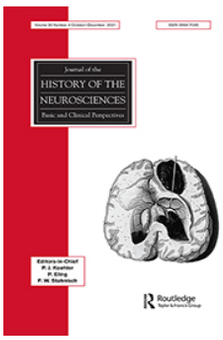

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Journal of the History of the Neurosciences
Basic and Clinical Perspectives

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/njhn20

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To cite this article: John S. Werner, Iwona Gorczynska & Lothar Spillmann (2021): Heinrich Müller (1820-1864) and the entoptic discovery of the site in the retina where vision is initiated, Journal of the History of the Neurosciences, DOI: 10.1080/0964704X.2021.1959165

To link to this article: https://doi.org/10.1080/0964704X.2021.1959165

Published online: 31 Oct 2021.

JOURNAL OF THE HISTORY OF THE NEUROSCIENCES
https://doi.org/10.1080/0964704X.2021.1959165

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Heinrich Müller (1820-1864) and the entoptic discovery of the site in the retina where vision is initiated

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ABSTRACT

Heinrich Müller was a nineteenth-century German retinal anatomist who, during his short career, was one of the discoverers of the rod photopigment rhodopsin and neuroglia in the retina, now known as Müller cells. He also described the ocular muscles and double foveae of some birds. An important, but largely neglected, insight by Müller was to combine careful psychophysical measurements and geometrical optics to find the location of the photosensitive layer of the retina in the living eye. Here, we provide translated passages from Müller's (1855) publication and compare his entoptic observations with retinal imaging using optical coherence tomography. Müller correctly deduced from his careful experiments that *vision is initiated in the photoreceptors located in the back of the retina*.

KEYWORDS

Entoptic perception; optical coherence tomography angiography; photoreceptors; psychophysics; Purkinje tree

1. Introduction

Czech physiologist Jan Evangelista Purkyně[1] described a variety of entoptic phenomena in his doctoral dissertation, published in 1819 and reprinted in 1823. His thesis was written in German (*Beiträge zur Kenntniss des Sehens in subjectiver Hinsicht*), and many of the phenomena he described are cornerstones of vision science. A partial translation by one C. W. (presumed to be Charles Wheatstone) was published in 1830, but a complete English translation by Wade and Brožek did not appear until 2001, as *Contributions to the Knowledge of Vision in Its Subjective Aspect* (see Wade and Brožek 2001).

Purkyně (1819) described how, when moving a candle flame several inches from his eye in different directions within the temporal visual field, he could observe in the diffuse light, "a dark pattern of vessels [on an orange background] that originates from the optic nerve [head] and has two principal branches toward the top and bottom; they ramify and bend toward the center of the visual field" (quoted in Wade and Brožek, 2001, 87). These vessels are the central artery and the central vein, which enter and exit the eye, respectively, at the optic nerve head (optic disk, blind spot). He observed a complementary pattern in his other eye and sketched their projections (now known as the Purkinje tree) as shown in Figure 1.1, reproduced from his thesis published in 1819. Note the similarity with fundus photographs shown in Figure 1.2; one can think of the photograph as "seen" from the front and the entoptic image as "seen"

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[1]His German publications were penned as Purkinje, and we use this spelling in translating from German; otherwise, we use his Czech spelling out of deference to his advocacy, both as a scientist and as a member of the Czech Parliament, for more widespread use of the Czech language (Weale 1969).

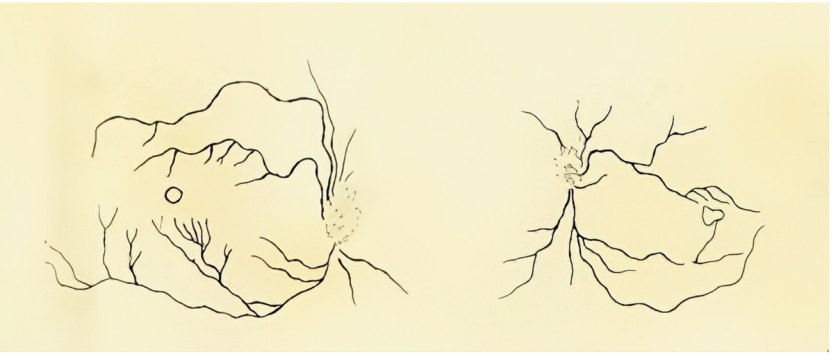


Figure 1.1. Purkyně's drawings of his retinal blood vessels in his right and left eyes. Use of a blue light source improves the visibility of the vessels owing to greater short-wavelength absorption by hemoglobin (Bradley et al. 1998; Cornsweet 1970; Remky, Beausencourt, and Elsner 1996). The most peripheral blood vessels are often difficult to visualize due to lower sampling density by the photoreceptors in that part of the retina (Adams and Horton 2003).

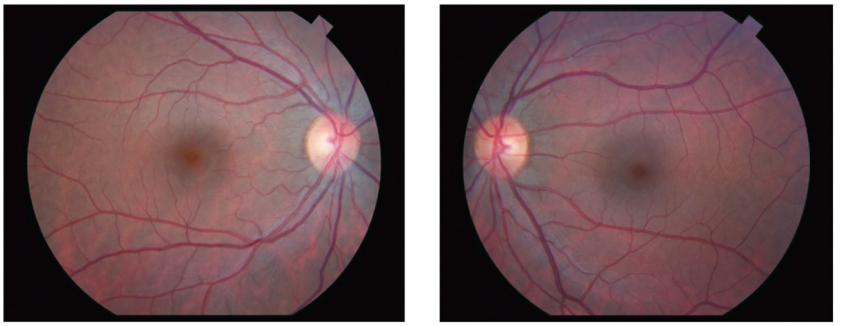


Figure 1.2. Fundus photographs (50°) of a young adult's right and left eyes. The dark spot in the center is due to the yellow pigment of the macula lutea and the center of that area is the foveal pit (fovea centralis). The bright spot in each is the optic disk where ganglion cell axons leave the eye.

from the back (Ratliff 1971). Snodderly et al. (1977) used an eye tracker with retinal image stabilization and demonstrated precise correspondence between threshold elevations for punctate stimuli and angioscotomata around the blind spot. Drawings of the entoptic image are remarkably similar to the corresponding color fundus photographs (Bradley et al. 1998) and provide an image of the foveal capillaries even superior to that in the fluorescein angiogram, a suggestion made earlier by Bird and Weale (1974).

Purkyně described three methods for visualizing the retinal vasculature: transscleral illumination, partial through-the-pupil illumination, and transpupillary illumination (terms from Bradley et al. 1998). Wheatstone (see [C. W.] 1830) and Horner (1834) suggested modifications of these methods to make the finest capillaries visible entoptically, as illustrated in Figure 1.3. All these methods have in common that movement of the eye or the light source is necessary to avoid fading (Troxler 1804) of the entoptic percept due to retinal image stabilization (Riggs et al. 1953) that may otherwise occur within 80 msec (Coppola and Purves 1996). With Purkyně's first method, a bright candle light may be shone onto the sclera, in the vicinity of the temporal limbus. When viewing a dimly lit surface the vasculature will appear dark, "ramifying in various directions like the branches

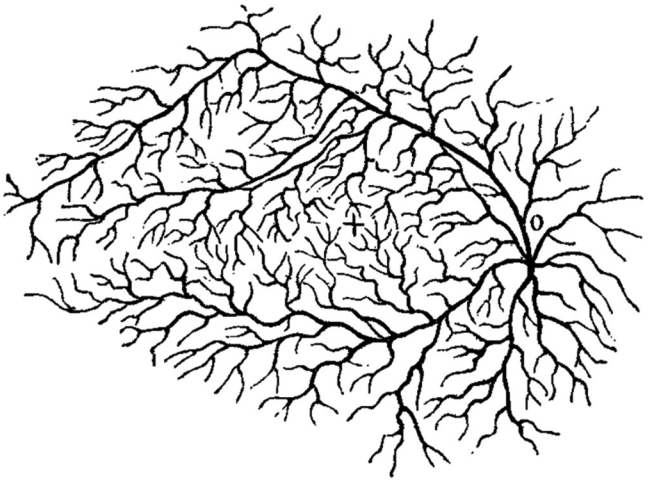


Figure 1.3. Entoptic visualization of the vasculature of the right eye. + denotes the point of fixation; O denotes the origin of the larger vessels (from Horner 1834).

of a tree" (von Helmholtz 1867; 1924 translation by Southall, p. 212). When the light source is rotated, the vessels are seen to move in the same direction in a central area spanning 30 to 50 deg. The smaller the focal point on the sclera, the better the detail of the vessels. Müller pointed out that with this method the center of fixation is devoid of visible capillaries and appears different from the surrounding fundus, possibly due to the yellow macular pigment.

