



William F. Hoyt, MD

Editor's Note: *William Fletcher Hoyt, MD, professor emeritus of Ophthalmology, Neurology, and Neurosurgery, University of California, San Francisco, was born and raised in Berkeley, California. He took his undergraduate education at the University of California, Berkeley, and his medical education at the University of California, San Francisco (UCSF). After a year's study at the Wilmer Institute, Johns Hopkins University, under the mentorship of Frank B. Walsh, MD, he returned to UCSF in 1958 to found the neuro-ophthalmology service. During a 36-year academic career—all of it at UCSF—he authored 266 journal articles, co-authored (with Frank B. Walsh, MD) the biblical third edition of Clinical Neuro-ophthalmology, and trained 71 neuro-ophthalmology fellows. In 1983, he received the title of Honorary Doctor of Medicine from the Karolinska Institute. He is widely acknowledged as one of the titans of twentieth century neuro-ophthalmology. In recognition of his contributions, the North American Neuro-Ophthalmology Society (NANOS), in conjunction with the American Academy of Ophthalmology, in 2001 initiated the Hoyt Lecture to be delivered each year at the Annual Meeting of the American Academy of Ophthalmology.*

The Vitality of the Pupil: A History of the Clinical Use of the Pupil as an Indicator of Visual Potential

H. Stanley Thompson, MD

It is obvious to neuro-ophthalmologists today that the reactivity of the pupil can serve as an indicator of an eye's potential for vision, but it was not always so clear. This clinical association between pupillary mobility and vision has been recognized for at least 2000 years, so it is strange that it seemed to pop up in 20th century ophthalmic practice as if it were a new test.

ANCIENT MEDICINE

Like so many things in medicine, it started with Galen in the 2nd century (Fig. 1). Claudius Galenus came from Pergamum, which is now in western Turkey, but at that time it was part of the Roman Empire. He began the study of medicine at age 16 and then went on to work in the great medical centers of the day—Smyrna, Antioch, and Alexandria—before returning to Pergamum. Then he moved to practice in Rome, the power center of the world. He soon became famous. He was a forceful and opinionated man who did not make himself popular with other Roman doctors.

In his practice he couched cataracts, as did many doctors, and like everyone else, some of his cataract patients were not helped by the surgery. If a patient came to Galen with a cataract in one eye, and asked him to fix it, he had, of course, the right to refuse to do the cataract couching. A high success rate would, naturally, be good for his reputation, and nothing was to be gained by operating on an

irretrievably blind eye, so he needed an indicator to predict the outcome of the surgery.

Galen must have noticed that he could not depend on a visible inequality of pupil size to decide whether the eye behind the cataract was sound. One eye or the other could be blind, either from the cataract or from something else, and still the two pupils could be of the same size.

He knew that the pupils were small when the eyes were exposed, and that they dilated when covered. His light source was the window, or the sky, and he controlled the light by putting a hand over one of the patient's eyes (Fig. 2). He noticed that if, in a patient with good vision in both eyes, he put his hand over one eye, the pupil of other eye would show a small but definite dilation. Galen's explanation for this observation was that there was a substance that he called the "breath of vision" ("pneuma") that came from the brain into the eye via the optic nerves. This pneuma served to keep the pupil wide as it emerged from the eye to mix with incoming external rays, thus facilitating the process of vision. When that eye was covered, the pneuma, finding itself no longer needed, went around, via the tubes of the chiasm, to the other eye to help it to see, and incidentally to dilate its pupil.

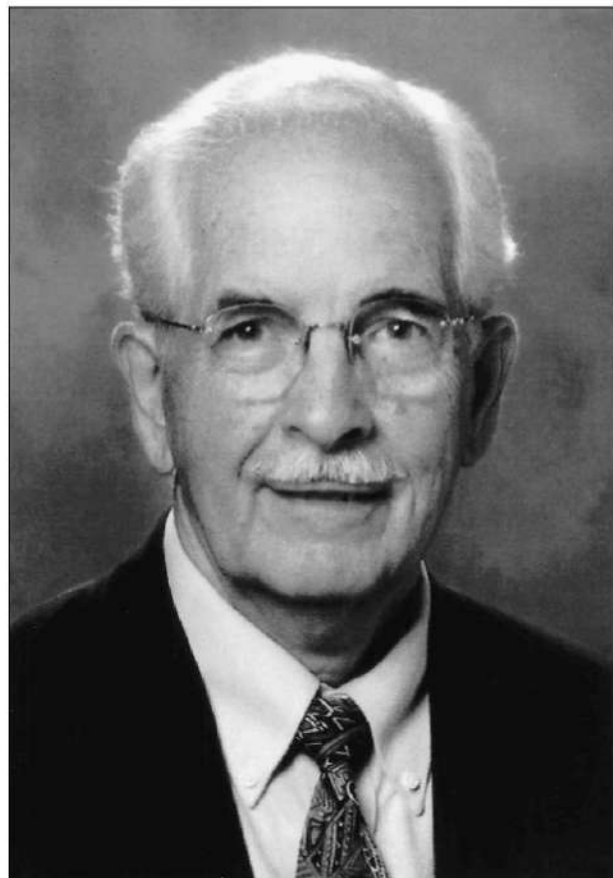
We would now call this dilation "consensual," and we would explain it by saying that the input from both eyes was contributing to the pupil size, and if one eye were covered, this "pupillomotor input" would be reduced by 50%, and this would, in turn, reduce the "pupillomotor output" to both eyes by 50%, resulting in a small but visible dilation of both pupils.

