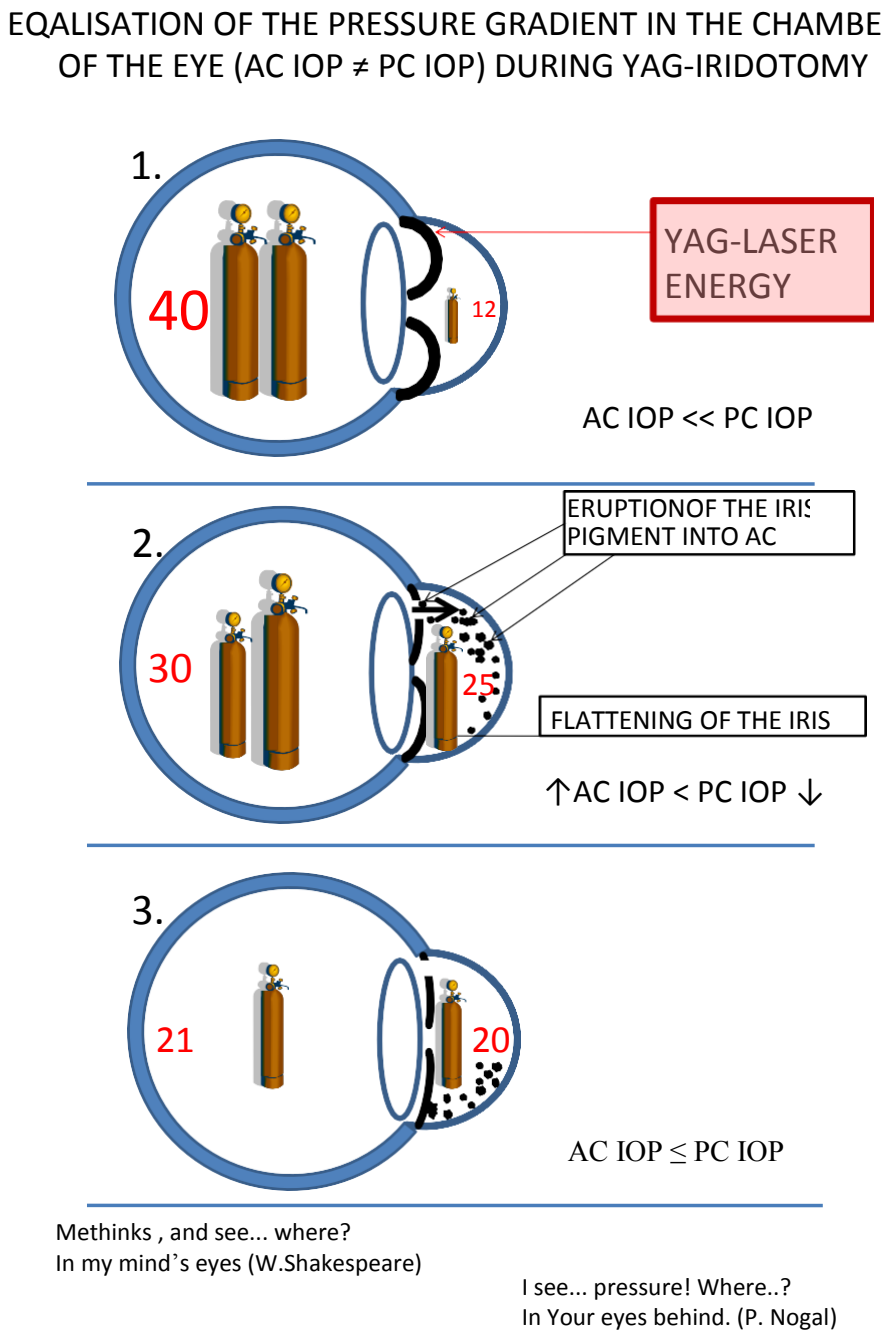
Poster presented by the author during the 6th International Symposium "Advances in diagnosis and treatment of corneal diseases" in Wisła in 2014.

The leading evidence for the existence of the gradient is also the phenomenon of pressures equalisation in both chambers of the eye while the iris is being laser blasted during a laser iridotomy surgery. It is worth mentioning

that YAG-iridotomy is used to treat pupillary block (often also causing the angle closure), and not the closed angle, which is treated during a peripheral laser iridoplasty, which I should like to remind the doctors arguing with me via my patients[30]. During successful perforation of the iris and interaction of both chambers of the eye, the therapist can observe in the microscope rapid aqueous humour escape from behind the iris (PC) into AC with accompanying eruption of pigment from the iris pigment epithelium (posterior layer) into AC. This phenomenon is often observed for not a few, but for up to several dozen seconds after the surgery, seeing the aqueous humour outflow from PC to AC through the hole made in the iris. The equalisation of pressures in both chambers separated by the iris is accompanied by the flattening of the iris (the previously convex iris collapses backwards like an open sail in the wind). The above phenomenon is presented on the following poster prepared by me for the International Symposium of Corneal Diseases in 2014 organised annually by Professor E. Wylęgała and his Team.



