

DEVELOPMENT OF THE OCULAR LENS

Edited by

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1

The Lens: Historical and Comparative Perspectives

Michael L. Robinson and Frank J. Lovicu

1.1. Lens Anatomy and Development (Pre-1900)

The past decade has witnessed a tremendous increase in the basic understanding of the molecules and signal transduction pathways required to initiate embryonic lens development. Other advances in this time period have elucidated structural and physiological properties of lens cells, often in an evolutionary context, making it possible to frame many pathological conditions of the lens as errors of specific developmental events. All of these recent advances rest on the fundamental observations of talented investigators in previous decades and centuries. While several texts describe the history of ophthalmology as a clinical discipline, the conceptual history of basic eye research as a science, and in particular the history of lens development research, is a much less traversed subject. Though it is inevitable that we cannot include all of the many important experiments and personalities that have played fundamental roles in shaping the field of lens development, we hope to stimulate appreciation for those pioneers, both past and present, to whom we owe a debt of gratitude for their contributions to the field.

Throughout human history, the sense of sight has been both treasured and revered. Without doubt, visual loss resulting from lens dysfunction has always plagued the human family. In the early years of lens development research, investigations of the eye were intertwined with the genesis of the field of ophthalmology. Two valuable texts, extensively cited in this chapter, provide much more detail on the origins of this medical discipline than we are able to offer here. For those particularly interested in the history of ophthalmology, we recommend *The History of Ophthalmology*, edited by Daniel Albert and Diane Edwards (1996), as well as Julius Hirschberg's eleven-volume series *The History of Ophthalmology*, translated by Frederick C. Blodi. We also highly recommend Howard B. Adelman's *Marcello Malpighi and the Evolution of Embryology* (1966). Adelman's text presents a good history of ocular embryology in volume 3 under Excursus XII, "The Eyes."

For many, the history of research in eye lens development largely dates back to the famous experiments of Hans Spemann and his work on lens induction at the turn of the twentieth century. However, descriptive knowledge of all the basic ocular structures was well established by the time Spemann began his experiments. Spemann's fundamental experiments on lens induction, along with those of Mencl and Lewis, are reviewed in subsequent chapters (see, e.g., chap. 2). One of the aims of the present chapter is to review the major recorded advances in the understanding of the anatomy, pathology, and development of the ocular lens from antiquity up to 1900.

The ancient Egyptians may have been the first to document cases of cataract, as this was likely the disease state referred to under the descriptions 'darkening of the pupil' and 'white

disease of the eye' (Edwards, 1996). The Greek philosopher Alcmaeon conducted the first recorded human dissections about 535 BC (Weisstein, 2003). Although these dissections included examinations of the human eye, no specific mention was made of the lens (Magnus, 1998). There is some debate as to when the lens was first recognised as a distinct anatomical entity. In the Hippocratic book entitled *Fleshes*, written about 340 BC, roughly 35 years after the death of Hippocrates, there is a description of the internal contents of the human eye that reads thus: 'The fluid of the eye is like jelly. We frequently saw from a burst eyeball a jelly-like fluid extrude. As long as it is warm it remains fluid, but when it cools, it becomes hard and resembles transparent incense; the situation is similar in man and animals' (Hirschberg, 1982, p. 72). The jelly-like fluid is often interpreted to be the vitreous, but the hard, transparent remnant described in the quotation is thought to be the lens. Prior to and during this period, it was believed that the lens was liquid and that it only became solid as the result of disease. The observation that the internal contents of human and animal eyes were similar suggests that the fundamentals of comparative anatomy were already familiar to the ancient Greeks. Some followers of Hippocrates performed detailed studies of chick development and discovered that the eyes were visible early in embryogenesis. This finding contradicted the belief, later expressed by Pliny the Elder (23–79 AD), that human eyes were the last of all human organs to develop in the uterus (Magnus, 1998). Aristotle (384–322 BC), often considered the founder of biology, performed numerous dissections of mature and embryonic animals. In describing the anatomy of a ten-day-old chicken embryo, Aristotle wrote, 'The eyes about this time, if taken out, are larger than beans and black; if their skin is removed the fluid inside is white and cold, shining brightly in the light, but nothing solid' (Magnus, 1998). Again, the failure to appreciate the solid nature of the lens suggests a general lack of knowledge of its precise structure (Fig. 1.1). While Aristotle recognised that the eyes begin forming early in embryogenesis, he also believed that the eyes were the last structures 'to be formed completely' and mistakenly thought that they shrink during later embryonic development (Adelmann, 1966). Neither the ancient Egyptians nor the pre-Alexandrian Greeks had an anatomical term to describe the lens of the eye. As stated by Magnus (1998), 'Of a certain knowledge of the lens, nothing is to be found in the writings of the pre-Alexandrian era' (p. 54). Alexander the Great founded the Alexandrian School in Egypt in approximately 331 BC. This school became a great centre of Greek learning, and it was here that the dissection of corpses became a regular practice.

Roman medicine was profoundly influenced by Greek medical philosophy, and the most complete surviving Roman medical text was written by Aulus Cornelius Celsus, who lived from approximately 25 BC to AD 50. Celsus's book *De Medicina* was written about AD 30, and his anatomical descriptions of the eye were likely based on descriptions provided by earlier Greek authors (Albert, 1996a). Celsus did specifically mention the lens as resembling egg white, and he expressed what would become a long-held belief that the lens was the organ from which visual function originated (Albert, 1996a). In his diagrams of the eye, Celsus also mistakenly placed the lens in the centre of the globe (Fig. 1.2). Although couching, a surgical procedure to treat cataracts, likely originated in Asia or Africa prior to the birth of Hippocrates (Hirschberg, 1982), Celsus's writings provide clear documentation of this procedure, which was either unknown to or rarely practiced by the pre-Alexandrian Greeks. Couching, the only form of cataract surgery prior to the eighteenth century, involves displacing lens opacities by inserting a needle into the eye and depressing the lens against the vitreous until the opacity no longer obscures the pupil (Albert, 1996b). Cataract surgery in the days of Celsus, prior to the advent of anaesthesia, was obviously not for the faint of heart. In the seventh book of *De Medicina*, Celsus described the characteristics of a