Interestingly, Galen went on to remark that he had noticed that if he put his hand over a blind eye—whether it had a cataract or not—the other pupil (the one that was still

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H. Stanley Thompson was born and raised in China, the son of Irish missionaries. Educated in China and Ireland, he spent the years of World War II in a Japanese concentration camp in China. Following the war, his family emigrated to the United States from Belfast, Northern Ireland. He completed undergraduate work and medical school at the University of Minnesota. In 1962, he interrupted his University of Iowa ophthalmology residency to work in the pupillography laboratory of Otto Löwenstein, MD and Irene Loewenfeld, PhD at Columbia University. So fascinated was he by their research that he settled on a career in neuro-ophthalmology. On completing his residency at Iowa, he completed a 1-year neuro-ophthalmology fellowship from 1966 to 1967 under the tutelage of William F. Hoyt, MD, returning to the ophthalmology faculty at Iowa, where he remained director of neuro-ophthalmology until his retirement in 1997. During his 30-year tenure at Iowa, he trained 40 neuro-ophthalmology fellows and authored over 200 articles and countless book chapters. Acknowledged internationally as the "master of the pupil," he used instrumental inventiveness and relentless, precise clinical observation to redefine pupillary physiology and its clinical application to the afferent pupil defect, Adie's tonic pupil, pharmacologic assessment of Horner syndrome, and observations of bizarre phenomena such as tadpole pupils. His trainees still cling to coffee napkins covered with quaint Thompson sketches of neural pathways illustrating the workings of the brain. In retirement, he studies the history of ophthalmology, and with his wife Delores, tends sheep and manages an on-line bookstore specializing in the illustrators of children's books and the history of medicine.

visible to him) would not dilate (1). Today we would say, "Well, that's easy! It is because the blind eye was not contributing to the pupil size, so covering it up would make no difference."

It is fascinating that neither Hippocrates nor Galen ever stated the apparently obvious fact that the pupils constrict when exposed to light and dilate again when the light is withdrawn. I imagine that this was because Galen was still trying to fit his observations into Plato's scheme of things, and this involved a pneuma emerging from the eye, and it just didn't occur to him to cover the good eye and then cover and uncover the eye with the cataract.

Galen's great contribution to clinical medicine at this point was his willingness to set aside his philosophical speculations about the mechanisms at work, and to simply recommend using the mobility of the pupils as a prognostic sign when considering a cataract for surgery. He would just cover the cataractous eye and watch the pupil of the other eye. If it dilated, he would conclude that there was visual potential behind the cataract that he had just covered, and he would schedule the cataract surgery (2). The importance of this pupillary sign rests on the fact that it was an observable and objective indicator, independent of the patient's feelings about his visual loss, that it made a statement about the integrity of a part of the visual system that was otherwise entirely invisible and unknowable to the doctor.

Because Galen actually wrote down many of the things he was thinking about, his fame lasted long after his death in 199 CE. In addition, Rome was soon to be in decline and the invading barbarians swooped down again and again to pillage and destroy, and thus contributed to the suppression of intellectual activity in most of Western Europe. Some of Galen's writings were translated into Arabic and survived. In the long run, all this had the effect of making Galen even more famous, and his writings became so authoritative that as they aged they took on the aura of canon law, and disagreement was not permitted. Galen's opinions and recommendations became the high water mark of medical knowledge on this subject for hundreds of years.

ARABIC MEDICINE

During the early middle ages, Galen's prognostic pupillary sign for cataract couchers was repeated by many Middle Eastern medical authors writing in Arabic, but, because of translation and transcription errors, it was not always passed along intact (3,4). It was not offered as an indispensable test, and I'm not sure that it was always fully understood, because once the concept was accepted that it was the light entering the eye that caused the pupils to constrict, then just looking at the direct light reaction was easier to understand and easier to do than Galen's test.

In the 7th century, Paul of Aegina was saying that a large pupil was common in an eye with bad vision, and he

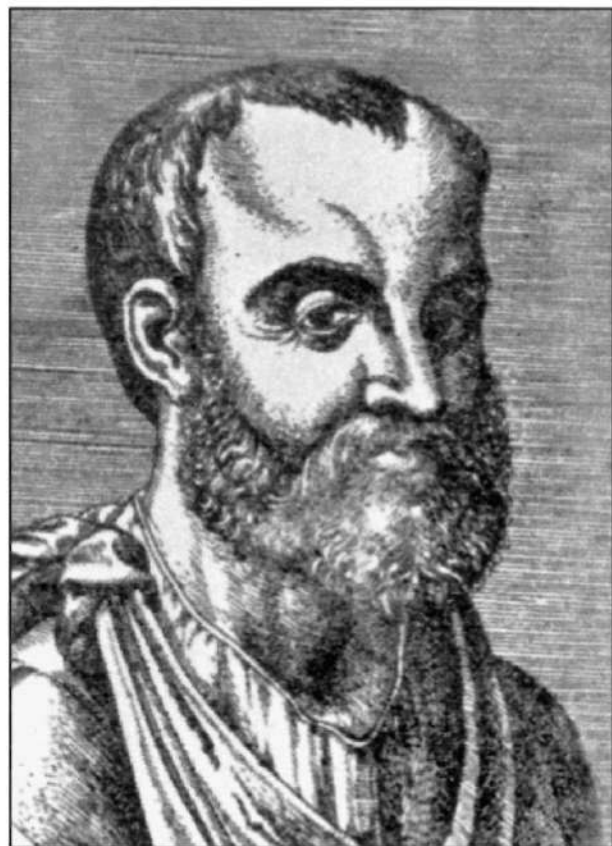


FIG. 1. Claudius Galenus of Pergamum and Rome (130–199 CE).