Second, as in the first method, a bright candle is moved back and forth slightly below or to the side of one's eye while one looks at a dark background. The main difference between this and the first method is that the light now enters partially through the pupil instead of only through the sclera. With lateral movement of the light, vertical vessels are better visualized, whereas with movement of the light up and down, the horizontal vessels are better visualized. With this method, the vascular image does not move uniformly in all parts of the visual field. In addition, the macula lutea surrounding the fovea may elicit a dark crescent shadow owing to the vignetting of the light by the edge of the foveal pit. Müller suggested that those who do not see this shadow have shallower foveal pits, but this has not been substantiated.

The third method requires one to look at a bright background (such as the sky) through a narrow aperture that is moved to and fro. Small vessels that are perpendicular to the motion are most readily seen, whereas those vessels that are parallel to the motion are invisible.

The shadow cast by a retinal vessel is not uniform. Adams and Horton (2003) reasoned that, because of scatter, any vessel illuminated by an extended (nonpoint) light source produces a shadow, consisting of a central umbra, or full shadow, surrounded by a penumbra, or half shadow (their Figure 6). The total width of the vascular shadow therefore equals the umbra plus penumbra. Light scatter and shadow width depend on the size of the light source and the distance of the vessel from the photoreceptors (their Figure 8). Therefore, if the vessel is small enough (such as near the fovea), or the pupil large enough, the shadows cast on the photoreceptors will consist of the penumbra alone. Only the largest vessels of the Purkinje tree will give rise to a visible umbra.

Helmholtz later summarized Purkyně's methods and noted that these methods were "perfected" by Müller. In particular, Müller developed a more quantitative approach to the entoptic phenomena described by Purkyně.

2. Heinrich Müller (1820–1864)

Heinrich Müller attended the University of Munich, but moved to Baden-Baden in 1840 due to illness (hemoptysis, or bleeding of the lungs or possibly airway). He then attended the universities in Freiburg and Würzburg, graduating in 1843. Müller subsequently attended medical school in Heidelberg and Vienna. In 1847, he became an assistant professor in Würzburg, but he left for Italy from 1850 to 1851 for health reasons (Hirschberg 1919). There, he devoted himself to comparative marine biology, mostly concerning the eye. He became an associate professor of anatomy at the University of Würzburg in 1852 and was promoted to full professor in 1858. He remained in Würzburg until his death in 1864 (Kölliker 1867).

Despite his short career, Müller made a number of landmark discoveries about the histology and anatomy of the visual system, thanks, in part, to enucleated eyeballs provided by Albrecht von Graefe. His 1851 paper described the red coloration of the visual pigment, now known to be rhodopsin (Müller 1851). This was before the celebrated work of Boll

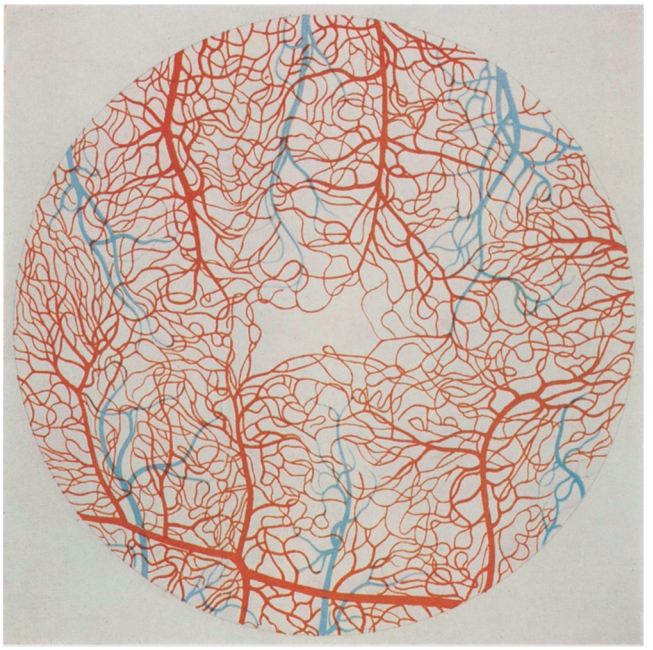


Figure 2.1. Drawing of the vasculature of the human retina based on injection of a dye by Heinrich Müller and completed by Becker (1881). Arteries (red) branch into capillaries and are re-assembled into veins. Estimates of capillary size are 3–5 μm while the larger vessels are ~65 μm or more. Vessel diameter estimated entoptically increases linearly with retinal eccentricity, from 15–20 μm near the fovea to 150–200 μm at 15–20 deg (Bradley et al. 1998). For comparison, Becker (1881) gives histological values of 88–134 μm for retinal arteries and 97–176 μm for veins (his Table 1). The vessel-free area varies in shape and size among observers (Kim et al. 2012). Some observers claim that they can identify arteries and veins in the Purkinje tree (Bradley et al. 1998).

(1876) and Kühne (1877), who credited him (Hubbard 1977). Additionally, in his 1851 paper, Müller described neuroglia in the retina now known as Müller cells (Müller 1851). He also published descriptions of the retinal vasculature, and Figure 2.1 shows an example in which he flattened a human cadaver retina and preserved it so that many of the finest capillaries could be traced, a work completed after his death by Becker (1881). Müller described muscles in the orbit and lids, and a double fovea in some species of birds (e.g., hawks). His interests in the pathology of the eye led to investigations of subcapsular cataract, pigmentary changes in retinitis pigmentosa, and age-related changes in Bruch's membrane now essential to our understanding of age-related macular degeneration. Müller's collected papers are contained in an anthology assembled by Becker (1872).

Müller was a dedicated teacher in formal lectures as well as in the laboratory. According to Hirschberg (1919), "The most ambitious students of ophthalmology at the time wanted to study anatomy in Würzburg with H. Müller, physiology in Heidelberg with H. Helmholtz, and clinical ophthalmology in Berlin with A.v. Graefe" (translation by Blodi 1992, 322). Figure 2.2 is a picture of Müller taken from Blodi's translation (1992, 319).

At the time of Müller's 1855 paper, it was known that light must be absorbed by a pigment in order to convert electromagnetic energy into neural signals. In the cadaver eye, the photopigment cannot be seen without careful preparation due to bleaching (photo-isomerization). It had generally been thought that transduction must occur in the ganglion cell layer because it is the

Figure 2.2. Heinrich Müller. This image was provided by his 90-year-old widow to be published in Hirschberg's (1919), *Geschichte der Augenheilkunde*. This portrait, taken from Blodi's translation (1992, 319), is digitally enhanced here.

