Introduction

> The gods put in a face in which they inserted organs to minister in all things to the providence of the soul. They first contrived the eyes, into which they conveyed a light akin to the light of day, making it flow through the pupils.
>
> (Plato, *Timaeus*)

The brain is the organ of perception and cognition and so it is understandable that it is studied by thousands of scientists around the world. But the brain is encased in solid bone, making it difficult to study. We can't see, probe, or touch it without major surgery, so we often rely on indirect methods such as personal interviews or autonomic measures such as heart rate or blood pressure. Other techniques to study the brain require expensive specialized equipment such as electroencephalograms, fMRI, PET scans, or magnetoencephalograms.

Fortunately, one tiny piece of the human brain is visible. The pupil is the opening in the center of the colored iris of the eye. The movements of the pupil are controlled by muscles that are embryologically related to the central nervous system. Consequently, modern techniques use the pupil to uncover useful information about the brain that was not possible with older methods.

Our understanding of the pupil has taken over 3,000 years to develop and is continuing. Several prominent scientists of the past have been intrigued by the pupil. Archimedes (287–212 BCE) devised a method to measure pupil diameter. In the seventeenth century, the famous astronomer Galileo Galilei (1564–1642) developed his own technique to estimate the size of the pupil. Descartes, Plato, Aristotle, Galen, and Scheiner all weighed in with their thoughts about the pupil. Leonardo da Vinci (1452–1519) was fascinated by the pupil. In his monograph on optics, he states the following: "O wonderful, O marvelous necessity, you (the pupil) constrain with your laws all the effects to participate in their causes in the most economical manner!! These are miracles!" (19, 20).

The opportunity to study the pupil scientifically was not possible until the late twentieth century. Strict attention and proper methods of measurement during this portion of the physical examination can provide useful information to the careful examiner. "Proper methods of measurement" does not necessarily mean a desktop pupillometer that can average several small responses to a repeated stimulus. With those expensive instruments, it is possible to detect minuscule pupillary size changes to attentional states because the instruments can use averaging techniques to extract small, evoked responses of the pupil out of chaotic pupillary movements.

For the physician who wants to examine the pupillary reactions, there is a middle ground between the office-based pupillometer and the naked eye examination. Portable hand-held infrared pupillometers are an outgrowth of the technology that revolutionized the study of the pupil in the 1970s. These instruments are now located in many emergency rooms, operating rooms, and intensive care units around the world. They provide data on the pupillary light reflex (PLR), pupillary reflex dilation (PRD), and pupillary unrest in ambient light (PUAL). Light reflex amplitude, constriction velocity, dilation velocity, and latency of the reflex are other parameters that can be retrieved from the portable instruments. Interpretation of these parameters is required to extract useful information that pertains to care of the patient.

The pupillary light reflex is an important segment of the physical examination. It therefore seems obvious that measurement of the reflex should provide accurate information. The problem with the traditional pen-light examination of the pupil is that over 50 percent of the world population have dark eyes. This means that to view the pupil, a high level of ambient light must be directed into or across the plane of the iris. Not only can adding this light confound the assessment of pupil size, because this ambient light constricts the pupil, but also, the important pupillary reflexes (light reflex and reflex dilation) are altered depending on the amount of light directed into the pupillary aperture. Infrared pupillometry can add value to these pupillary measures because the infrared light that illuminates the pupil does not alter pupil size or elicit a light reflex. There are several other issues that can confound the pen-light examination of pupil size and pupillary reflexes. The visual acuity of the examiner can be a factor. Also, the ambient light in the room, near fixation, extraneous alerting stimuli, and different examiners can all alter the assessment of the pupil. For these reasons, it is important to have a consistent method of pupillary examination, not only for the pen-light examination, but also when using the portable infrared instruments. Much of the valuable information that arises from measuring the pupil comes from trending the size and reactions over several hours or days. Clearly, if the measurements are done differently, then the trend becomes meaningless. The pupil can provide other information on the effect of drugs and neuropathology by recording the degree of pupillary unrest and pupillary reflex dilation.

The pupil has been and is continuing to be studied by several branches of medical and physical sciences. There are several hundred peer-reviewed manuscripts on the pupil published each year. As medical scientists become more and more specialized, their language and word usage take on specific meanings that are only completely understood by colleagues within the same specialty. Consequently, when an ophthalmologist interacts with a specialist in intensive care medicine and they discuss the pupil, certain sentences fail to convey their intended meaning. For example, a neurologist's use of the term "relative afferent defect" might go completely unnoticed by the pulmonologist who is directing the care of the patient, and this oversight might have important clinical ramifications. One method by which to correct this miscommunication is to examine the terms that have been used historically to describe pupillary behavior. Hopefully these specialized terms will then be more easily transferred across specialties so that more comprehensive discussions can take place.