FIG. 2. A late Roman wall decoration showing a doctor examining the eyes of a patient.

recommended rubbing both eyes through the eyelids in connection with checking the pupils. Soon the Greek idea that rays emerging from the eyes contributed to the process of vision had been abandoned, and it was clear to both Rhazes (865–925) in the 10th century and to Ammar Ibn Ali in the 11th century that the pupil was constricting in response to light entering the eye (5). This made it possible to think of Galen's test as a rather roundabout way of evaluating the direct pupillary reaction of the cataractous eye to exposure to light.

RENAISSANCE MEDICINE

During the 16th century, European intellectual activity was experiencing a dramatic rebirth. In Venice, Galen's work was translated for the first time from its original Greek straight into Latin, without going through Arabic. Greek and Latin versions of Galen's works were then published by the Aldine Press in 1525, using moveable type.

The Swiss barber-surgeon Pierro Franco (1504–1578) specialized in hernias and cataracts. The most experienced and skilled cataract coucher of the 16th century, he had three criteria for judging the readiness of a cataract for the couching needle: 1) The color of the cataract (*pearly white is best*); 2) The degree of loss of vision (*it should be severe*); and 3) The pupillary mobility (*it should be normal, despite 1 and 2 above*). Franco asserted that:

One should rub the cataract-stricken eye a little, after first closing the other eye. If then the cataract expands and widens, and then returns to its previous status immediately ("upon lifting the lid" seems to be left unsaid) then that is an indicator that the eye is well suited for the operation, otherwise not (6).

Felix Platter was born in 1536 into a well-to-do family in Basel (Fig. 3). He had read Galen and various Arabian medical authorities when he was in medical school in Montpellier. Platter was the first to clearly state that the eye was an optical instrument, that vision did not take place in the crystalline lens, and that the lens served only to focus the light onto the retina, which, he believed, was an extension of the nervous system and the true percipient layer within the eye (6).

Platter compared a cataract to a tree-ripened fruit. If the surgeon would just wait until the cataract was "ripe," he could save himself a lot of trouble, and eventually the cataract would fall easily from the tree into his waiting hands. For Platter, the color of a ripe cataract should be "like the skin that envelops the white of a cooked egg." He also used pupillary reactivity as a sign of a "ripe" cataract (6).

Ambroise Paré was born into a French family of barbers, and his education was scanty. He knew no Greek or Latin (Fig. 4). At first he apprenticed to his brother, a barber-surgeon, and then moved to Paris to a similar position.



FIG. 3. Felix Platter (1536–1614).

He worked as a house surgeon at the Hotel Dieu, and then as a military surgeon. Since he was not taught to bow down to the ancient teachers, he learned to trust his own observations. For example, he quickly rejected the common practice of pouring boiling oil into a chest wound on the grounds that it did more harm than good. He taught surgeons to be gentle with tissue and he became the best-known surgeon of the 16th century. Paré’s precataract pupil check was very similar to that of Pietro Franco, but more detailed and explicit. Here is Ambroise Paré’s comment, as translated at the time into Elizabethan English, on the “ripeness” of a cataract, under the heading “By what signs ripe and curable cataracts may be discerned from unripe and uncurable ones”:

If the sound eye being shut, the pupill of the sore or suffused eye, after it shall be rubbed with your thumbe, bee presently dilated and diffused, and with the like celerity returne into the place, color and state, it is thought by some to shew a ripe and confirmed cataract. But an unripe and not to be couched, if the pupill remain dilated and diffused for a long time after. . . . Cataracts are judged uncurable . . . whose pupill becometh no broader by this rubbing: for hence you may gather that the stopping or obstruction is in the opticke nerve, so that how cunningly or well soever the cataract bee couched, yet will the patient remain blind (8).

All three of these 16th century surgeons—Franco, Platter, and Paré (6)—as well as Bartisch (7), recommended using the pupils as a predictor of visual success in cataract couching just as Galen had recommended 1300 years before, but their test was a little different and definitely easier to do. As the Arabian authorities had done, they closed both of the patient’s eyes, and pressed and rubbed the eyes through the eyelids with their thumbs. This may sound like hocus pocus, but it gave the doctor an opportunity to palpate the orbits for prominence, resistance, or discomfort. It also helped the pupil testing by briefly dark adapting the eyes, and this probably strengthened the direct pupillary response to light that could be seen when one eyelid was suddenly lifted.

Notice that these Renaissance doctors, even though they had access to a fresh translation of Galen, did not choose to make clinical use of Galen’s test. They were no longer burdened with the idea that some component of vision streamed out of every seeing eye towards the object of regard, so that they were able to just watch the direct pupillary reaction to light. On the strength of Paré’s fame, checking the direct light reaction of the pupil became standard practice for all cataract surgeons. For the next 300 years,



FIG. 4. Ambroise Paré (1510–1590).

doctors were taught to look at the direct reaction to light in the eye that was up for cataract surgery (19), rather than looking, as Galen had originally suggested, for a weak consensual dilation of the other pupil when the cataractous eye was covered.

It is interesting that Hieronymus Fabricius ab Aquapendente (1513–1619), professor of Anatomy at Padua, said that Father Paul of Venice (Pater Paulus Venetus, or Paolo Scarfi, 1552–1623) was the one who had demonstrated to him that the pupils contract and dilate with variation in light intensity. Later Plenpius (1648) gave Father Paul the credit for being the first to make this observation (5), which disregards centuries of Arabic medicine.

EIGHTEENTH CENTURY

By the 18th century, there seemed to be a better understanding of how pupillary signs could be of help to the practicing eye doctor. For example, Charles de Saint-Yves (1667–1733), in his textbook *New Treatise on the Diseases of the Eyes* (1722), a book that remained in print for more than 80 years, said, on the clinical value of pupil watching:

I have noticed over and over again in my patients that the extent of the visual impairment closely matches the impairment of iris movement. In fact I have found that, without talking to the patient about the visual problem, I have been able to make a fairly good estimation of the quality of the patient's vision, based only on my examination of the pupillary movements (9).