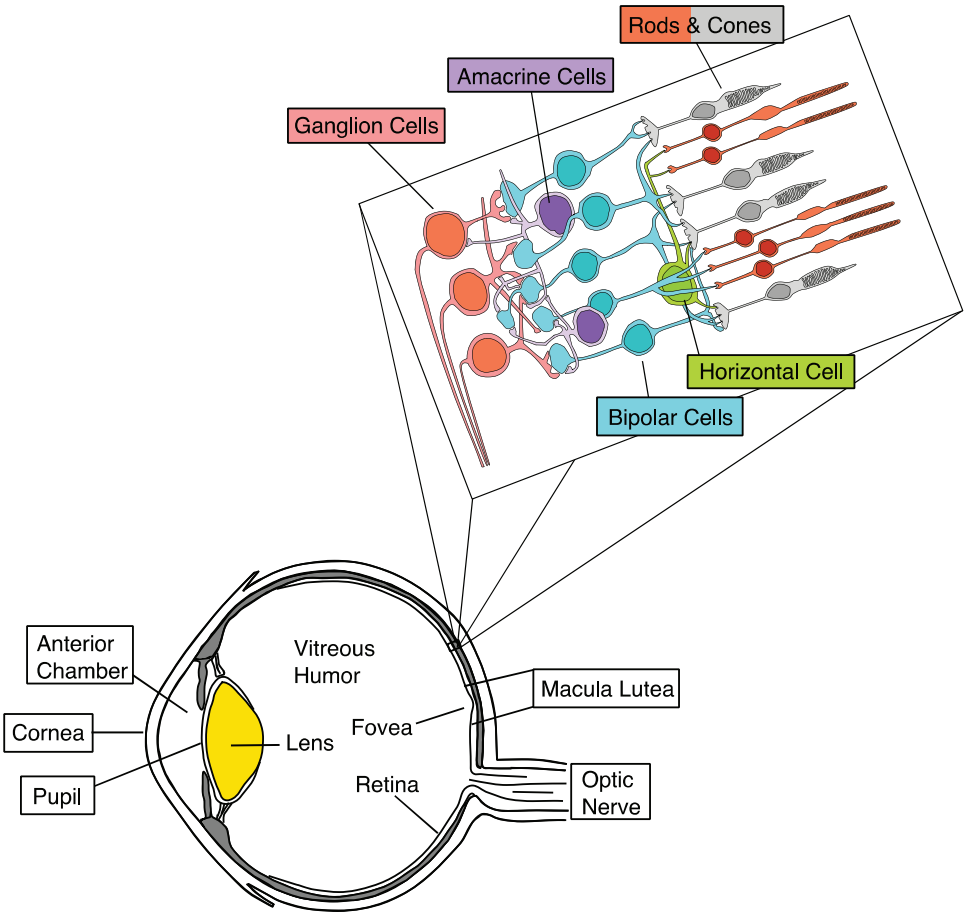


Figure 2.3. Schematic cross section of the human eye with the retina shown in enlarged view. The ocular media include the cornea, aqueous humor in the anterior chamber, lens and vitreous humor. Müller referred to the macula lutea as the yellow spot which derives its coloration from carotinoid pigments that form a yellow filter in the retina. The principal cell types of the retina identifiable by 19th Century light microscopy are shown. These include the photoreceptors (~120 million rods and ~ 6 million cones in each eye), horizontal cells, bipolars, amacrines and ganglion cells (~1.5 million, which each have an axon that collectively forms the optic nerve). After Werner (1998)

first retinal layer that is reached by the incident light, as shown in Figure 2.3. Müller correctly deduced from his careful entoptic experiments using the Purkyně tree that this was incorrect and that, instead, vision is initiated in cells we now know to be the photoreceptors located in the back of the retina. The elegance of Müller's (1855) experiments and analyses prompted us to translate his paper. His scientific approach stands out for his use of perceptual observations to understand anatomical and physiological function, an approach used by other nineteenth-century anatomists and histologists such as Max Schultze, Hermann Munk, and others—a perspective that continues to guide vision science. Müller showed how careful observations (entoptic phenomena) and simple mathematics can be used to make inferences about retinal structures.

Our translation (to follow) makes no attempt to convey all of the literary nuances in Müller's paper that prevailed in the nineteenth century. Complex constructions in the original text were often simplified to comport with modern scientific writing, and some digressions are not included. The most significant passages are set in italics. The italics are not in the original. In addition, we have converted Müller's terms and units of measurement that are no longer used to terms that are used today. The original figures were published in a single plate at the end of his paper, but they are redrawn here (with a few minor corrections) and placed in the text where they are described. For the figure numbers to correspond to those in Müller's paper, the numbers in the translation start from 1, rather than as a continuation of the numbering here, and thus the figure sequence begins anew in each section. We have attempted to translate this paper to be understood by contemporary readers in order to maximize appreciation of its significance. Heinrich Müller should be remembered—along with Albrecht von Graefe, Franciscus Cornelius Donders, William Bowman, Albrecht Nagel, Carl Friederich Richard Foerster, and Ferdinand von Arlt—among the leading ophthalmologists of the nineteenth century.

3. On the entoptic perception of retinal vessels, particularly as evidence for the light perception through the distally located retinal elements

Translated from H. Müller. 1855. Ueber die entoptische Wahrnehmung der Netzhautgefässe, insbesondere als Beweismittel für die Lichtperception durch die nach hinten gelegenen Netzhautelemente. *Verhandlungen*. ***Physikalisch-Medizinische Gesellschaft in Würzburg*, 5: 411–47.**

Page 411: Some time ago, I presented a short summary (see *Verhandlungen* [*Proceedings*], vol. 4, page 100) suggesting that the Purkinje tree, particularly its motion parallax, can provide proof that stimulation of the eye by light begins at the outer layers of the retina. The most common method to elicit the Purkinje tree is by moving the flame of a candle in front of the eye. However, this turned out to be so cumbersome that I could not acquire any quantitative information about the parallax observed. Mr. Hofrath Ruete then pointed out to me that the method of passing the light through the sclera, which Purkinje had already described (Part II, page 119), is much safer and easier for visualizing the vascular tree. At the meeting of the *Society of Physical Medicine* on May 27, I gave a detailed account of my experiments using the various methods described by Purkinje.

Page 413: Purkinje himself has explained[2] the entoptic figure as a shadow of the central vessels, and this view has become widely adopted. It seems to me that the presupposition that the figure is produced by a shadow is consistent with the known facts. On the other hand, I think that the emergence of the shadow must, in part, be interpreted differently from the way this has usually been done up to now. This explanation applies only to the three modifications of the experiment described by Purkinje—namely, that a candle is moved in front of the eyes, a paper with a small hole is slightly moved back and forth near the pupil, or a bright light is projected onto the sclera with a lens. I will also discuss the appearance of a similar figure produced without light but by pressure.

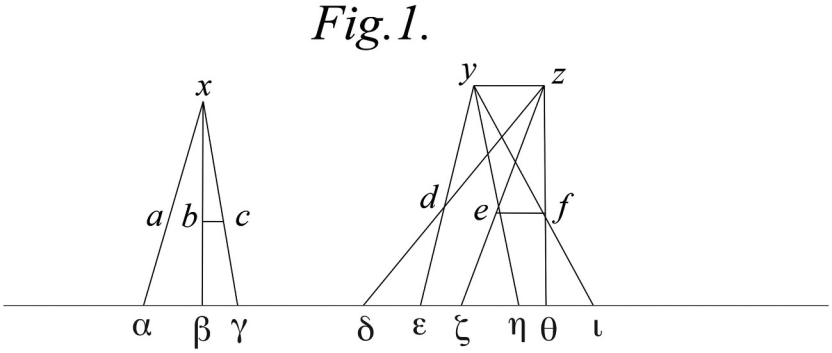
[2]Unfortunately, I was unable to obtain the first edition of Purkinje's contributions, which was sold out in bookstores, which is why I may unintentionally leave out details of those meritorious investigations.