Life and death, awareness, cognition, sensation, perception, anxiety, pain, and drug intoxication . . . these are the issues that physicians contend with daily. The pupil and its reflexes can provide useful information on many of these topics. However, unless the practitioner admits that there is a problem with the evaluation of pupillary reflexes as it is often performed, then there will be little motivation to use a newer technology that can provide valuable data affecting the care of patients.

Before proceeding, certain facts about the portable infrared pupillary measurements should be made clear. First, it is not possible at the present time to measure the pupil continuously. Second, it is not possible to extract meaningful information through the closed eyelid. Ultrasound images of the pupil have been reported that can detect the presence or absence of the light reflex (21), but these methods have not yet been confirmed. In the future there might be methods that will be able to measure the pupil through the closed eyelid, but for now the cornea must be exposed. Third, midbrain and spinal cord clusters of neurons control the pupillary movements, so a functioning cerebral cortex is not necessary for pupillary reactions to be present. There are cortical influences on the pupillary light reflexes that will be discussed later, but the presence or absence of the reflex depends entirely on subcortical pathways. If the clinician understands how the pupil is controlled from the central nervous system, then at appropriate times these measurements can be taken, and useful information can be obtained. Finally, these instruments can measure the presence or absence of the consensual reflex, but giving a precise value to that reflex is not possible. It is possible to stimulate one eye with a pen light and measure the reflex in the opposite pupil with the portable instrument set at a zero-background light intensity. The stimulating light would vary between different measurements, so the light intensity would not always be the same. A modification of the Neuroptics pupillometer was described 20 years ago that would measure the consensual reflex with a portable pupillometer, but it is not commercially available at this time (22).

The normal human pupil ranges in diameter from 3 to 5 mm and over a daily 24-hour cycle may change from 2 to 8 mm. No other autonomic measure exhibits such a wide range of activity. The pupil fluctuates widely during periods of fatigue and in the interval just before sleep. It is miotic during slow-wave sleep and dilates during arousal and in darkness. Pupillary reactivity is maintained throughout the day and night. This is the normal behaving pupil.

During critical illness, there are factors that interrupt this normal behavior. These factors include the use of drugs that alter pupil size and reactivity, and the interruption of normal circadian rhythms. These changes in pupillary behavior are predictable and are well known to the average practitioner. Some pupillary changes, however, are outside the normal range of what is expected and thus represent erratic behavior. For example, 15 mg of intravenous morphine should produce a miotic pupil in the range of 2 to 3 mm as measured in darkness. If this does not occur, it would raise certain diagnostic questions regarding that patient (see Chapter 12). The pupil therefore provides information about the patient that might otherwise go undetected. Several other examples of how pupillary signs can assist the physician in the safe management of patients will be discussed in the following pages. Of primary importance is a thorough understanding of the light reflex and pupillary reflex dilation, the two basic pupillary reflexes.

This monograph traces the historical development of our present-day understanding of the pupil as it relates to the clinical practice of acute medicine. It is also a clinical guide to the diagnosis and interpretation of pupillary behavior in the hospital and office setting. It is not a book for the neuro-ophthalmologist who can study the pupil with specialized equipment in the office. Therefore, the author has purposely not emphasized several techniques used by the neuro-ophthalmologist such as the slit lamp and large office-based pupillometers. Also, the author will not discuss the detailed clinical use of many of the topical medications such as cocaine, methamphetamine, dapiprazole, brimonidine, and dopamine. Except for special clinical situations, these methods are omitted because other books provide a thorough treatment of this subject, and in the acute setting their use can result in anisocorias that further complicate evaluation of the patient.

New information about the pupil in the past 10 years has enabled the author to emphasize points that are not commonly known by many physicians. The book is intended to review this most recent information on the pupil and its reactions and thereby encourage other practitioners to intermittently measure the pupil with a portable instrument. Hopefully the following chapters will provide the framework to elevate this long-held interest in the pupil from just one of casual observation to an understanding that can benefit patients.