Now there is a very modern sounding voice!

William Porterfield (1696–1771) knew of the work of his Edinburgh colleague Robert Whytt (1714–1766), who recognized that the pupillary response to light had an afferent and an efferent arm in separate nerves. In 1759, Porterfield seemed to understand that Galen sign was an example of consensual dilation of the pupil of the other eye when the cataract eye was closed, and that when both eyes were stimulated, more pupillary constriction was produced than when only one eye was exposed to light (10).

NINETEENTH CENTURY

Benjamin Travers (1783–1858), a prominent English surgeon, viewed the pupil as part of a muscular system. His 1820 book, *A Synopsis of the Diseases of the Eye*, stated that “. . . its contractility (is) in proportion to the strength and perfection of the nerve of sense with which it is associated.” (11).

Travers was voicing a very old concept that had become generally accepted during the 18th century (see Saint Yves above), namely, that there is a “proportionality” between the integrity of the optic nerve and the strength of the pupillary response. This proportionality, or something like it, may have even been brought up in about 1250 by the

Franciscan encyclopedist Bartholomaeus Anglicus (12). He was working in Paris when he wrote about vision and the pupil:

Caecitas est privatio visus. Privatur autem homo visu, aliquando propter organorum defectum, et pupillarum improprietatem ad spiritum visibilem. Ad hoc enim quod formetur visus, exigitur debita proportio organum, spiritum recipientis ad ipsum spiritum (12).

(“Blindness is the deprivation of sight. An eye can be blind because of a defect in the eyeball itself, with the result that the pupil is no longer proportionate to the quality of vision in that eye. In fact, to see well, everything needs to be working properly: there must be an “appropriate proportionality” in the eye itself—in that the eyeball must be fit to accept the “image.”)

By forcing this statement into modern idiom, I may have distorted what Bartholomaeus was trying to say in the 13th century. He might have simply been saying that in a good eye the pupil moves well, while in a bad eye it moves poorly. In this translation, the word “image” has been substituted for “visual spirit” even though Bartholomaeus knew nothing of optical images in the eye and may not have been able to distinguish in his thinking between “light reaching into the eye” and “sharp vision reaching into the eye.” A cataract certainly spoils the image falling on the retina and impairs vision, but it blocks very little light. This might account in retrospect for the mysterious breakdown in a cataractous eye of the customary proportionality between the vitality of the pupil and the quality of vision, the anomaly that attracted Galen’s attention.

ARE PUPIL SIGNS UNTRUSTWORTHY?

William Mackenzie (1791–1868) of Glasgow wrote a famous textbook that dominated English ophthalmology in the 1830s and 1840s. He found it necessary to warn his readers that sometimes the pupil would react well to light “in cases of total blindness,” (13) and this began a long period of doubt about the trustworthiness of pupillary signs.

In 1855, Albrecht von Graefe, at the age of 27, was already the acknowledged leader of German-speaking ophthalmology, and in that year, just as the new ophthalmoscope was becoming popular, he warned ophthalmologists not to be in such a hurry with the dilating drops that they missed important pupillary signs (14). Von Graefe was particularly interested in using the pupil reactions to decide whether a patient was *pretending* to be blind in one eye. He accepted the fact that there often was doubt about the real cause of the visual loss and that there remained some uncertainty about the dependability of the pupil responses in some conditions, so he offered pupillary reactivity only as a confirmatory sign of good vision in the tested eye. This

cloud of doubt about the clinical reliability of pupillary signs continued to hang over the office and bedside use of pupillary reactivity for the next 50 years.

Nineteenth century ophthalmologists did know, in general, that the absence of a pupillary light reaction was a classic and important sign of true blindness, as Boerhaave had taught early in the 18th century, and many doctors were writing about the pupil. The German word for a poorly reacting pupil was *Pupillenstarre*, and when this “stiffness” or “rigidity” of the pupil was complete it was sometimes called *absolute Pupillenstarre*. If the pupil reacted poorly to light but well to a near stimulus, it was called *reflektorische Pupillenstarre*, and if the failure of the light reflex was due to an input (afferent) problem, it was called an *amaurotische Pupillenstarre*. Ludwig Bach’s 1908 344-page book *Pupillenlehre* seems almost bogged down by this terminology. Heddaeus (15), reaching for a better term for the afferent kind of pupillary defect, and making an analogy to another sensory input, suggested the term *Reflextaubheit*, or reflex deafness of the pupil. He championed this awkward term vigorously throughout the 1880s, but it was generally rejected. These lengthy discussions were mostly about terminology and they seemed to do very little for the clinician. Young ophthalmologists were still not taught to make daily use of the pupil as an indicator of vision.

In 1889, Ernst Fuchs (1851–1930) wrote a very influential textbook called *Lehrbuch der Augenheilkunde* that was widely used for the next 40 years. On the clinical pupillary examination he said only that “*The reaction of the pupil to light is . . . used with great advantage to determine objectively whether an eye has any sensation of light or not (particularly in children, malingersers, etc.)*.” (16).

William Fisher Norris (1839–1901), son of a well-known Philadelphia surgeon, served in the Medical Corps of the Union Army in the American Civil War. He then spent 5 years (1865–1870) studying ophthalmology in Vienna with Mauthner, Arlt, and Jaeger. Upon return to Philadelphia, he soon became professor of ophthalmology at the University of Pennsylvania. William Pepper, Professor of Medicine at the University of Pennsylvania, put together a multivolume *System of Practical Medicine*, to which Norris contributed a chapter on medical ophthalmology. Strangely, in the 67 pages of his chapter, there is no mention of using pupillary reactivity as an indicator of the potential for vision in an eye (17).