Page 413/414: From the outset, the whole appearance of the figure in those experiments suggests that it is a shadow silhouette of the vessels on the illuminated retina. The ramification of the vessels appears under favorable conditions always dark on a bright ground. This is most clearly the case with the second method suggested by Purkinje, requiring one to look at a bright background (like the sky) through a narrow aperture that is moved to and fro. This method seems to be the one by which one can most certainly and completely elicit the figure in all individuals who have even a moderate ability to observe. The phenomenon is particularly impressive when, by means of a lens inserted into an opaque screen, one projects a small but very intense point of light onto the sclera with the eyes closed and manually lifts the lid of one eye to expose enough sclera to slightly move the light back and forth.[3] The field of vision then appears intensely golden (*goldgelb*), and the sharply defined vascular tree figure can be traced down to the finest capillaries. The capillaries lying in and around the yellow spot (macula lutea), outlining the avascular zone, can be discerned just as well as in the experiment with the pierced paper. Here, however, the whole extent of the vascular tree appears equally sharp. You need to be careful in all these experiments, considering both the intensity of light on the retina and the heat of the focused sunlight. It is therefore advisable to use only very small lenses, to take a pierced screen, as Ruete[4] suggests or, finally, to use a lamp instead of the sun. In this case, the appearance is less intense, but the vasculature can still be discerned, and it would be easy for someone with lower visual acuity to accurately describe the topography of the vessel branches surrounding the yellow spot.

Page 415/416: The assumption that the figure (i.e., the perception of the vascular tree) arises directly from the shadow of the vessels is consistent with the fact that the thickness and sharpness of the vessel image depend on the size of the light source. This can probably also be perceived in the other experiments, but it is most vivid with focal illumination of the sclera. In the latter experiment, I believe it is most important to realize that the light projected onto the sclera does not proceed in a straight line through the ocular tissues into the interior of the eye, as Purkinje and others seem to have assumed. Rather, by illumination of the sclera, a new light source is formed from which the light diverges in all directions. The ocular tissues behave like a frosted glass lampshade that is dense enough to make the flame of the candle itself invisible, while every illuminated part of the screen emits light diffusely all around. Only in unusually transparent eyecups will a part of the light pass through in its original direction. If, by focusing the light with a lens, a very small spot of the sclera is illuminated, even the most delicate vessels within the eye will throw sharply defined shadows. If, however, by increasing the distance of the lens to the light spot, a larger circle is illuminated on the sclera, the various points of it will all emit diverging light, and larger vessels will cast a larger shadow than in the previous case, but it will be darkest only in the middle; whereas, on the sides there exist only a gradually decreasing semishade (penumbra). On the other hand, very small vessels will be unable to block the light from any given point. So, the large semishadow they produce will be so subtle that it can easily be overlooked. These conditions can be readily simulated by using a lamp with or without frosted glass covering it to cast a shadow of needles. This is shown schematically in

[3]Through this manipulation, one can visualize the vascular tree without the use of sunlight and a magnifying glass, provided the opening of the eyelid is small and the eye is slightly moved. Of course, the image is weak under these conditions.
[4]*Physicalische Untersuchung des Auges*, Leipzig 1854.

Fig. 1. Point *a* produces a sharp shadow at point α in the cone of rays diverging from the small luminous point *x*; object *b-c* likewise produces a shadow on surface β-γ. With a more extended light source *y-z*, a shadow of the point *d* falls onto δ-ε, but because light also falls on the whole surface from the other points of the light source *y-z*, the slight shadow will be hardly noticeable. Similarly, object *e-f* casts an extended shadow ζ-ι, which is completely dark only within η-θ, but which tapers off toward ι and ζ.

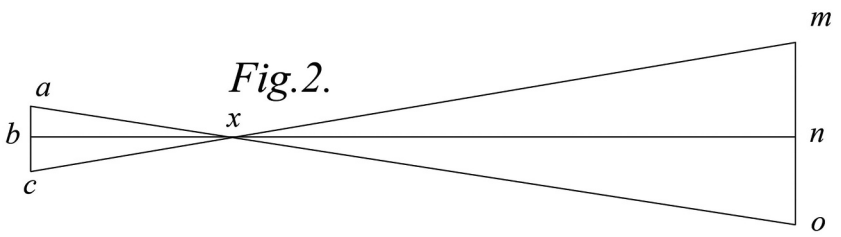


Page 416/417: This observation corresponds perfectly to theoretical predictions. If one illuminates a larger circle on the sclera, broad, diffuse shadows of the larger vessels appear, whereas the finest calibers of vessels are not perceived. However, as soon as the tip of the cone of light is focused on the sclera by adjusting the lens, the larger branches of the vascular figure appear less broad but more sharply outlined. At the same time, all the detail of the finest ramification in the area of the yellow spot emerges.

Page 417: Why is it that the finest shadows can be seen only within close proximity to the fovea, and even the larger branches' shadows do not extend to the outer periphery of the retina? This is due to the decline in neural resolution of the retina with increasing eccentricity. This observation, too, suggests that the percept of the vessels is mediated by the retinal regions that are nearest to them, which is further explained by the direct projection of the shadows of the vasculature. One could even use the perception of the finest and less subtle shadows to determine the relative resolution of the retina as a function of the distance from the fovea.

Page 419: The fixation point under consideration lies in a place that appears completely free of vessels. One can use this observation to calculate the size of this zone. At least in my case, only the illumination by a tiny opening in front of the pupil or through the sclera is suitable for this purpose, whereby the vessel-free zone is projected onto a surface at a specified distance. From the diameter of the latter and from the known position of the point of intersection (i.e., the nodal point) in the eye, the true distance of the two capillaries surrounding that zone can be determined. Let *om* in Fig. 2 be the apparent size of the vessel-free zone at the distance *nx* from the nodal point, *bx,* the distance of the latter from the retina, and *ac* the size of the vasculature-free spot on the retina. It is then:

$$ac = om \times bx/nx$$



Page 419: This calculation, however, cannot yield an exact result, as the shadows of the vessels do not perfectly correspond to the distance of the vessels themselves, and the position of the nodal point changes with different states of accommodation. Nevertheless, the calculation should be erroneous only to the extent that the shape of the eye deviates from the approximately round shape in the area of interest.

Page 420: Using the methods described above, I have found my own eyes to have an avascular zone diameter of approximately 0.4 mm. For another observer whom I asked to conduct the same test, the calculation yielded a value between 0.36 and 0.42 mm.[5]

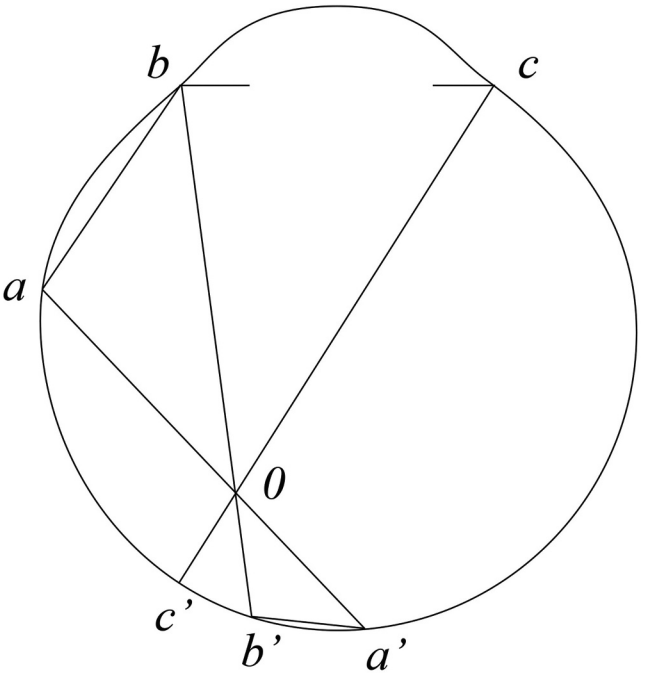
Page 424: It is well known that in the Purkinje experiments, the vascular figure appears to move when the light source moves. In particular, *I believe the most obvious explanation is that the vascular image is formed by the vessels casting a shadow onto the retina*. Because there are differences in the individual methods of the experiment, it is necessary to consider them separately.