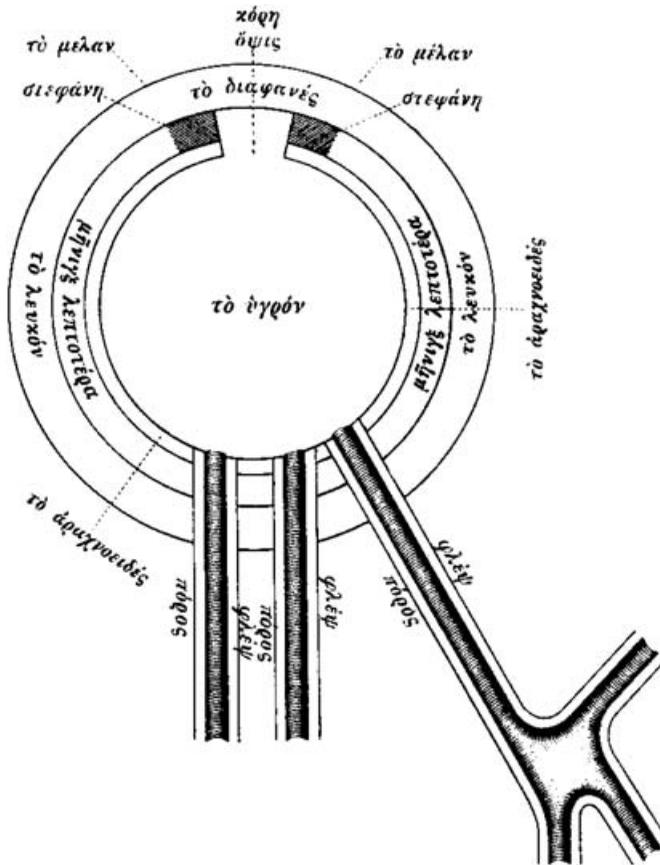


Figure 1.1. Reconstruction of the eye according to Aristotle. Note the absence of a structure representing the lens and the inclusion of three different vessels thought to transport fluids to and from the eye. (Reprinted from Wade, 1998b, after Magnus, 1901.)

desirable surgeon, as ‘a young man with a steady hand who could remain unmoved by the crying and whining of his patients’ (Albert, 1996a, p. 24).

Another important figure in early ophthalmology, and indeed all medical disciplines, was Claudius Galen (AD 130–200). Galen was born in Pergamon (currently in Turkey), was educated in Alexandria, and practised medicine in Rome. According to Galen, ‘1. Within the eye the principal organ of sensation is the crystalline lens; 2. The sensation potential comes from the brain and is conducted via the optic nerves; 3. All other parts of the eyeball are supporting structures’ (Hirschberg, 1982, p. 280). It was Galen’s view that the lens formed from the vitreous and that the function of the retina was to nourish the vitreous and lens as well as to transmit the visual information gathered from the lens to the brain (Albert, 1996a). Galen’s anatomical description of the eye, in contrast to that of Celsus, placed the lens in the proper location, in the ocular anterior near the pupil, which was identified by Rufus of Ephesus (Fig. 1.3) several years before Galen’s birth (Albert, 1996a). While Rufus had described the lens as ‘lentil- or disc-shaped with the same curvature on the front and back surfaces’, Galen recognised that the lens was more flattened on the anterior than on the posterior surface (Fig. 1.4; Magnus, 1998). According to Galen, cataracts, which

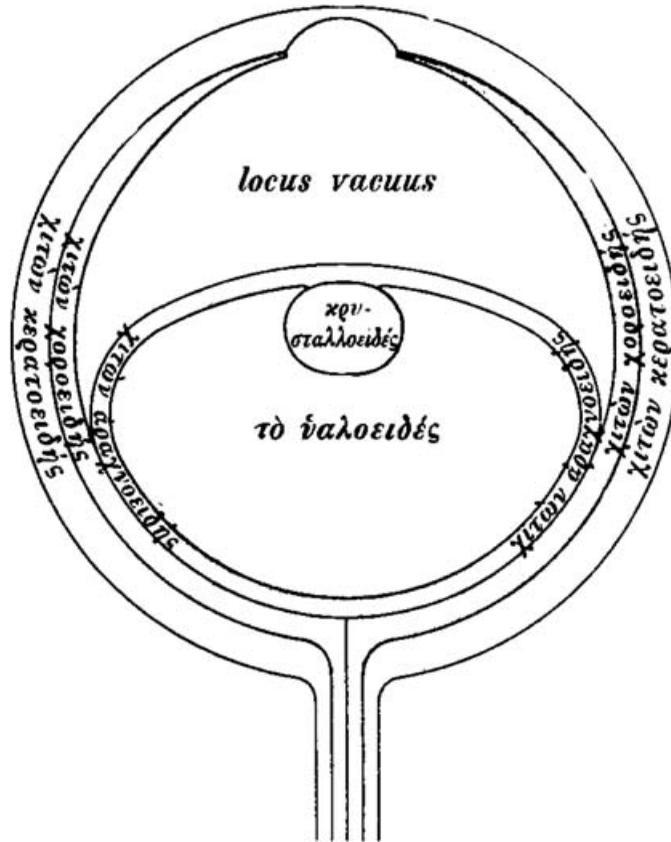


Figure 1.2. Reconstruction of the eye according to Celsus. Note the centrally located lens ‘chrysalloides’ within the vitreous ‘hyaloides’. (Reprinted from Wade, 1998b, after Magnus, 1901.)

he called ‘hypochyma’, were the result of a thickening or condensation of aqueous fluid that clots and lies between the iris and the lens (Hirschberg, 1982). Galen wrote over a hundred surviving books, and his influence on European medicine was so profound that he was referred to as the ‘final authority’ for nearly fourteen centuries after his death (Albert, 1996a). After Galen, only minor changes in the understanding of lens anatomy, development, function, and physiology occurred for the next 1,250 years. Certainly some advances were made in clinical ophthalmology during this period. Notably, around AD 1000, an Arabian ophthalmologist named Ammar produced a manuscript entitled *Choice of Eye Diseases* in which he described the removal of soft cataracts by a modification of the couching procedure: the opacity was removed by suction through a hollow needle rather than by depressing the lens against the vitreous (Albert, 1996a). This procedure was the first step toward the treatment of cataracts by lens extraction pioneered by Jacques Daviel (1696–1762), a method that would ultimately replace couching (Albert, 1996a).