Chapter 1 Early History of the Pupil

> The radiation diffuses from the psychic spirit that emerges from the brain to the pupil through the two hollow nerves that pass from the brain to the pupil. From there it spreads out in the air to visible objects so as to be an organ of the viewer.
>
> (Qusta ibn Luqa, *Book on the Causes of the Difference in Perspectives*)

1.1 Ancient Greek and Roman Thoughts about the Pupil

Prehistoric societies would have readily learned the importance of the inner black circle (pupil) of the eye. Any obstruction to the passage of light through the pupil would block vision. Simply lowering the eyelid to cover the pupil obstructs vision, a fact the first humans would readily discover. Because of the vital importance of vision to survival in these early societies, preservation of the pupil and the apparatus of vision would have been paramount to survival. Little wonder therefore that the two concentric circles, the iris and the pupil, became one of the earliest icons of human societies, eventually to be replicated in all societies in their visual arts and religious symbols.

The mechanisms involved in vision have perplexed scholars for over 3,000 years. Hippocrates (460–370 BCE) mentions the pupil briefly and observed that it was a colorless, transparent liquid. He stated that it was only black because it was situated in the depths of the eye and surrounded by dark membranes. Over time, the ancient Greek philosophers developed conflicting ideas about vision and the function of the pupil. Two schools of thought emerged: the extramission theory and the intromission theory.

Plato (428–348 BCE) thought vision involved a vital energy that originated within the eye and passed through the pupil to the object in view. This energy or force was then combined with a visual ray emanating from the object and the combined force was then redirected into the eye where the image was formed and transmitted to the brain. This was the extramission theory that has persisted in one form or another even up to the present day. Plato was not the first to describe the extramission theory, but he promoted it, and it is often referred to after the Renaissance as the Neo-Platonism theory of vision.

Aristotle (384–322 BCE) drew upon the Hippocratic doctrine because he stated that the pupil was water (liquid) and furthermore it was in this liquid where the image was formed. His idea was that the viewed object sent out invisible rays and these rays reformed the object inside the pupil. This was the intromission theory. Aristotle's idea followed the well-known observation that a reflected image can be observed when one looks (carefully) at the pupil of another person. To Aristotle, this image in the water of the pupil was transmitted by the blood to the heart where perception took place. This intromission theory promoted by Aristotle rejected any rays coming out of the eye through the pupil, but instead noted that light passed into the eye. The actual image-forming portion of the eye was not known to the Greek or Roman thinkers, but both Aristotle and Plato thought that the image was formed within the pupil or just behind it in the crystalline lens.

Over 500 years later, Galen of Pergamon (129–216 CE) (Figure 1.1) was taught early in his career by Greek physicians founded in the cult of Asclepius, a society without a firm scientific foundation. During his life, Rome had emerged as the dominant society and his wealthy patrons were high-ranking Roman citizens, even the popular emperor Marcus Aurelius. Although he was a skilled theorist, many of his contributions were based on his own tireless observations. His early papers were the first ones to document life (i.e., movement) in the pupil. Galen thought that nature did nothing without a purpose and he saw marvelous workings in the human eye. Galen was a strong proponent of the

Figure 1.1 Prominent scientists who studied the pupil and pupil reactivity. Galen: Wellcome Library, London. Public Domain Mark, Reference 3349i. Ibn al-Haytham: Wikimedia Commons. Creative Commons CCO License. Creative Commons Attribution-ShareAlike 4.0 International License. Johannes Kepler: Wellcome Library, London. Line engraving by N. Dietz. Public Domain Mark. Reference 4989i. Pourfour du Petit: Wellcome Library, London. Photogravure by I. Schutzenberger after J. Restout, 1737. License: Public Domain Mark. Robert Whytt: Wellcome Library, London. Available for reproduction under Creative Commons Attribution CC BY 4.0. Loewenfeld image: License Number: 5603830631563 from Wolters Kluwer Health, Inc. Lowenstein Image: License Number: 5614231355848 from Wolters Kluwer Health, Inc.

extramission theory and used his ideas to formulate diagnostic tests for visual acuity in preparation for cataract surgery (23).

Galen observed that if he blocked the light from entering one eye, it produced a dilation (widening) in the opposite pupil. His idea was that by blocking the vital spirits with an obstruction over one eye, they were prohibited from passing through that pupil, so they were then directed into the other side, i.e., the opposite pupil. With one side blocked from light, the spirits which would normally be directed through both eyes were now directed only into one eye, producing a more dilated pupil. He also thought that by closing one eye, this directed twice the amount of "pneuma" into only one eye and this improved the vision in the open eye.

Galen made the first true observations of pupillary activity, but his theory was erroneous and could not hold up to careful examination, even by his contemporaries who practiced medicine during his time. Pneuma, for example, was not supposed to be a substance at all . . . in other words, Galen's own description of pneuma that passed into the iris to inflate it and make it dilate was not matter at all because it was only a spirit. This pneuma was supposed to escape from the eye, then meet the object in view, and then return to the eye again and produce the image within the lens. From there, it was transported back to the lateral ventricle where perception took place.