In 1893, Norris and his student Charles Oliver wrote a one volume *Text-Book of Ophthalmology* (Lea Brothers, Philadelphia). This was so popular that they decided to edit a 4-volume, multiauthored *System of Diseases of the Eye* (1897–1900) (Fig. 5). In this set, there is a thoughtful chapter by S. Baudry of Lille on the subject of simulated blindness (18). Almost half a century after von Graefe’s comments on the value of the pupil’s reaction to light in cases of

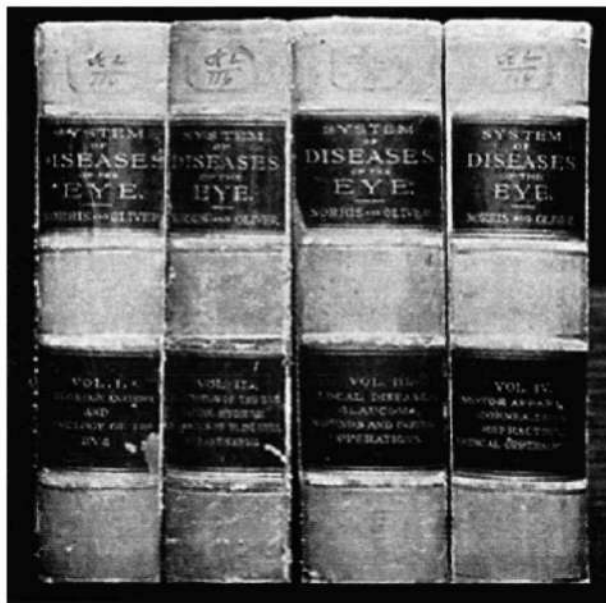


FIG. 5. Norris and Oliver’s *System of Diseases of the Eye*, published in 1897.

simulated blindness, very little had been added except that an eye with profound optic nerve dysfunction (“amaurosis”) shows more impairment of the pupillary light reaction than an eye with moderate optic nerve dysfunction (“amblyopia”), that the confusion between these entities and nonorganic (“hysterical”) visual loss and suppression amblyopia (“amblyopia ex anopsia”) was producing more diagnostic uncertainty and anxiety than ever, and that the clinical examination of the pupils was not any further advanced.

Charles Oliver’s own little 1895 book on how to examine the eye for optic nerve disease would be expected to have something about the pupillary examination, but this is all he had to say: “*The two (eyes) are then to be covered and alternately exposed to the entering light stimulus until surety is made that there is muscular response or not.*” (19). Nothing new since Ambroise Paré!

The long legacy of writings about the pupil had apparently had little impact on the routine examination of the eyes. Some 1800 years earlier, Galen had insisted that the two pupils worked together when one eye was covered, and he had applied this observation to the indications for cataract surgery. Some 200 years before the publication of Norris’ textbook, Saint-Yves had been saying that looking at the pupillary responses should be an early part of every eye examination, and yet somehow this part of the examination had fallen into disfavor in the 19th century. Why?

I believe that this apparent lapse was the natural result of the steady accumulation of knowledge. As new clinical observations were confirmed, it became possible to ask

some difficult questions about the pupils, but the details of the anatomy and physiology of the pupillary light reflex were not fully understood until late in the 19th century. Without these details, it was hard to account for some of the observed pupillary behavior. There seemed to be too many exceptions to make it a dependable tool.

What kind of exceptions are there to cast doubt upon the ancient rule that pupil reactions and remaining vision always go hand in hand?

1. *There were some patients with good vision whose pupil(s) reacted weakly to light or not at all.* Patients with one fixed pupil could have vision that was good, but many of them had vision that was less than perfect; trauma or iritis could have damaged the iris; and in younger patients, denervation of the iris sphincter usually also induced visual complaints at near. These “efferent” (pupillomotor output) problems such as third nerve palsies, Adie pupils, and atropinic drug responses generally resulted in a pupil with a weak light reaction on the affected side, and this produced a pupillary inequality that increased with the brightness of the light. By the middle of the 19th century it was recognized that these patients usually had good vision even when looking through a large or unreactive pupil. In fact, this had been clearly stated by Platter in the 16th century (20).

Sometimes an eye that could read the 20/20 line had a clinically visible impairment of the direct light reaction, compared with the response when the other eye was stimulated. Some of these eyes were found to have a considerable loss of peripheral visual field, which accounted for the loss of pupillomotor input.

2. *An eye with poor vision would sometimes seem to have perfectly normal pupil responses to light (21).* Of course, many allegedly blind eyes were not truly blind. For example, eyes with very poor vision due to a large central scotoma or a deep suppression amblyopia, or with non-organic visual loss, seemed to have good, or at least reasonably good, pupillary responses. This was because most of the retina was still in good working order and properly wired up to the midbrain. An effort was made to dodge this problem by reducing the clinical examination of the pupillary light reactions to a “yes” or “no” question where any consistent response to light was accepted as a normal response. This added to the difficulties. It should be noted that in the late 19th century there were still very few eye doctors who actively set out, in their examination of the patient, to compare the direct light reaction in the two eyes.

Occasionally, the pupil of a truly blind eye could be seen to constrict during the examination and an “eyelid-closure pupillary constriction” (thought to be a stray near response) was not recognized (22).

If a bright slit-lamp beam shines directly upon a truly blind eye, a definite light reaction can sometimes be seen, and the examiner may never suspect that the light is being reflected off the patient’s face and then off the examiner’s white coat and thence into the patient’s other eye—an eye that is sound, dark adapted and, at that moment, exquisitely sensitive to light.