Leonardo da Vinci (1452–1519) has often been called the first great modern anatomist, and he did not ignore the eyes in his work. He made drawings from cadavers and is credited with devising the ‘earliest technique for embedding the eye for sectioning by placing it within an egg white and then heating the embedded specimen until it became hardened

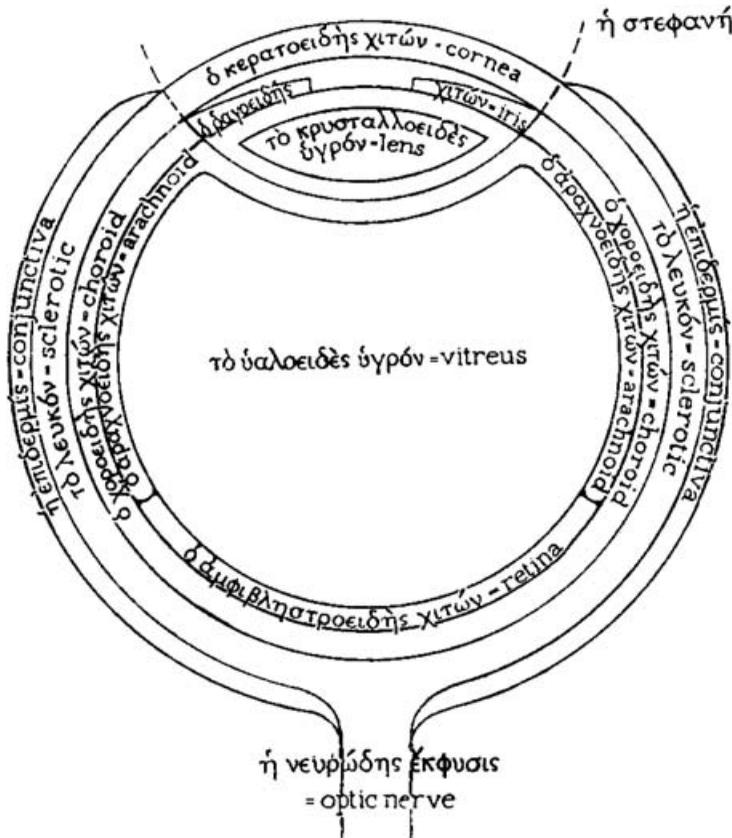


Figure 1.3. Reconstruction of the eye according to Rufus of Ephesus. Note that the lens is now represented directly behind the iris. (Reprinted from Wade, 1998b, after Magnus, 1901, with English labels added by Singer, 1921.)

and could be cut transversely’ (Albert, 1996c, p. 47). While not always correct in his interpretation of the results of his ocular studies, da Vinci did reject the view, then current, that the lens was the primary sensory organ of the eye. In his drawings, da Vinci depicted the lens as focusing incident light directly onto the optic nerve (Albert, 1996c). His drawings also showed the lens as overly large and placed in the center of the eyeball. The work of da Vinci was largely unappreciated by ocular anatomists for more than 250 years after his death.

Andreas Vesalius (1514–64) published an anatomical work, *De Humani Corporis Fabrica*, in 1543 while teaching anatomy in Padua. This work was widely copied throughout Europe and succeeded in becoming the anatomical standard, replacing the writings of Galen, which had dominated European medicine for more than 1,300 years. Vesalius continued the misconception that the lens was in the centre of the eyeball (Fig. 1.5), but he did demonstrate that the isolated lens acted ‘like a convex lens made of glass’ (Albert, 1996c, p. 48). Georg Bartisch (1535–1606) correctly positioned the lens behind the iris in his 1583 publication *Ophthalmodouleia: das ist Augendienst*, considered by Albert (1996c) to be ‘the first modern work on ophthalmology’ (p. 49). Bartisch’s work was also notable for being published in the vernacular German rather than Latin, as had been the tradition for medical texts until

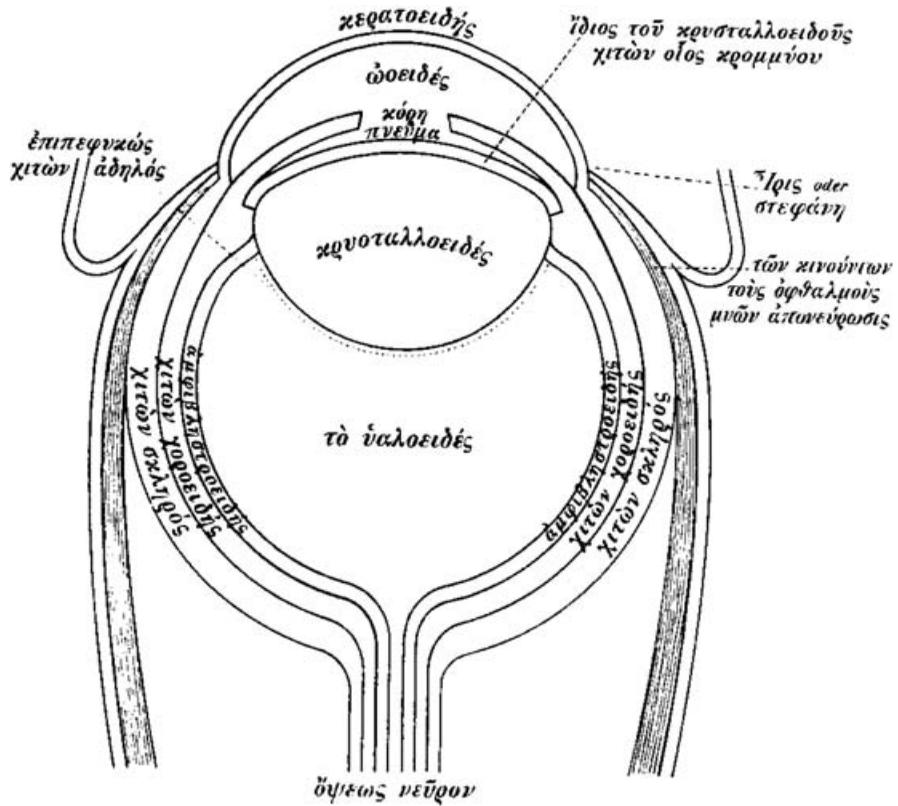


Figure 1.4. Reconstruction of the eye according to Galen. (Reprinted from Wade, 1998b, after Magnus, 1901.)