Page 424: First of all, if one moves a circumscribed light source on the sclera, then the entoptic image makes an apparent movement. The vascular tree also moves in a concordant manner so that it goes to the right when the light source goes to the right and so forth. This is most clearly observed for the vessels near the yellow macular spot. This agrees with the explanation I have given. From the illuminated point on the sclera, the light diverges as it goes straight through the eyeball. The (crystalline) lens plays no role in this as the rays from the sclera (which are directed towards the back of the eye) do not pass through it. Even so, any light rays traversing the lens would become less divergent. And the shadow of a vessel on the parts behind the lens must be in the opposite direction as the light source. But it appears to us in the same way as the movement of the point of light because we are accustomed to seeing the object on the right side of the retina to the left, and vice versa.

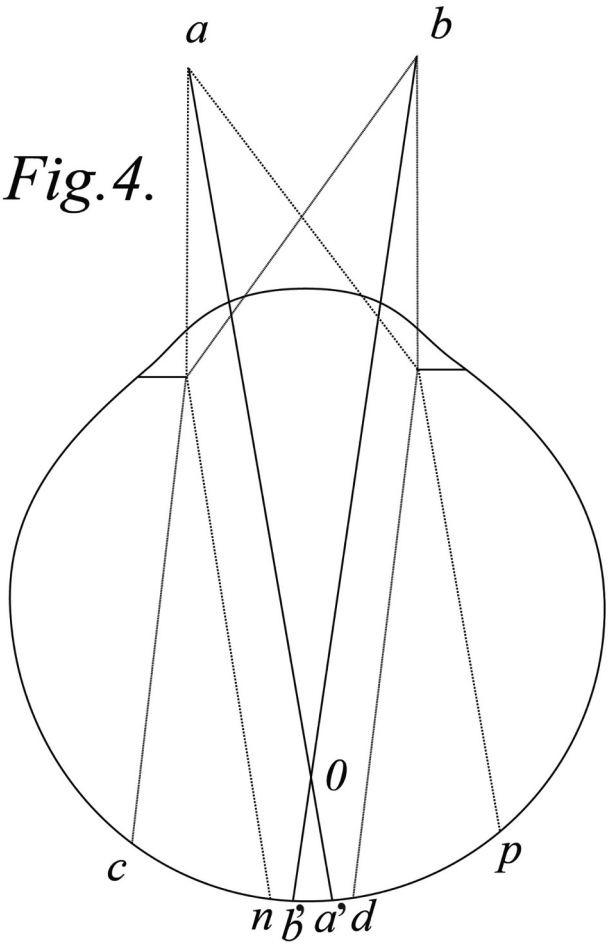
Page 424: If *O* is a vessel in Fig. 3, its shadow must fall to *a'* when the light source is at *a*. The shadow rushes to *b'* and *c'* when the latter goes to *b* and *c*. Because *a'* corresponds to a point in the outer world more to the left, *b'* and c' to points more to the right, the apparent movement of the shadow must be in the same direction as the movement of the light source.

[5]For these calculations, I have used a somewhat greater distance of the point of intersection (or nodal point) for reasons similar to those set forth by Zehender (*von Graefe Zeitschrift für Ophthalmologie* I. S. 132).

Fig.3.



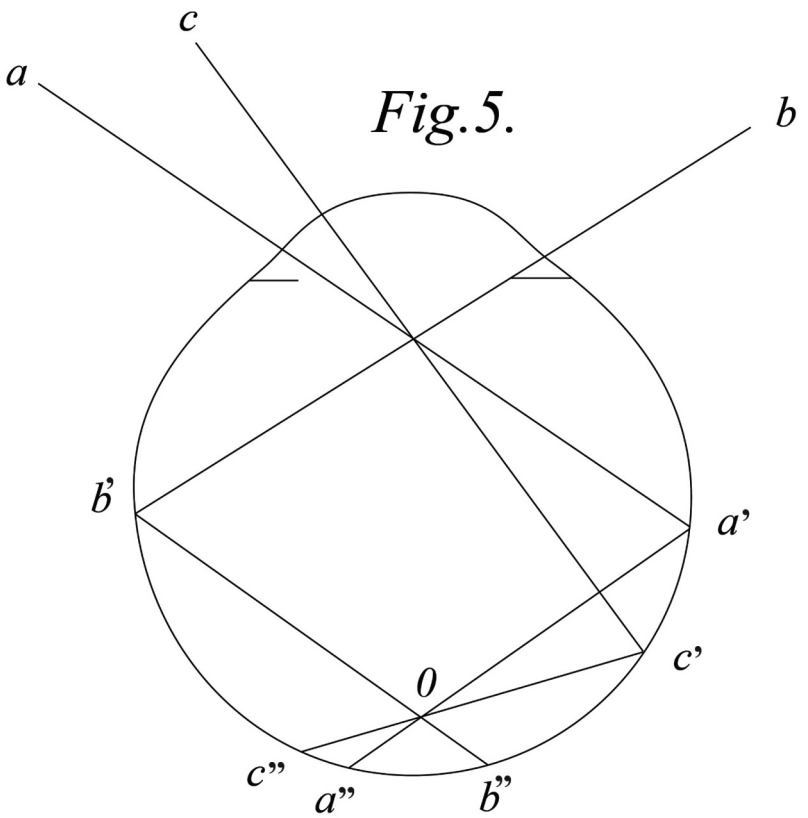
Page 425: Using the second method, if one moves a small opening in front of the pupil, the relation between (the location of) the vessel and (that of) the shadow is quite similar. As Meissner reported, the apparent movement of the vascular figure occurs in the same direction as that of the perforated sheet. If the aperture is very small and the background very bright, it may simply be regarded as a source of divergent light rays that converge while passing through the lens. These rays are blocked by the vessels so that an intense shadow arises behind them. In any case, the opening must not be so great that a cone of converging light with such a broad base arises in the vitreous body that the vessels can no longer cast a dense shadow. If the opening, which determines the direction of the light falling on a certain vessel, moves to the right, then the shadow must fall further to the left, to which then the inversion in the projection moves outward to the right. If, in Fig. 4, the opening moves from *a* to *b*, the actual movement of the shadow is also from *a*' to *b*', but the apparent movement is reversed; hence, if movement of the light source is counter-clockwise, movement of the perceived shadow is clockwise.



Page 426/427: Using the third method of the experiment, if one rotates a candle in front of the eye,[6] the perception of the vascular figure is, as one can easily confirm, a different one. It moves around in the same circular direction as the light flame, but the shadow is always on the diametrically opposite side of the circle. This observation does not agree with the earlier, generally accepted explanation of the formation of the vascular image. For if the flame would illuminate the retina, except for the places covered by the vessels, the shadow would not behave in the manner observed, but just as in the other two experiments; namely, it would appear on the same side of the flame. In the experiment in question, I do not think the flame but rather its inverted image on the retina or even the choroid is the (light) source, which illuminates the interior of the eye uniformly, save the locations onto which the vessels cast shadows. Instead, an inverted picture of the vessels arises on the retina or actually behind it on the choroid. The motion behaves completely as the theory demands. In Fig. 5, when the light flame is at *a*, its picture falls on *a'*. If the flame goes to *b* in a semicircle, the image of it falls on *b'* and the shadow of the vessel *O* on *b"*. The shadow, then, is in fact physically on the same side as the light flame, but it is perceived on the opposite side, just as the observation shows. However, the theoretical

[6]It is also possible to elicit the percept of the vascular figure if one looks past a strong, steady flame into the dark and makes some eye movements.