But Galen describes the iris as inflating by an infusion of some substance like air or fluid, and in fact Galen claims to have demonstrated that the pupil could be made to dilate by injecting air or fluid into the anterior chamber of the eye. So, with Galen we have the first discovery, but also the first inconsistent and erroneous conclusion about how the pupil works. This uneasy balance between an observation and the explanation of why it occurs will be a consistent theme as we wind our way through this historical account of pupillary physiology.

Galen's discussion of the pupil was a practical one and directed toward the question of when (and if) to operate on a patient with a dense cataract. Removal of a cataract would only be beneficial if the visual apparatus behind the pupil was functionally intact. If a cataract was removed, the patient might still be blind if disease was also present behind the cataract. Thompson states (23) that Galen's test was to observe the good eye while blocking light intermittently to the diseased eye (the one contemplating extraction). With an intact posterior portion of the eye, the good eye should then intermittently constrict and dilate. Failing that sign, Galen would refuse to operate. As we further develop the story of the pupil, we will realize that Galen's test was valid, but his reasoning was faulty.

Galen's influence extended into the Renaissance. Paolo Veronese Caliari (1528–1588) created "The Creation of Eve" that can be viewed in the Art Institute of Chicago (Figure 1.2). The painting might be interpreted according to Galenic idea of vital energy emerging through the pupil. In the painting, the Lord covers one of Eve's eyes and observes the other eye. Galen had speculated that the opposite eye dilated because the vital energy that normally emanated through both eyes was now constrained to be released through only one eye. With this test, the Creator would confirm intact vision for Eve. Of course, the painting has many interpretations (24, 25).

Today, the science of ophthalmology is firmly in the intromission camp, but public opinion continues to be fascinated and wants to believe that there is an inner light that shines out through the pupil into three-dimensional space and illuminates objects in view. Science fiction movies commonly show creatures with light and laser beams emanating from the eyes that exert special powers on their intended targets. Is there

Figure 1.2 Paolo Venonese Caliari, *The Creation of Eve*, 1565–1575. The Art Institute of Chicago. The painting has many interpretations, but some authorities suggest that the Lord is testing for the presence of the light reflex. Image is made available under Creative Commons Zero designation from the Art Institute of Chicago CCO Public Domain Designation.

a role for the extramission theory in our modern construct of vision? It is now known that vision is not simply the processing of the retinal image by the visual cortex, a process that is well known to the perceptual sciences. But the inner light directs the pupil to focus a small area of the world view onto the fovea (see discussion in Chapter 2). The mobile eye is therefore crucial to our visual process and has its foundation in the works of scholars dating back several hundred years.

1.2 Arabic Scholars Advance the Science of Optics

With the fall of Rome, Western society slowly drifted into the Dark Ages, and Galen's work was nearly forgotten. The pupil was initially misunderstood by the early Arabic scholars (Figure 1.3) taking the Hippocratic idea that the pupil was a dark membrane inside the eye containing clear liquid.

Fortunately, Islamic medicine translated the works of the Greek physicians into Arabic, leading to the next major developments in our understanding of the pupil. Starting in the ninth century, several Arabic scholars such as Avicenna, Alhazen, Rhazes, and al-Kindi borrowed upon the optical treatises of Euclid, a Greek mathematician who lived in the third century BCE. They confirmed Euclid's theories that light travels in straight lines, but could not agree that light was emitted from within the eye.

Cambridge University Press & Assessment
978-1-009-43629-8 — A Practical Guide to Portable Pupillometry
Merlin D. Larson
Excerpt
More Information

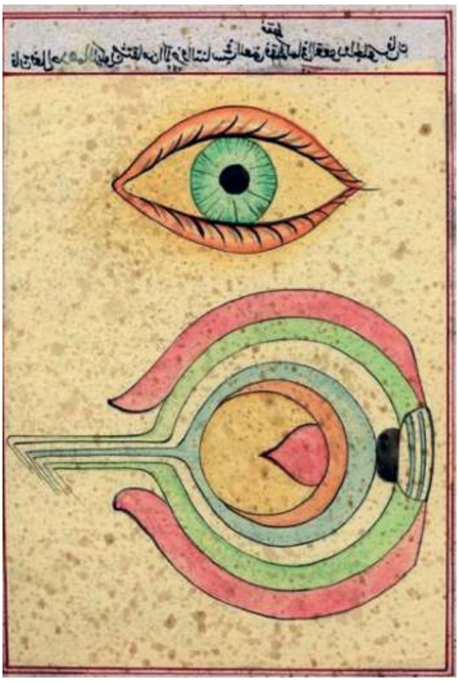

Figure 1.3 Early ninth-century Arabic illustration of the eye anatomy. Artist unknown. Property of author.