that time. Falloppio Hieronymus Fabricius ab Aquapendente (1537–1619), like Vesalius, became a professor of anatomy at Padua. Fabricius studied anatomy, embryology, muscular mechanics, and surgery. He is also known for being a mentor of William Harvey, who later discovered the process of blood circulation. Fabricius's work in embryology mostly concentrated on chick development. Fabricius incorrectly believed that the chicken embryo was derived from neither the egg white nor the yolk but from the chalazae, the rope-like strands of egg white that anchor the yolk. He constructed several arguments to support his belief. He asserted, for example, that the three visible nodes in the chalazae are the precursors of the brain, heart, and liver and that 'the eyes are transparent, so are the chalazae, therefore the latter must give rise to the former' (Needham, 1959, p. 108). To his credit, Fabricius, in the *Tractatus de Oculo Visuque Organo*, published in 1601, depicted the lens directly behind the iris and not separated from the pupillary margin by the 'cataract space' (Albert and Edwards, 1996c, p. 49). Harvey himself investigated the developing embryos of the chick and other animals, such as deer and sheep. He made the observation that 'the eye in embryos of oviparous animals is much larger and more conspicuous than that of viviparous animals' (Adelmann, 1966, p. 1238).

Felix Platter (1536–1614) was an anatomist in Basel who carried out the first public dissections of the human body in a Germanic country (Albert, 1996c). In 1583, Platter published *De Corporis Humani Structura et Usu*, relying heavily on previous illustrations

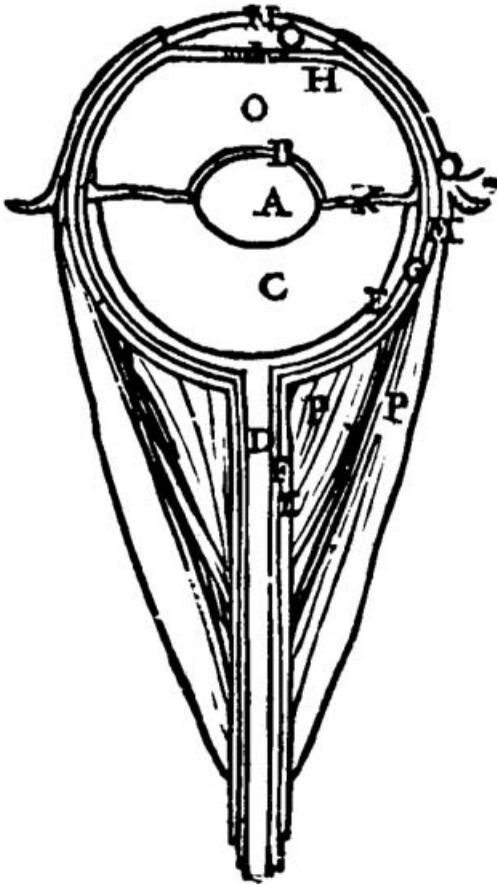


Figure 1.5. The anatomy of the eye according to Vesalius. A, crystalline lens; B, portion of the capsule; C, vitreous body; D, optic nerve; E, retina; F, pia-arachnoid coat of optic nerve; G, choroid; H, iris; I, pupil; K, ciliary processes; L, dural coat of the optic nerve; M, sclera; N, cornea; O, aqueous humour; P, ocular muscles; Q, conjunctiva. (Reprinted from Wade, 1998b, after Saunders and O'Malley, 1950.)

from Vesalius (Fig. 1.6). Notably, in *De Corporis*, Platter concluded that it was the retina, rather than the lens, that was the primary visual sensory organ in the eye, and he emphasised this view in a subsequent publication, *Praxeos Medicae*. Platter's nephew, Felix Platter II (1605–71), disseminated his uncle's view that the retina was the primary visual structure, and the publication of his dissertation, *Theoria Cataractae*, was responsible for 'finally displacing the crystalline lens as the true seat of vision' (Albert, 1996c, p. 50). The primacy of the retina in visual perception was confirmed by the work of Johannes Kepler (1571–1630). Kepler was an astronomer whose work with glass optical lenses shaped his views on the functional anatomy of the eye. Kepler published *Ad Vitellionem Paralipomena* in 1604 and *Dioptrice* in 1611, and both of these works had a substantial impact on the field of ophthalmology. In *Dioptrice*, 'Kepler convincingly demonstrated for the first time how the retina is essential to sight and explained the part that the cornea and lens play in refraction' (Albert, 1996c, p. 51). In 1619, Christoph Scheiner (1575–1650) supported Kepler's beliefs about the retina with his work *Oculus hoc est*, in which he presented diagrams of the eye

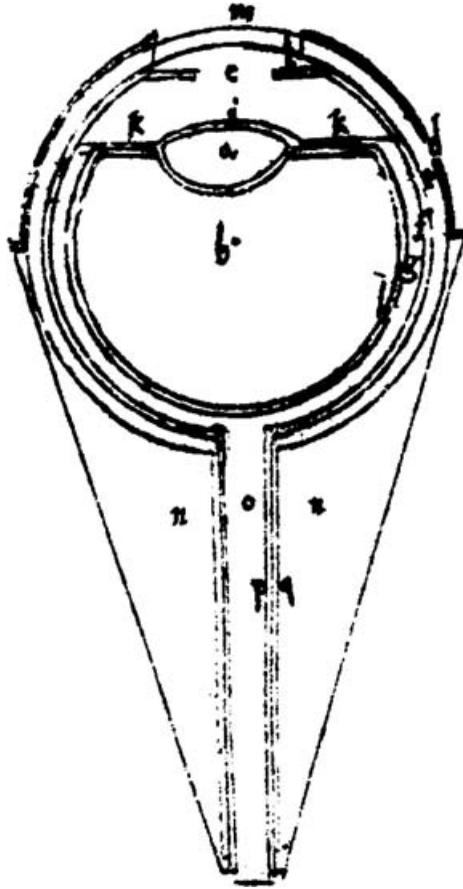


Figure 1.6. The anatomy of the eye according to Platter. a, crystalline humour; b, vitreous humour; c, aqueous humour; d, related coat; e, opaque part of the sclerotic; f, choroid; g, retina; h, hyaloid; i, crystalline capsule; k, ciliary processes; l, boundary of the choroids on the sclerotic; m, cornea; n, ocular muscles; o, optic nerve; p, thin nerve membranes; q, thick nerve membranes. (Reprinted from Wade, 1998b.)

showing how images are projected onto the retina. Scheiner is also given credit for drawing the first anatomically correct diagrams of the eye (Fig. 1.7) and for understanding that the optic nerve head is not in the optical axis but enters the right eye on the left side and the left eye on the right side (Wade, 1998a, pp. 78–80). He also described how the curvature of the lens could change during accommodation and devised a pinhole test for illustrating accommodation and refraction (Albert, 1996c).