When von Graefe wrote in the 1850s of using the pupillary light reaction to distinguish a real optic neuropathy from the simulation of blindness, he brought up the possibility that a patient could have a stroke or an injury that would damage the visual cortex and make the patient “cortically blind” without damaging the pupillary light reflex to and from the midbrain, so that the patient would retain normal pupillary responses to light (14). A generation later, when autopsies were more common, this became well established (23).

In the hope of explaining some of these mysterious exceptions to the old rule that vision and pupil responses should go hand in hand, it was speculated that the pupillary afferent pathways and the visual pathways, although adjacent, were actually fundamentally different and responded differently to injury and disease. Either the pupillary fibers

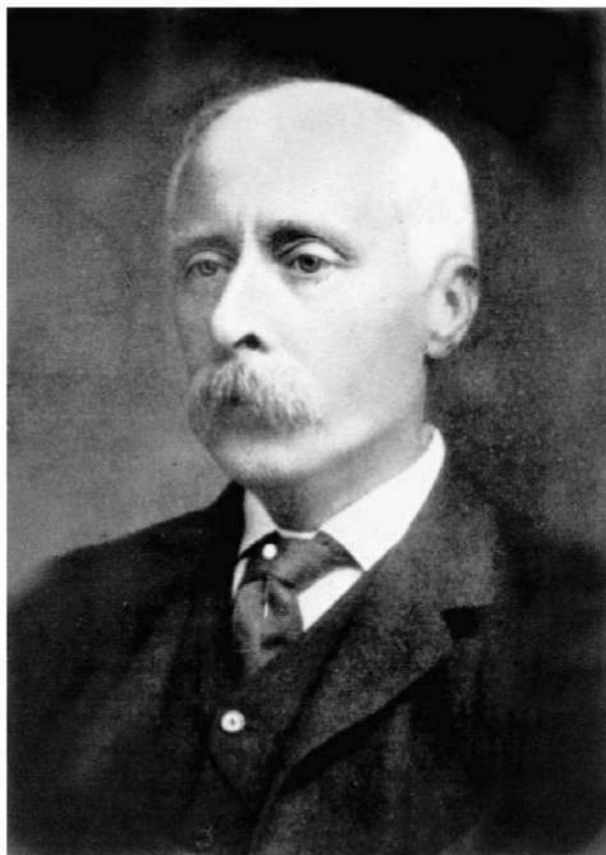


FIG. 6. Robert Marcus Gunn (1850–1909).



FIG. 7. Alfred Kestenbaum (1890-1961).

were thicker and more resistant to injury, or they were in separate fascicles and followed a slightly different path. These suggestions were never firmly proven, but a considerable literature was generated for many years (24) that may

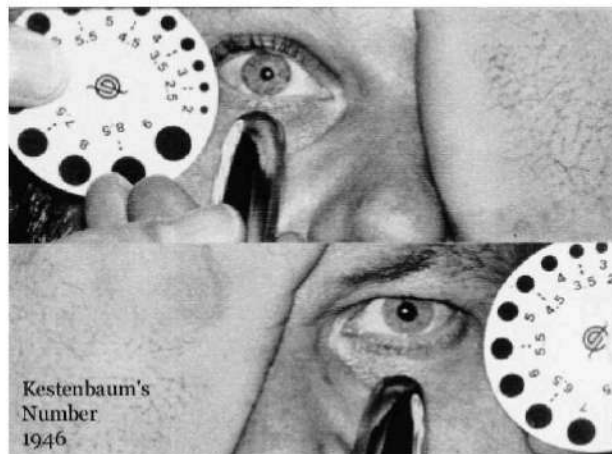


FIG. 8. Measuring Kestenbaum's pupil number.

have diverted attention from the clinical use of pupillary signs in optic nerve disease. The matter of whether the pupillary light reaction is served by different ganglion cells with different properties and different receptive fields is still under discussion (25,26).

At the very beginning of the 19th century, anticholinergic mydriatics had been suggested by Karl Himly for use in cataract examination. In 1851, when the ophthalmoscope arrived on the scene, atropine was already in clinical use in cataract surgery and in iritis, so it was now used to open up the iris for this wonderful new view of the depths of the eye. This may have been another factor that contributed, in the last half of the 19th century, to the fall of pupillary observations into a secondary position in the routine eye examination: occasionally the professor wanted to look at the fundus without delay. Even though von Graefe had, in 1855, expressly warned against skipping the early careful examination of the pupils, his advice was not always taken, *partly because in the same paper he admitted that the pupillary reaction to light was not an altogether trustworthy indicator of visual potential.*

TWENTIETH CENTURY

Towards the end of the 19th century, confidence in the dependability of the pupil responses was growing. In

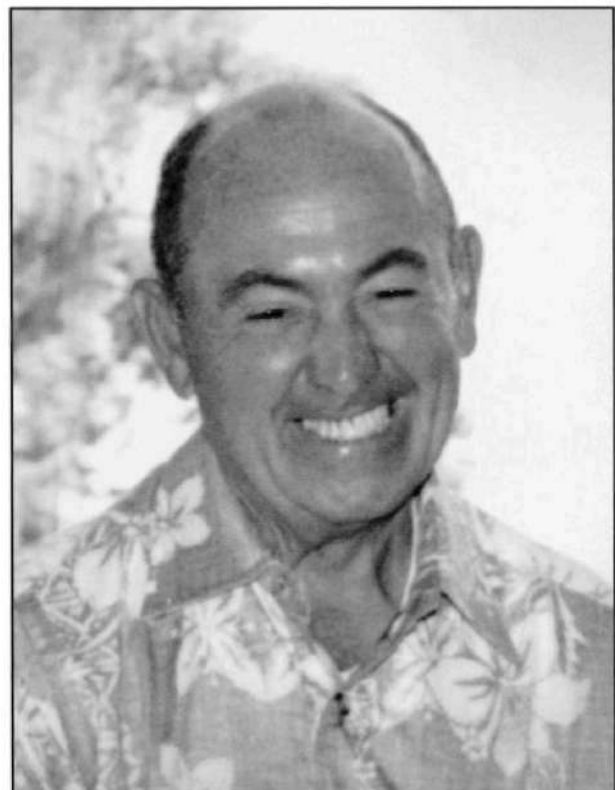


FIG. 9. Paul Levatin (1989).