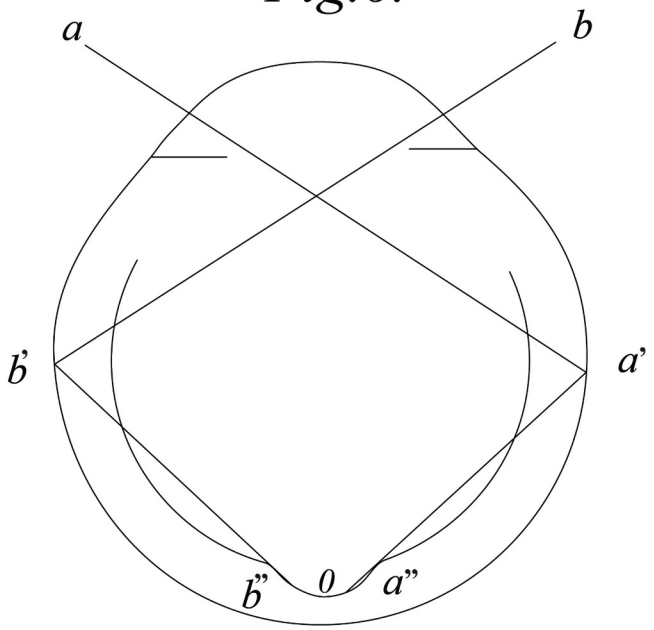
consideration further shows that this reversal of the situation could only take place if the light flame rotates around sections of the pupil. But as soon as the movement is directed in a straight (radial) direction toward the center of the pupil, the shadow does not need to move in the opposite direction but must move in the same direction. A view of the diagram shows this. When the flame moves from *a* to *c*, the image of it moves from *a'* to *c'*, and the shadow of the vessel *O* moves from *a"* to *c"* and vice versa, from which an apparent identical movement of the shadow with the flame must result. This is consistent with what one observes in the experiment. In fact, the shadow moves in unison with the flame as long as one does not make circular movements but radial ones bound within the center of the cornea. By leaving the candle as a whole in the same position, it is possible, by means of small movements in different directions, to alternately elicit an opposite displacement of the vascular figure.



Page 428: The apparent movement of the vascular shadows in the last experimental method now explains some other phenomena that have been described by Meissner, such as the bright disk with the crescent-shaped shadow that is observed in the area of the macula. According to Burow (*Müll. Arch.* 1854, I66) and Meissner, the position of the shadow is always on the side of the disk where the flame is located. Burow believed that this is a conical projection against the vitreous body, which would explain the phenomenon if the flame were the light source. Meissner has already pointed out that this assumption does not explain the other motion phenomena of the vessels, and he has likewise raised doubts on

anatomical grounds with which I agree: Namely, a protrusion does not usually occur; rather there is a deepening of the fovea in the location under consideration. Whether it is developed in all eyes to the same extent, I do not know. A foveal pit, however, would explain the position of the shadow perfectly if one assumes that not the flame but the image of it constitutes the light source. If, in Fig. 6, *O* denotes the fovea centralis, then the shadow produced by the higher and denser part on one side of the pit must appear to lie on the same side of the bright disk as the flame in front of the eye. It is also evident that using the candle flame is most suitable for demonstrating this shadow, as in it, the light source is produced farther back and laterally from the fovea centralis than with the other methods. Due to the lateral illumination, the movements of the shadow appear more conspicuously.

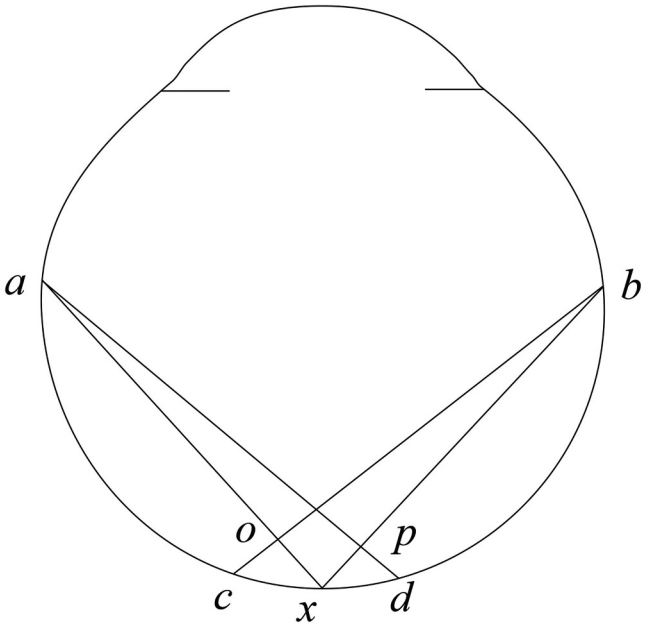
Fig.6.



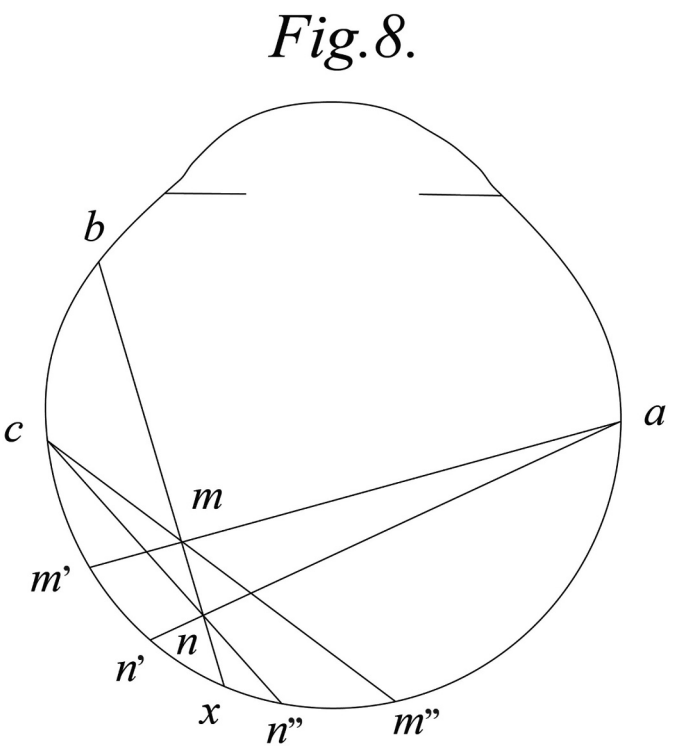
Page 428/429: The observation that it is not only the shadow but also the brighter disk of the macula that moves with the vessels is not surprising. If the disk originates from the middle part of the thinner and more transparent retina below the yellow spot, it must appear to move, provided that the percipient elements are in the outer retina. If one considers the disc as an optical effect, then the direction of movement of the shadow is as apparent as that of the vessels, inasmuch as here the greater brightness impinges onto the sensory elements as much as the shadow does in the other location. By contrast, the fixation point at the center of the field remains unchanged. An instructive phenomenon of relevance emerges when one applies an intense light source to the sclera of, let's say, the left eye, first on the nasal then on the temporal side of the eyeball. One then observes that the fixation point comes to lie once to the right edge, then on the left edge in the vascular-free area, respectively, perhaps even on the surrounding vessels. The shadow of the capillaries surrounding the vessel-free location on the right-hand side falls closer to the sensory elements at the point of fixation. In Fig. 7, the shadows emanating from the light source *a* fall from the two vessels *o* and

p onto *x* and *d*, but fall onto *c* and *x* when the light source is at *b*. Therefore, the shadow of *o* and *p* alternately falls onto the fixation point *x*. This can be understood by producing a long-lasting afterimage in the eye and then moving the point of light on the sclera. As should be expected, the vascular figure visibly shifts relative to the afterimage. If the bright disc with the crescent-shaped shadow, which is seen by some at the yellow spot, is really the optical effect of the fovea centralis, then it must also move relative to the after-image and point of fixation.