Until the seventeenth century, all the investigations of the adult and developing eye were the result of indirect or direct observations of living or postmortem specimens with the naked eye. The course of eye research changed dramatically with the invention of the microscope. The invention of this instrument also set the stage for the emerging fields of embryology and developmental biology to diverge from more medically related disciplines, such as anatomy and pathology. According to Albert (1996c), the first microscopic investigation of an eye was by Giovanni Battista Odierna (1597–1660), who extensively described the fly eye in his treatise *L'occhio della Mossca*, published in 1644. Marcello Malpighi (1628–94),

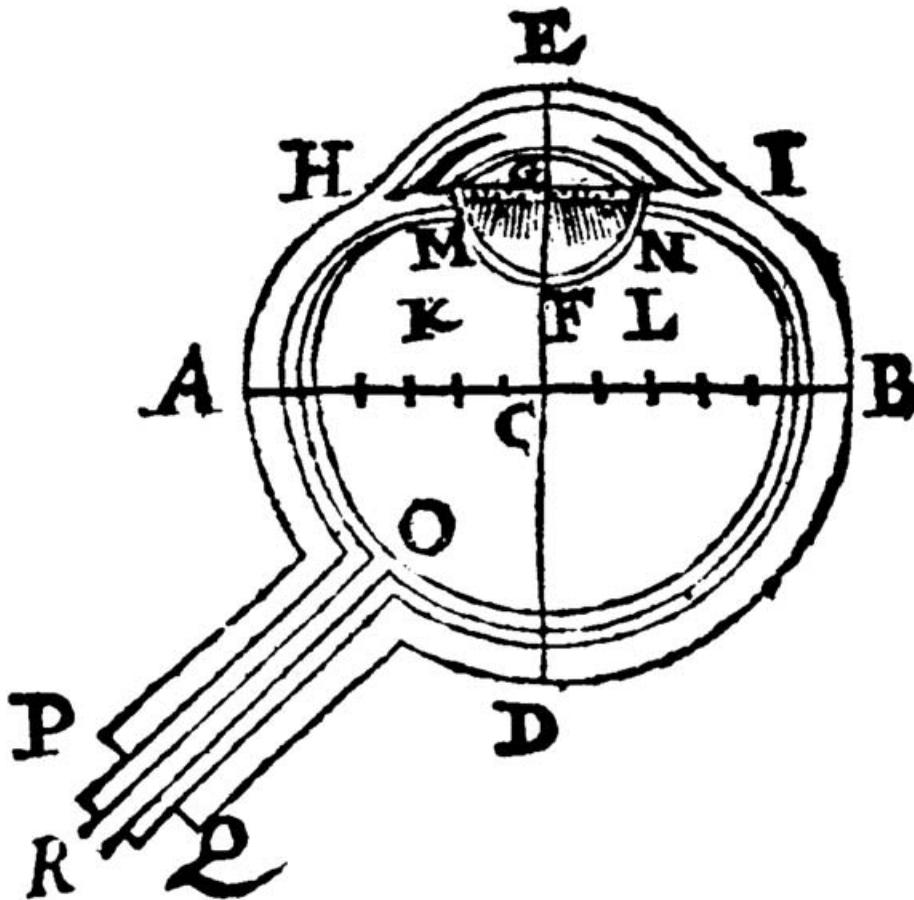


Figure 1.7. Anatomy of the eye according to Scheiner. Note that, in contrast to the previous illustrations of ocular anatomy, the optic nerve is not drawn in a direct line with the lens and cornea. (Reprinted from Wade, 1998b, after Scheiner, 1619.)

known as ‘the founder of histology’, was a professor of anatomy at Bologna, Pisa, and Messina and became a physician to Pope Innocent XII in Rome shortly before his death (Albert, 1996c). In 1672, Malpighi submitted two dissertations describing the embryonic development of the chick – *De Formatione Pulli in Ovo* and *Appendix Repetitas Auctasque De Ovo Incubato Observationes Continens* – to the Great Royal Society of England (Adelmann, 1966). The former described the development of the chick with the blastoderm lying on the yolk. In the latter, Malpighi described an isolated embryonic blastoderm mounted on a piece of glass and viewed under a microscope (Adelmann, 1966). Malpighi made several fundamental observations regarding the development of the eyes. He did not recognise their connection to the forebrain, but he did discover the optic vesicles, and he made many detailed illustrations of the developing chick eye that would be unsurpassed for decades after his death (Adelmann, 1966). While Nicolaus Steno (1638–86) was probably the first person to identify the choroid fissure, during his observation of the developing chick in 1665 (Steno, 1910), he did not publish his manuscript *In Ovo et Pullo Observationes* until 1675 (Adelmann, 1966). Therefore, Malpighi’s illustrations of the choroid fissure were published

before those of Steno. Anton van Leeuwenhoek (1632–1723) also used the microscope to investigate the eye in the late seventeenth and early eighteenth centuries. Though a shop-keeper and civil servant by profession, he is credited with discovering the retinal rods, the fibroepithelial layers of the cornea, and the fibrous structure of the lens (Albert, 1996c).

From the time of Galen, cataracts were thought to be the result of insoluble substances (humors) or membranes forming between the iris and the lens. This view persisted well into the seventeenth century. Antoine Maître-Jan (1650–1725) was a French ophthalmologist and surgeon who suspected in the 1680s, during couching surgeries, that cataracts were actually opacities within the crystalline lens (Albert, 1996c). Maître-Jan confirmed his suspicions in 1692 during an examination of the lens from a deceased cataract patient. In 1707, his findings were published in the *Traité des Maladies des Yeux* (Albert, 1996c). In addition to his work with living and postmortem human eyes, Maître-Jan also studied the eyes of embryonic chicks. In the course of his studies, Maître-Jan was the first to introduce the use of chemical fixatives to preserve ocular structures and for discovering the ‘onionlike’ layered structure of the crystalline lens (Adelmann, 1966).