FIG. 10. Otto Löwenstein (1952).

1884, Julius Hirschberg, the historian of ophthalmology, considered it worthwhile to publish a case report of a 17-year-old girl with recent unilateral visual loss (27). He had been able to say with confidence that the patient was not just pretending to be blind because he could see that her pupils failed to react well when the affected eye was stimulated with light. This degree of confidence was not shared by most eye doctors.

In 1901, Elia Baquis of Livorno also spoke of the value of a careful pupil examination in cases of suspected nonorganic visual loss, and emphasized comparing the direct and consensual reactions of the 2 eyes (28).

Vössius also made good use of pupillary signs in a compensation case in 1906 (29).

Hirschberg remarked in 1901 that one of the oldest clinical observations ever made about the pupils was seldom mentioned in modern ophthalmic texts. He was referring to Galen's observation about the behavior of the other eye. He demonstrated, in a series of patients and normal subjects, that the dilation of the uncovered eye could indeed be seen and was worth watching for (30). William Porterfield had made a similar observation in 1759 after reading Galen (10).

Robert Marcus Gunn (1850–1909) was a well-known London ophthalmologist, a careful cataract surgeon, and an observant ophthalmoscopist (Fig. 6). He described "Gunn's dots" (bright points near healthy discs, that he always called "Crick Dots" after the family in which he first noticed them), "Gunn's sign" (arteriovenous nicking of the retinal vessels), and "Gunn's jaw-winking phenomenon." Gunn went out of his way in 1897, and again in 1902 (31), to get his fellow ophthalmologists to pay attention to pupil responses as a sign of real optic nerve disease. Gunn emphasized the clinical value of the pupillary response to light in recognizing nonorganic visual loss and the inability of the pupil of the defective eye to maintain the contraction under direct exposure to light. He repeated these statements in a paper at the 1902 meeting of the British Medical Association on the recognition of nonorganic blindness that was published in *Ophthalmic Review* in 1904:

It is not sufficient to find that it (the pupil of the affected eye) contracts well or fairly well on exposure; the eye

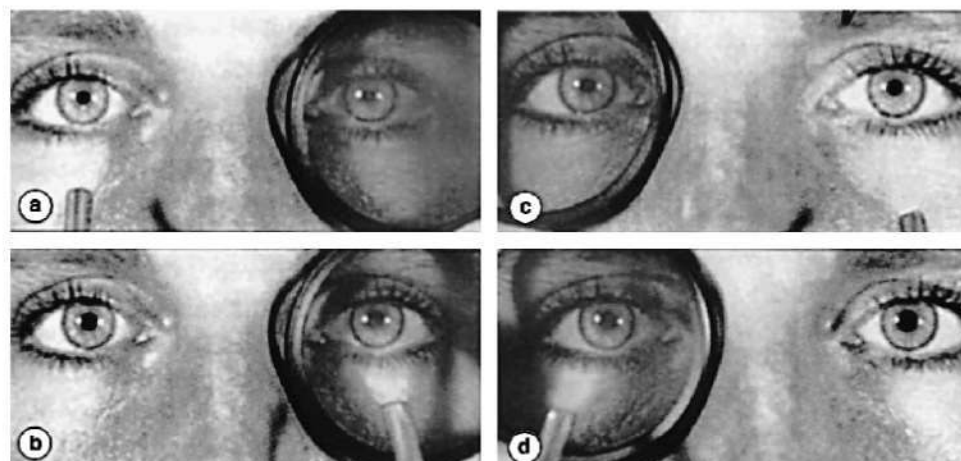


FIG. 11. The Tilt Test: Using a neutral density filter to confirm a "threshold" afferent pupillary defect. In (A) and (B), a 0.3 log neutral density filter is held over the OS of a normal subject while the light is alternated from one eye to the other: It can be seen that both pupils constrict more in (A) when the light is brighter, i.e., without the filter. In (C) and (D), the filter is moved to cover the subject's OD, and again a small relative afferent defect can be seen when the shaded eye is stimulated (D). This "tilting" of the relative afferent defect by the same amount in each direction can be used to confirm a small input defect of clinical significance, because a 0.3 filter over the apparently affected eye will make a real asymmetry much larger, and the same 0.3 log filter over the other eye should make a real asymmetry disappear.

must be kept under the direct stimulation of light and the pupil watched, as to whether it shows that secondary dilatation under continued exposure that is found associated with the amblyopia of retro-ocular neuritis (32).

He went on to remind his audience that both pupils showed this "secondary dilatation" (later called "pupillary escape") when the affected eye was stimulated, whereas the same light held on the normal eye would keep both pupils down.

Gunn was clearly stimulating one eye and then the other, but he does not tell us about the nature, intensity, and duration of the light stimulus used. Perhaps he merely had the patient look out of the window while he alternated the cover, but he does not report this. In his later writings, he was impressed that the pupils would constrict when the good eye was illuminated, and would ("paradoxically") dilate when the bad eye was illuminated. This statement, all by itself, suggests that he had started to alternate the cover.