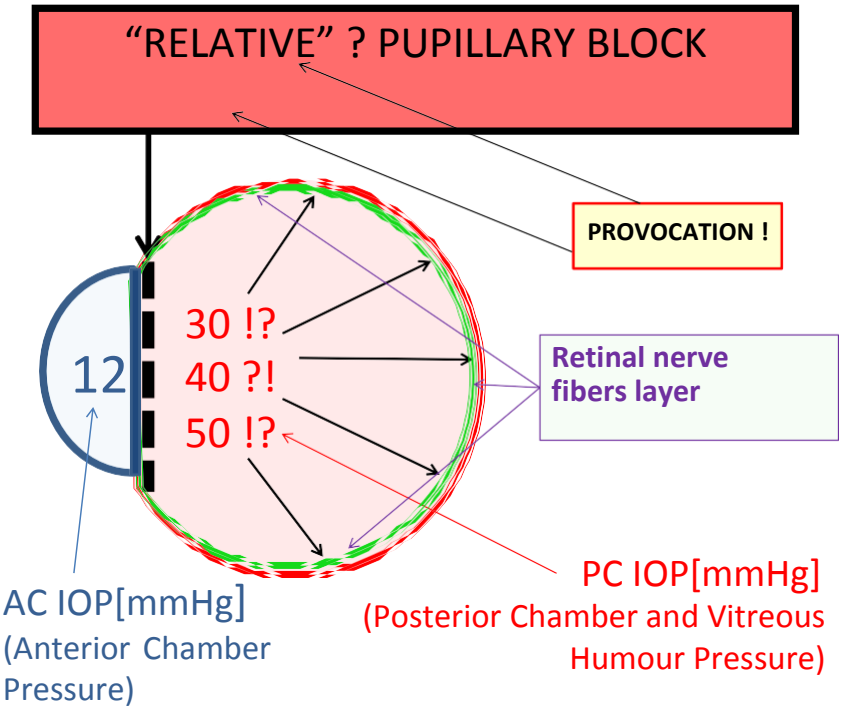
Poster presented by the author during the 6th International Symposium "Advances in diagnosis and treatment of corneal diseases" in Wisła in 2014.

[30] Both surgeries along with indications and technique for their performance are perfectly described and depicted on illustrations by Doctor J. Jurowska-Liput in the book by Polish Authors: Prof. M.Misiuk-Hojło and Doc. Ł. Szelepin; "Laser therapy for glaucoma".

Question 4:
How to find increased intraocular pressure in "normal" pressure glaucoma?

How to find **high IOP** in <u>"Normal"</u> Pressure Glaucoma?

Look for it where it is essential for the glaucomatous optic nerve atrophy ... In the **posterior chamber** and **vitreous humour chamber**...



...and we'll discover the expected!

Poster presented by the author during the 6th International Symposium "Advances in diagnosis and treatment of corneal diseases" in Wisła in 2014.

The prevailing measurements of pressure “at the front” (on the cornea; AC) as well as research and treatment of glaucoma based on these measurements in my opinion were very often an error that being unrecognised led to the situation that in subsequent tens of years the issue of physiological block of the outflow through the "pupillary valve” (the lens in the eye) was overlooked in ophthalmology. This block led in the way described by me above to an increase in the pressures gradient between the chambers of the eye. Even in the best publications concerning glaucoma and discussing the issue of production of the aqueous humour and its outflow from the eye, the issue of the flow of aqueous humour through the pupil is almost entirely omitted!!! This issue is very rarely raised in the literature and if it does occur, it is addressed indirectly, like e.g. in "Terminology and Guidelines for Glaucoma - 3rd Edition" of the European Glaucoma Society 2009, in which on page 146 in chapter 3.5 - "Laser Surgery”, subsection 3.5.1 - "Laser Iridotomy" there are indications for performing YAG-iridotomy:

1. Clinically relevant or **suspected <u>pupillary block.</u>** **(!)**

2. Prevention of acute and chronic angle closure (prevention of peripheral anterior synechiae formation [on the iris])

I hope that after reading this study many of you have become convinced to the idea of the necessity of creating a device for measuring intraocular pressure in the "posterior segment" of the eye (posterior chamber and vitreous humour chamber) and taking pressure measurements with such a device that measures a parameter most desired by ophthalmologists, which is the pressure behind the lens and iris, triggering a specific pressure on the bottom of the eye. Because it is the determination of the compression on the nerve fibers and blood vessels on the bottom of the eye that we most concerned about in terms of such diseases as glaucoma or migraine according to the mechanism described by me.

"Medicine is a beautiful and interesting science. The more interesting it is, the more difficult it is to discover its mysteries when still the unknown is concealed behind the mist of ignorance and the way ahead of us is not easy..."

Piotr Nogal, Mount Taranaki Track, (New Zealand), 2010.