Albrecht von Haller (1708–77) initially began studying the development of the chick to observe the formation of the heart, but he was drawn into the study of ocular development as well. He wrote in 1754 that ‘the beauty of the structure of the eye has beguiled me into making some observations lying outside my primary purpose’ (Adelmann, 1966, p. 1245). Haller’s contribution to ocular embryology lay primarily in his descriptions of the ciliary body and ciliary zonule and how these are related to the lens and vitreous. Much of the necessary observation was done by or with the assistance of his prized student at the University of Göttingen, Johann Gottfried Zinn (1727–59). In 1758, Haller wrote,

Some very careful anatomists have seen in man and in the quadrupeds a thin, pleated lamina detach itself from the membrane of the vitreous and attach itself to the capsule of the lens. This lamina is what forms the anterior wall of the circle [canal] of Petit. Zinn, my illustrious pupil and my successor, has described this lamina and called it the ciliary zone. (Adelmann, 1966, p. 1247)

Zinn would ultimately die before Haller, but he did publish *Descriptio*, which was the first complete publication on ocular anatomy and which remained a standard atlas of the eye well into the nineteenth century (Albert, 1996c).

While descriptions of the anatomy of the vertebrate embryonic and adult eye had progressed a great deal in the 2,122 years between Aristotle’s death and 1800, a true understanding of the embryonic origins of the lens or other ocular tissues was still lacking at the dawn of the nineteenth century. The descriptive embryology of the eye was to blossom in the 1800s, providing the framework necessary for Spemann and others to carry on the work of experimental rather than descriptive developmental biology in the twentieth century.

Karl Ernst von Baer (1792–1876) was a Prussian embryologist who laid many of the foundations of comparative embryology. Von Baer is often recognized for discovering that the optic vesicles were indeed an outgrowth of the embryonic forebrain. This discovery, however, was first published in the 1817 Latin dissertation of one of von Baer’s friends, Christian Pander (1794–1865), who is best known for discovering the three embryonic germ layers (Adelmann, 1966). Von Baer extended the observations of Pander, suggesting that fluid pressure from inside the central nervous system was the motive force for the outgrowth of the optic vesicles. He also believed that the optic vesicle opened at the end to form the future pupil and that the vitreous body and lens were formed by the coagulation of fluid

within the optic vesicle (Adelmann, 1966). Von Baer's views on eye development were presented in *Entwicklungsgeschichte der Thiere*, published in two parts in 1828 and 1837.

Emil Huschke (1798–1858) in many ways demonstrated a better fundamental understanding of vertebrate eye development than von Baer. Among his most important contributions was the recognition in 1830 that the lens forms not from the fluid of the optic vesicle but as an invagination of the integument (surface ectoderm). In his 1832 manuscript *Ueber die erste Entwinklung des Auges und die damit zusammenhängende Cyklopie*, he stated 'The lens capsule is a piece of the outer integuments which separates off and retreats inward, to be covered again later by several membranes, for example, by the cornea' (Adelmann, 1966, p. 1272). However, he mistakenly believed that the substance of the lens was a fluid secreted by the walls of the lens vesicle. Huschke is also given credit for discovering that the optic vesicle forms the double-layered optic cup, though he misinterpreted the ultimate fate of the individual optic cup layers (Adelmann, 1966). His description of the formation of the optic cup and choroid fissure also corrected von Baer's erroneous views of the formation of the pupil.

Wilhelm Werneck (d. 1843) announced in his 1837 publication *Beiträge zur Gewebelehre des Kristallkörpers* that the internal substance of the lens was not fluid: 'The contents of this capsule [the lens] are not fluid, as I earlier believed, but are of a more pulpy character' (Adelmann, 1966, p. 1277). Werneck also realised that lens fibers grow during embryogenesis – 'the fibers, continuing to grow from the periphery toward the centre, become increasingly visible' – but he apparently did not recognise that elongation of the primary lens fibers occurred in a posterior to anterior direction (Adelmann, 1966, p. 1277).

In 1838, Matthias Jakob Schleiden (1804–81) and Theodor Schwann (1810–82), both students of the German physiologist Johannes Müller (1801–58), formulated what would become known as the 'cell theory'. According to this theory, all living things are formed from cells, the cell is the smallest unit of life, and cells arise from preexisting cells. The cell theory had a profound impact on all aspects of biological study, and Schwann himself made several important contributions to the understanding of lens development in his book *Mikroskopische Untersuchungen über die Uebereinstimmung in der Struktur und dem Wachsthum der Thiere and Pflanzen*, published in 1839.

The lens is known to be composed of concentric layers, made up of characteristic fibres, which, not to go into details, may be said to pursue a general course from anterior to posterior surface. In order to become acquainted with the relation which these fibres bear to the elementary cells of organic tissues, we must trace their development in the foetus. . . . In a foetal pig, three and a half inches in length, the greater part of the fibres of the lens is already formed; a portion, however, is still incomplete; and there are many round cells awaiting their transformation. . . . The fibers may readily be separated from each other, and proceed in an arched form from the anterior towards the posterior side of the lens. . . . Nuclei are also frequently found upon the fibres of the foetal pig. Some of the fibres are flat. I have, also, several times observed an arrangement of nuclei in rows; but I do not know what signification to attach to the fact. (Henry Smith's 1847 English translation, Adelmann, 1966, pp. 1278–79).