In 1904, at a British Medical Association discussion on "retro-ocular neuritis," (33) Gunn and others only briefly mentioned the pupils as if it were well known that the pupils could be used to distinguish retrobulbar neuritis from non-organic visual loss. When printed in the *Ophthalmic Review* in 1905, the comment was "*the pupil reaction is invariably impaired when there is even moderate amblyopia from neuritis, while it remains normal in cases of functional origin.*" (34). No mention was made of the pupillary-escape-under-steady-illumination phenomenon. Getting ophthalmologists to incorporate this test into their routine examination must have been an uphill battle. When Gunn died in 1909 at age 59, the obituaries were filled with praise for his personality and his work, but no one mentioned any of his contributions to the examination of the pupils.

Alfred Kestenbaum came to America in 1939, bringing with him his skills in neuro-ophthalmology (Figs. 7, 8). In 1946, more than 40 years after Gunn, he offered two ways to demonstrate the existence of an asymmetry of pupillomotor input: (35)

1. With the patient in the light, he covered first one eye and then the other, remarking on the dramatic difference in the response between the good eye and the bad eye. He called this a "Modified Marcus Gunn Pupillary Sign."
2. Using a small pupil gauge or ruler, he measured the diameter in millimeters attained by each pupil in diffuse bright light when the other eye was firmly covered. Assuming that the pupils were equal in size when both were uncovered, the eye with the larger pupil (the weaker direct light reaction) had the relative afferent pupillary defect. He called this finding the "pseudo-anisocoria sign."

He also offered a way to roughly quantify the difference in pupillomotor input between the two eyes. He did this sim-

ply by subtracting these two pupil diameters. The resultant number, in millimeters, is an expression of the difference in pupillomotor input between the two eyes, because the pupillomotor output is assumed to be the same for OU. I like to call this "Kestenbaum's Pupil Number" to avoid using the distracting word "pseudo-anisocoria." Even though this number is in millimeters, it roughly corresponds to the relative afferent pupillary defect measured in log units of neutral density filter (36).

It is interesting to note here that, starting with Galen, the emphasis in this part of the eye examination was to check the vigor of the pupillary reactions of one eye as the lighting conditions were varied. Sometimes the other eye was examined in a similar manner, and sometimes the pupil responses were compared from memory. Kestenbaum emphasized the clinical value of knowing the difference in pupillomotor input between the two eyes. He was the first to offer a simple way to attempt the quantification of this difference in the clinical examination.

In 1959, Paul Levatin (37) made a very important contribution (Fig. 9). He noticed that moving a hand-light (rather than a cover) quickly across the nose from one eye to the other seemed to bring out an asymmetry of pupillary input between the eyes. He called it the "swinging flashlight test." With this quick switch of the light stimulus from one eye to the other, the consensual dilation of the pupil in the second eye that resulted from taking the light away from the first eye was algebraically summed with whatever pupil constriction was generated by the light arriving at the second eye. Switching the light from one eye to the other thus amplified any difference in their pupillary contraction to light, and made that difference easier to see. Levatin knew Lowenstein and Kestenbaum and built on their contributions by focusing on the difference between the two eyes, by turning the alternating cover pupil test into an alternating light test, and by echoing Kestenbaum's observation that alternating the light between the two eyes seemed to amplify this difference. This made it possible to answer a question about asymmetry of pupillomotor input with a simple "yes" or "no"; it was no longer necessary to enter into a confusing discussion of direct and consensual reactions.

Otto Löwenstein (1890–1965), a neuropsychiatrist with an interest in understanding the pupils by recording their actions, also came to America in 1939 (Fig. 10). He noticed that the shape of the pupillary tracing in an eye with optic nerve disease had a characteristic shape and behavior (a longer latency, less amplitude of movement, a lower peak speed attained) and that these features could be reproduced in a normal eye by just reducing the intensity of the stimulus light (38).

From these observations, it followed that in unilateral optic nerve disease, it might be possible to dim the stimulus to the better eye with a neutral density filter until the pupillary responses to light seemed visibly matched in the two eyes.

The density of the filter would then be a measure of the asymmetry of pupillomotor input between the two eyes (39).

PERSONAL RECOLLECTIONS

In 1963, after spending some time with Löwenstein and Loewenfeld in New York, one of the things that impressed me about trying to use pupillary reactivity to estimate the visual potential in an eye was the odd disparity between what people *said* and what people *did*. Everyone acknowledged that the mobility of the pupil was an indicator of residual vision, and that this had probably been known for millennia, but in the 1960s very few ophthalmologists seemed to be making daily use of the sign, with the exception of Kestenbaum, Levatin, Lawton Smith, John Stanley, Robert Drews, and their students. Edward Fineberg, of Miami, stirred me into adding neutral density filters to my regular clinical toolbox (40). The filters made it possible to quantify the asymmetry of pupillomotor input while using Levatin's alternating light test.

Aki Kawasaki and Randy Kardon have pointed out that this asymmetry of pupillomotor input is not an absolutely stable quantity (41). Even when the asymmetry is carefully measured in normal subjects with a sophisticated instrument, under stable conditions, the amount of asymmetry seems to fluctuate a bit, so that an apparent 0.2 log asymmetry may sometimes turn out to be within the normal range (Fig. 11).

Looking carefully at the past is sometimes quite humbling because there were people centuries ago who made some amazing leaps of the imagination when there was little but intellectual rubble around their ankles. When almost every "discovery" turns out to be a rediscovery, our modern clinical contributions begin to seem like just another car at the end of a long and magnificent train of observations.

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