The Arabic scholars correctly thought that light enters the pupil and forms an image within the eye that is transferred to the brain for interpretation. Arabic scholars studied the works of Galen carefully, but they did not read his work as the final authority. Consequently, Islamic physicians made important original contributions to pupillary physiology.

Abu Bakr Muhammad Ibn Zakariya al-Razi, known as Rhazes (864–925 CE), is usually credited with being the first physician to note that light constricted the pupil. Rhazes, considered by some to be one of the greatest medical clinicians of all time, practiced in Baghdad and wrote extensively on many topics ranging from music to philosophy. He was the first to describe smallpox and differentiate that disease from measles. Although Rhazes described the light reflex, he continued the error that image formation occurred on the lens (or within the vitreous glassy humor), an error that was not corrected until the seventeenth century.

In retrospect, we know that Galen was really observing the effect of light on pupil diameter in the opposite eye (consensual reflex). Unfortunately, his adherence to the idea of vital spirits coming out of the eye prevented him from recognizing the fact that an increase in ambient light constricted the pupil. Today, we refer to this phenomenon simply as the light reflex, one of the most valuable clinical signs in the physical examination. In later chapters, we will return to the light reflex and explain why it is so important to clinical medicine. For now, however, it is only necessary to explain that Rhazes described the reflex, but was unable to explain why or how it occurred.

The observation by Rhazes significantly simplified the cumbersome test that Galen used to establish a functional retina and optic nerve behind a diseased lens. Rhazes and others observed that it was only necessary to observe the presence or absence of a light reflex in the diseased eye. Without the presence of a light reflex, there would be no point in removing a cataract because the clinical examination would indicate disease behind the lens. There are exceptions to this rule in patients who have tonic pupils and oculomotor nerve deficits that will be discussed in Chapter 5.

The optical treatises of Ibn al-Haytham (latinized as Alhazen, 965–1040 CE) became the initial source of information on how light is transmitted through the eye to produce an image. Alhazen was an Arabic philosopher who lived in the eleventh century. His interests were varied, but his legacy is due chiefly to his book entitled *Book of Optics*, written while he was sentenced to house arrest from 1011 to 1021. Alhazen was placed under house arrest because he thought he could dam the Nile River at Aswan. The Fatimid Caliph of Egypt (Al-Hakim bi-AmrAllah) commissioned him to achieve this feat, which with the engineering methods available in the eleventh century was soon discovered to be impossible. The Caliph was an intolerant ruler who severely punished his subordinates who were unable to fulfill their missions. To avoid being put to death, Alhazen feigned madness and was placed under house arrest where he had time to think about the nature of light and optics. During this time, he discovered basic principles of the camera obscura.

In the fourth century BCE, Aristotle had observed that, during a partial eclipse of the sun, crescent images were projected on the ground as the sunlight passed through a tree canopy (Figure 1.4). But Aristotle was not aware that light traveled in straight lines, so he was not able to envision the concept of the pin-hole camera. As previously discussed, Aristotle thought the visual image was captured by the lens and transmitted to the heart, where the image was processed. Although the Islamic scholars were familiar with Greek and Roman science, it is unlikely that the discovery of the camera obscura by Alhazen was influenced by Aristotle.

During the long hours that he spent under house arrest, Alhazen had time to contemplate the nature of light and develop his optical theories. The Caliph's edict thus eventually led to a book that has been ranked as one of the most influential books of all time relating to vision and optical theory. Alhazen observed the effect of light passing through small apertures. His famous experiment revealed that the passage of light through small holes (pupils) will project a reversed and inverted image on a screen. He reiterated Euclid's theories that light traveled in straight lines and then described the effect of lenses, mirrors, and prisms on the path of light rays. He successfully projected an

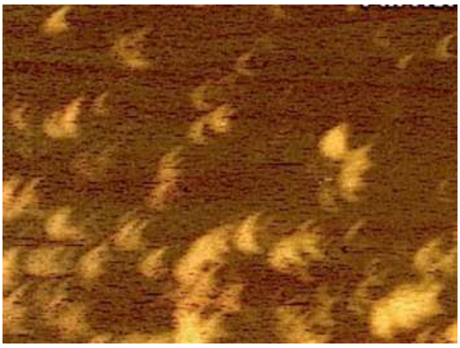

Figure 1.4 Images on the pavement below a tree canopy during a partial eclipse of the sun on October 23, 2014. Photograph by author.