Fig. 7.



Page 429/430: I will not analyze the movement phenomena that arise at the point of entry of the optic nerve when the flame is moved in front of the pupil, as I am yet unaware of sufficient evidence on the matter, but they can be interpreted in an analogous manner. On the other hand, Meissner observed that if one moves the light more abruptly in front of the pupil, the vascular figure suffers sudden (jagged) distortions as the relative positions and distances of the vessels change. This is explained by the change of the light source and the vessels within the eye being at variable depths. This allows for situations in which, depending on the position of the light source, not only the widths of the shadows of two vessels are changed but so are their relative positions. The distance of the shadows of the two vessels *m* and *n* in Fig. 8 is *m' n'* when the light source is at *a*, whereas the shadows of *m* and *n* fall onto *x* when the light source is at *b*, and the shadows change their relative positions (*m' n'* and *n" m"*) depending on the vessels and from where they are illuminated.



Page 432/434: The greater the number of phenomena that can be explained by a theory, the more likely the theory becomes. Other phenomena exist that are similar to those hitherto considered inasmuch as they elicit in our visual organ an image of a vascular ramification that is undoubtedly from the retina. I am here referring to the appearance of a vascular figure through pressure on the eye ball whereby the movement of the blood cells in the vessels is perceptible. It should be noted that not every flicker in the visual field may be attributed to the movement of the blood corpuscles, only movements that are consistent with the course of the vessels. As far as the perception of this course is concerned, consider the following observation: External pressure, or merely the pressure of the blood, causes some parts of the vascular tree to appear bright yellowish when I close my eyes. This appearance changes over time, different parts standing out at different times. Only the larger vessels are fully discernible, whereas the detailed ramifications are not at all, and the entire appearance lacks in sharpness and distinctness, remaining far less defined than the previously mentioned appearances of the vascular image. Sometimes a movement can be noticed, but individual blood cells cannot be recognized with certainty. It seems to me then that one must not seek the same explanation for this phenomenon as for the earlier ones. Those were shadows cast by the action of objective (physical) light, whereas this entoptic percept appears to arise from the increased pressure of the blood in the vessels. It is well known that sensitive parts of the retina can be stimulated by pressure, and that this pressure reflects the shape of the vessels when it originates there. However, it is also true that in this way no sharp picture can be obtained, and the figure does not appear dark, but luminous. It is not necessary that the same elements of the retina are primarily affected. For my part, I believe that, under ordinary circumstances, only elements of the

outer layer are sensitive to objective light, whereas the nerve fibers and the cellular elements are probably susceptible to pressure. The latter elements, and perhaps the cells in the general vicinity of the vessels, convey the pressure exerted on them as a sensation of light.

Page 435/436: It has already been stated that the width of the shadow of a particular vessel and the relative location of the shadows of different vessels vary according to the position and nature of the source of light that causes the shadow. It seems to me that not only do the shadows form in different ways, but also the luminous ramifications produced by pressure are of essentially the same apparent size.[7] Indeed, they are of a size similar to the ratio of the corresponding parts of the vascular tree to the extent of the whole retina.[8] If a more thorough investigation should confirm this, then the agreement between the shadows produced by different methods speaks for a common principle of origin. Furthermore, the size ratio relative to the visual field suggests that the shadows are mediated by the adjacent sensitive elements. *Finally, the similarity of the image of a vessel elicited by pressure to the image elicited by transillumination supports the view that the ganglion cells of the retina are responsible for the localization of the vasculature produced by pressure, whereas the objective light is only detected by the cones.*

Page 438: *I now turn to the conclusions that arise from the appearance of the vascular image and its explanation for the functional significance of individual retinal layers. If the shadow cast by the vessels illuminated by a light source located in front of them is perceived visually, the sensory elements of the retina cannot lie before the vessels. The light must have gone past the vessels before it results in a perception, precluding the possibility that there are elements before the vessels, which are capable of reporting a light sensation when struck by the light entering the eye. If one then examines the position of the vessels relative to the individual retinal layers, especially in vertical sections of histological preparations,*[9] *it is observed that they are not spread on the inner surface of the human retina but at varying depths in the substance of the retina itself. The larger trunks are occasionally found within the nerve fiber layer, but the smaller branches associate more closely with the layer of nerve cells, which are often surrounded by the vessels from all sides. However, most of the capillary vessels do not enter the cell layer, stopping at the granular layer. The majority of the vessels lie behind both the optic nerve fibers and the inner ends of the radial fibers, with a small part of them also lying behind these cells. It appears that the optic nerve fibers belonging to the innermost layer, the inner ends of the radial fibers, and potentially even the cells themselves are not sensitive to light.*

Page 439: *Not only can it be inferred from the phenomena of the vascular figure that the light-perceiving elements do not lie in front of the vessels but also that they are at a certain distance behind the vessels. This is because the vascular shadow cast on the retina's sensory*

[7] Meissner said that when moving a small opening in front of the pupil, the vessels appear to be more magnified, but that this could also be illusory due to the perception of the fine detail and the movement of the visual field.

[8] It goes without saying that, when estimating the apparent size of the vascular figure, the distance of the surface onto which it is projected must always be taken into account. In this respect, it seems like an afterimage that looks small when one looks close and is then big when one looks from a distance. However, the retinal size remains the same. For comparison, I have used the distance of the entry point of the optic disk from the fixation point, which as far as I could see, was as great in the vascular figure as the distance of the blind spot, when viewing external objects. J. Müller (*Vergl. Phys. des Gesichtssinnes*, 61) also described the network of black vessels as comprising the whole visual field.

[9] These relationships may be different in other species.

elements undergoes displacement when the light source is moved. According to this, one must conclude that one of the outer layers of the retina, which is separated from the vessels, detects the light.

Page 439/440: *Because the size of the displacement (parallax) of the vascular shadow is linked to the distance between the vessel and the plane that receives the shadow, it is possible to calculate this distance and to compare it with the anatomical distance between the vessels and the retina.* The method I used to calculate the anatomical distances was as follows: By moving a light spot on the sclera a certain distance while projecting the entoptic image of the vessels onto a sheet at a known distance from the eye, I recorded the apparent shift of the vascular shadows. The measurement was most easily accomplished for the small branches above or below the vessel-free site. By moving a light source backward from the edge of the cornea to the equator of the eye, this technique was also used to measure the distance from the yellow spot to individual points of the sclera in several eyes. In Figure 3, if *o* refers to the vessel at the yellow spot, *a* and *b* to the two points on the sclera between that the light point alternates, *a'* and *b'* to the two points on which alternately the shadow of the vessel *o* falls, and *a-o-b* and *a'-o-b'* are considered triangles, then

$$a' - o : b - o = a' - b' : a - b$$

$$a' - o = \frac{a' - b'}{a - b} b - o$$

and

$$b' - o : a - o = a' - b' : a - b$$

$$b' - o = \frac{a' - b'}{a - b} a - o$$

a'-o and *b'-o* specify the distance of the vessel from the retinal layer receiving the shadow. I have used these distances to calculate the perpendicular distance in relation to the measured diameter of the eye. The same applies to the cornea. So, it follows that

$$c' - o : b' - o = b - o : c - o$$

$$c' - o = \frac{b' - o \times b - o}{c - o}$$

Page 440: It should be noted that it is quite impossible to perform such a computation with absolute accuracy. It is difficult to measure precisely the movement of the light source

and the displacement of the vascular figure in the absence of conspicuous markers. To mitigate error, one should use a second observer to assist in one or the other.[10]

Page 440/441: Likewise, the quantification of the distance of a vessel from the various points on the sclera is error prone because it varies appreciably in different eyes and can only succeed approximately in a given eye. I have measured the distances, histologically, between the inner layer of the sclera and the retina in the area of the yellow spot to the endpoints of the lines to be measured within eyes hardened or frozen in chromic acid. From the select averages of the values so obtained, I have drawn up a scale that enabled an estimation of the distance of the yellow spot in 1 mm steps from the edge of the cornea. The uncertainty of the position of the intersection for some conditions[11] and the nonspherical shape of the posterior segment of the globe are also known limitations of this approach. For these reasons and the large error factors they produce, I have not endeavored to give the calculation a strict form. With the limited series of measurements that have hitherto been possible, it was only necessary for the time being to ascertain whether there is an approximate agreement between the anatomical findings and the size of the parallax results. I believe this to be so despite the numerous sources of error. *The simplest explanation of the observations is that the vascular figure in the experiments in question is a silhouette and that the outer retinal layers receive this shadow.*

Page 441/442: The individual values I obtained in the above manner for the distance of the vessels from the surface receiving their shadows were as follows:

0.17
0.19–.21[12]
0.22
0.25–.29
0.29–.32 mm.