Robert Remak (1815–65) was also an embryologist who studied under Johannes Müller at the University of Berlin. Remak was the first to apply the cell theory to the three primary embryonic germ layers first described by Christian Pander. It was Remak who gave these germ layers their current names: ectoderm, mesoderm, and endoderm. His descriptions of embryonic eye development were the finest of the mid-nineteenth century. With respect to

the lens, Remak recognised that the ectoderm (*Hornblatt*) thickened to form what we now refer to as the lens placode as it is contacted by the optic vesicle. Remak also described the fate of the lens vesicle in previously unparalleled detail in his 1855 book *Untersuchungen über die Entwicklung der Wirbelthiere*:

That the lens invaginates into the optic vesicle from the outside, Huschke, as we know, discovered. But what this investigator did not and in the state of the science at his time could not know, is the fact which I have discovered, namely that this invagination proceeds from the upper germ layer, which later furnishes the cellular (epidermal) coverings of the body. . . . The bulk of the wall of the lens, after being constricted off, consists of cylindrical, radially arranged cells, which also resemble strongly the cells of a columnar epithelium in that they appear very sharply delimited on their free surface facing the cavity. Each cell contains one, in rare cases even two, nuclei. These nuclei do not, however, lie at the same level. . . . This layer of cells is surrounded by a . . . very thin, apparently 'structureless' membrane. . . . This is the anlage of the lens capsule. . . . All fibers pass without visible interruption from the posterior wall of the lens capsule to the anterior almost parallel to the visual axis; the fibers are, consequently, shorter the farther away they lie from the visual axis. Their anterior and posterior ends are cut off sharply. At some distance from its anterior end each fiber contains a nucleus, but no trace of nuclei can be detected at the posterior end. . . . The posterior end of each fiber is directly in contact with the lens capsule; the anterior end, on the other hand, is separated from it by an epithelium consisting of nucleated cells which adheres to the capsule. Hence it follows that the cells of the posterior wall of the lens vesicle form the lens fibers, those of the anterior wall, on the contrary, form the epithelium. (Adelmann, 1966, pp. 1293–4)

With these observations by Remak, the basic descriptive embryology of lens formation was virtually complete, though many fine points, such as the origin of the lens capsule, would remain subject to debate and investigation for several more decades. Remak was a rather tragic figure in the history of nineteenth-century embryology. He received his medical degree in 1838 but was initially barred from teaching by Prussian law because of his Jewish faith. After graduation, he remained as an unpaid assistant in Johannes Müller's laboratory, where he conducted basic research on the nervous system and supported himself with his medical practice. Remak was eventually granted a lectureship in 1847, becoming the first Jew to teach at the University of Berlin (Enersen, 2003). Remak's descriptive work on the development of the eye was a very small part of his substantial body of research, but despite this he only succeeded in attaining the rank of assistant professor in 1859, six years before his death. Remark was the father of neurologist Ernst Julius Remak (1849–1911) and the grandfather of mathematician Robert Remak (1888–1942), who was killed in the Nazi concentration camp at Auschwitz (Enersen, 2003).

After Remak, who studied eye development in the chick, frog, and rabbit, others added details concerning lens formation in other species. For example, in 1877, Paul Leonhard Kessler described the development of the mouse lens in his work *Zur Entwicklung des Auges der Wirbelthiere*. Carl Rabl also published a marvelous book in 1900, *Über den Bau und die Entwicklung der Linse*, which describes and illustrates lens development in fish, mammals, reptiles, amphibians, and birds. While these publications added details, they still built on the common theme elegantly described by Remak. Thus, at the close of the nineteenth century, the stage had been set for the descriptive embryology of the lens to give way to the experimental embryology of the lens that continues through the twentieth and into the twenty-first centuries. In particular, the groundwork had been laid for Hans Spemann (1869–1941) to perform his classic experiments revealing the induction of the

lens by the optic vesicle and establishing the theory of embryonic induction, which would become part of the foundation of developmental biology and lead to the discovery of the Spemann–Mangold organiser. Embryonic induction was an idea whose time had come.

1.2. Comparative Ocular Anatomy

Over time, developmental biologists have focused much of their attention on understanding the mechanisms underlying cell and tissue differentiation and the orderly manner in which they grow, developing to the size and shape appropriate for the body's requirements as well as forming in the correct anatomical relationship with each other. These events are thought to depend on inductive cell and tissue interactions. As will be appreciated in the following chapters, for over a century the lens of the vertebrate eye has provided numerous researchers with a means of examining inductive tissue interactions involved in tissue differentiation throughout development and growth. The lens has readily been adopted as a model for such studies because, as will be described later, it is a relatively simple tissue made up of cells from a single cell lineage. The lens retains all the cells that are produced throughout its life, and it is isolated from a nerve and blood supply. The positioning of the lens in the eye, on the surface of the body, has made it easily accessible for experimentation, but most importantly the lens has proved to be suitable for the study of cell differentiation *in vitro* and *in vivo*, as not only do differentiating lens cells synthesise uniquely defined proteins such as the crystallins, they also undergo very distinct morphological changes, including cell elongation, cell membrane specialisation, and the loss of cytoplasmic organelles and nuclei.

The remainder of this chapter will therefore be devoted to introducing the ocular lens by reviewing in brief its structural diversity in a range of organisms and highlighting its adoption as an ideal tissue model for cell and developmental biologists alike. Sections of this part of the chapter summarise the wealth of information documented by Sir Stewart Duke-Elder (1958) in "The Eye in Evolution" a book volume on the ontogeny and phylogeny of the invertebrate and vertebrate eye, which the reader is encouraged to read in its entirety.

For many animals, the sense of vision is the most important link to the environment. Animals have adapted for survival in a variety of climatic conditions and terrains and thus have evolved a diversity of eye designs. Despite this diversity, each of the visual organs has a common functional role, the perception of light. The sensation of light is the most fundamental of the visual senses. The acquisition and development of vision has stemmed from the dependence of living organisms on light, with light influencing many aspects of survival, such as general metabolism and the control of movement (characteristic of the most primitive of animals), as well as influencing the behaviour and consciousness (through the visual senses) of higher animals.

Unicellular organisms such as ciliate and flagellate protozoa (e.g., *Euglena*) provide us with examples of the earliest stage in the evolution of an eye. These organisms contain a small region of protoplasm that has differentiated into a photosensitive 'eyespot'. This specialised light-sensitive area, partially covered by a pigmented shield close to the root of its motile flagella, not only can receive a visual stimulus but is also utilised to orient the organism and direct it to more favourable regions in its environment. With the evolution of multicellular organisms came the differentiation of light-sensitive cells that allowed these higher organisms to distinguish between light and dark and even determine the direction of light. From this, eyes went on to become more specialised, evolving further to detect motion, form, space, and color.

The visual organs of invertebrates show a much greater diversity in structure than those found in vertebrates, varying in complexity from the simple eyespot to the vesicular eyes of cephalopods and the compound eyes of insects. Despite this diversity, many of the eyes of these unrelated invertebrate species comprise analogous photoreceptive cells. The entire bodies of primitive invertebrates, such as jellyfish, coral, sea anemones, worms, and echinoderms, are sensitive to light. Their eyes are no more than a collection of eyespots or photosensitive cells, frequently associated with pigment, which serves as a light-absorbing agent. These light-sensitive cells are ectodermally derived and can be found alone or in association with other cells to form an eye. Depending on the structural organisation of these cells – whether they form an organ singly or as part of a community – an invertebrate eye can be classified as either a simple eye (or ocellus) or a compound eye. Intermediate forms are referred to as aggregate eyes and are usually composed of a cluster of ocelli packed so closely that they resemble a compound eye. The major distinction is that each ocellus in an aggregate eye is anatomically and functionally separate.

1.2.1. *The Simple Eye*

The ocellus, or simple eye, can be defined as a light-sensitive cell or a group of such cells that are not functionally associated but each act independently. The simple eye has many different forms, from its primitive beginning as a single cell to a more complex structure represented by the vesicular eye (Figure 1.8). The most primitive association of light-sensitive cells is seen in the ‘flat eye’, which comprises a number of specialised contiguous surface cells that form a plaque (found in some unsegmented planarian worms and leeches).

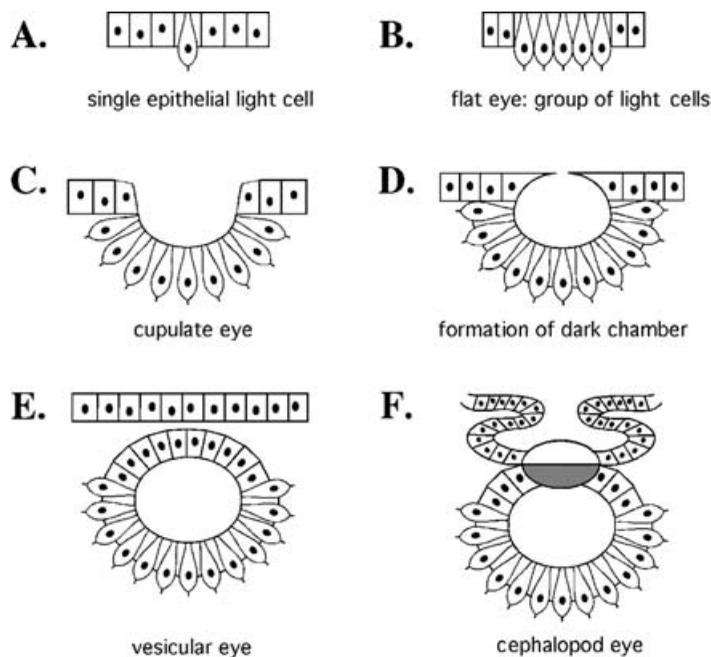


Figure 1.8. Schematic diagram depicting the comparative anatomy of the simple eye of invertebrates. (Adapted from Duke-Elder, 1958.)

In more advanced organisms, these patches of photosensitive epithelium indent to form a depression, giving rise to the 'cupulate eye' or 'cup eye'. This structural change had the functional advantage of allowing for the development of a primitive sense of direction. Cupulate eyes have several forms, depending on the degree of invagination of the light-sensitive epithelium. The most primitive form can be found in the larva of the common housefly (*Musca*), present as a shallow pit in the epithelium. A deeper invagination, together with an increase in the number of photosensitive cells, converts this depression into a cavity with a small opening. As the opening of the depression continues to narrow, a dark chamber with a pinhole opening is formed. Such an eye is found in the chambered nautilus (a primitive cephalopod). Although the photoreceptors of the nautilus are indented to form an optic cup, the cup does not contain a lens, and its operation is based on the same principles as a pinhole camera. The pinhole is used to focus images, and although this provides excellent depth of field, a lot of light is required to provide an image of any quality. The optic cup can be filled with sea water, as in the case of the nautilus, or with secretions, as found in the ear shell (*Haliotis*). The final form of the cupulate eye is characterised by the closure of the cavity by the growth of an overlying transparent acellular cuticle which will one day go on to form the lens. The enclosed secretory mass forms the vitreous body, as seen in *Nereis*, the marine polychaete worm. Improvements on this design are found in some insects. For example, hypodermal cells might form a thickened cuticular layer which acts as a refringent apparatus. The optical arrangements of such an eye may further be improved, as seen in *Peripatus* (a caterpillar-like arthropod), in which the hypodermal cells form a large lens in place of the vitreous. These hypodermal cells, usually continuous with the surface ectoderm or with the sensory cells of the cupula, may also edge themselves underneath the cuticle and go on to form a transparent refractile mass below the cuticular lens, thereby constituting a primitive lens or vitreous. Overall, the lens of a simple eye may be either acellular and cuticular or cellular.

The vesicular eye may be considered the final stage in the development of the simple eye. This type of eye is marked by the closure of the invaginated light-sensitive epithelium, which gives rise to an enclosed vesicle separated entirely from the surface ectoderm by mesenchyme. In its simplest form, the vesicular eye is spherical and lined with ectodermal cells, as found in the edible snail *Helix pomatia*. The vesicle has a specific polarity, with the more posterior cells being partly light sensitive and partly secretory while the more anterior cells remain relatively undifferentiated. The cavity of the vesicle is filled with a refractile mass of secreted material, homologous with the vitreous of higher organisms.

In a further stage of complexity, the vesicular eye takes the form of a camera-like eye through the addition of a lens and now resembles the eye of vertebrates. The best example of this can be found in cephalopods (e.g., octopus), which have the most elaborate eyes in the invertebrate kingdom. The eye vesicle of cephalopods is filled with a vitreous secretion. The posterior cells lining it form the retina while the anterior cells fuse with an invagination of the surface epithelium to form a composite spheroidal lens (see Fig. 1.8F). The posterior half of the lens is thus made up of vesicular epithelium while the anterior half is derived from the surface epithelium. Encircling the lens, the fusion of the vesicular and surface epithelium gives rise to a 'ciliary body', with an 'iris' derived from the surface epithelium. This type of cephalopod eye is highly complex, is capable of image formation, and has the ability to accommodate. In contrast to other invertebrates with fixed-focus lenses, cephalopods can focus for near and far vision by changing the position of the lens relative to the retina. Although at the morphological level these eyes rival those of vertebrates, they are simple