I have never obtained values above or below the designated extremes. For the eyes of three observers other than myself, the distances were as follows:

0.19
0.26
0.33 mm.

I should mention here that for the latter, especially during the first observations, much higher values of up to 0.53 mm were found. However, I believe this is due to the fact that one naturally overestimates the displacement of the vascular shadow by following it with the eye, instead of maintaining strict fixation. Once subjects learned to avoid this behavior, larger values were no longer recorded.

Page 442: The method of calculation would likely improve if, while strictly fixating, one alternately projected a light spot first at the inner, then at the outer corner of the eye on the sclera, thereby for each condition observing the apparent location of a given vascular shadow. I have performed a similar measurement to determine the size of the avascular area in the middle of the retina by moving the light source at the sclera from the edge of the

[10]Messrs. Althof and A. v. Franque assisted me in these experiments.
[11]It seems doubtful that mere mathematical demonstrations produced here are suitable to provide the exact method it deserves.
[12]Where two numbers are given for one observation, two quantities are taken into account for the displacement of the light source at the sclera or the vascular shadow in the visual field, because the observation was not quite decisive between the two magnitudes.

cornea backward (i.e., toward the periphery) until the shadow of the innermost vessel fell onto the fixation point (10–11 mm). For the distance of this spot on the sclera, the macula lutea, and the corresponding spot on the other side of the eye, a value of 0.21–.23 mm was the recorded distance from the innermost capillary vessel at the macula lutea to the layer receiving the shadow (cones). However, I would like to consider this quantity with reservation until a more exact measurement becomes available.

Page 443: The values found above need to be compared with the distance between the outer layers of the retina and the vessels. This study has determined that the distance of the vessels from the rods and cones in the area of the yellow spot for most subjects is between 0.2 and 0.3 mm. The significant variability is explained partly by the vessels lying at different levels, and partly because the individual layers of the retina in that area vary in thickness. In total, however, only a few vessels in the yellow spot and its surroundings may be assumed to be closer to or farther from the cones than 0.2–.3 mm. With this anatomical finding, the above result of the calculation (0.17–.32 mm) is remarkable considering the many experimental sources of error.

Page 444: *From the relative agreement of the results obtained from both the calculations based on the entoptic visualization of the retinal vessels and those based on anatomical investigation, I have drawn two conclusions. First, I confirm the above arguments about the nature and mode of origin of the vascular figure. Second, if the outer layer of the retina is the one that distinguishes the shadow of the vessels from the surrounding illuminated field, then it must contain the elements excitable by light*. Of course, it would be inappropriate to conclude from the data taken from the parallax of the vascular shadows whether cones or external grains (the outer granular layer) are the sensitive elements; but for one of these outer layers, the conclusion seems to be inescapable, *for the light is not perceived before it reaches the outer layers where the vascular shadow falls*.

From a teleological point of view, the possibility that the light-sensitive elements lie in the back of the retina always has seemed paradoxical. If our interpretation is correct, the location of the sensory elements next to the other ocular tissues may allow it to remain in a fixed position, a certain prerequisite of sensory elements.

Page 447: In summary, based on the perception of light by elements of the outer retinal layer (cones and rods), the following may be concluded:

(1) Such elements are connected through some (a part, a portion, a number) of the radial fibers including the granules (*Körner*) with the axons (*Fortsätzen*) of the ganglion cells and through those with the optic nerve fibers.
(2) Optic fibers, the inner ends of the radial fibers, the nerve cells, and the granules cannot possibly mediate perception of an image.
(3) *The phenomena of Purkinje's vascular figure directly support the conclusion that vision (Auffassung des Bildes) is initiated in the outer retinal layers.*

4. Comparisons with contemporary *in vivo methods*

Entoptic visualization of the retinal vasculature compares favorably with fundus photographs (Bradley et al. 1998). Both are inherently two-dimensional as are the more detailed clinical images afforded by fundus angiography following injection of a fluorescent dye

(fluorescein or indocyanine green). None of these techniques, however, can be used to evaluate Müller's estimates of the distance between the vasculature and the photoreceptors. This measurement could be obtained from histology that was already well established at the time by Müller himself, among others. However, two difficulties arise from this technique. First, the retinal samples are obtained from deceased donors and subject to postmortem artifacts. Second, the process of sample preparation can alter the architecture of the retinal layers and vasculature. *In vivo* and *in situ* three-dimensional visualization of the retina and perfused blood vessels are possible with optical coherence tomography (OCT) angiography.

OCT is a noninvasive tool that provides high-resolution (1–6 μm) cross-sectional imaging of the laminar structure of the retina (Huang et al. 1991). This imaging modality produces structural images of retinal morphology that agree well with histology (Gloesmann et al. 2003; Xie et al. 2018). By itself, visualization of the vasculature is limited, but the contrast of perfused vessels may be enhanced by OCT angiography methods that detect blood flow in the vasculature (e.g., Kim et al. 2011; Migacz et al. 2019). OCT angiography signals are extracted from interferometric detection, usually using a Michelson or Mach-Zehnder interferometer. Phase and/or amplitude changes are computed from multiple sequential frames, and variation caused by blood flow is calculated using one of several different metrics (Gorczynska et al. 2016).

As discovered in 1876, 21 years after Müller's experiment, by Franz Boll (1876) and further investigated by Wilhelm Kühne (1877), the light-sensitive pigment (rhodopsin) initiating visual processes is located in the outer segments of rods. Later discoveries also found visual pigments in the outer segments of cones (Wald 1937). In OCT, rods and cones are visualized as a series of bright and dark bands located between the external limiting membrane (ELM) and the retinal pigment epithelium (RPE), as demonstrated in an example image obtained with a research-grade swept-source OCT device (Figure 4.1).[13] With the aid of adaptive optics techniques incorporated into OCT systems, high isotropic imaging resolutions (~2–3 μm) can be achieved to visualize single photoreceptor cells (e.g., Jonnal et al. 2017). Currently, the photoreceptor outer segments are identified as the dark bands between two bright flanking bands: photoreceptor inner/outer segment junction (IS/OS) and photoreceptor outer segment tips (POST; see Figure 4.1). This knowledge provides precise localization of the layer from which to measure the distance to the retinal vasculature.

The retinal vasculature is derived from the retinal artery that emerges from the optic nerve head and produces a network of vessels that covers the retina. The larger retinal vessels are in the superficial (anterior) retina in the retinal nerve fiber layer and divide into a network of smaller vessels in the inner plexiform layer and, in turn, give rise to yet smaller vessels in the outer plexiform layer (see Figure 4.1 for identification of the layers in OCT images). These three vascular networks are shown in Figure 4.2 for data acquired using a research-grade OCT system. Additional capillary vessels branching from superficial retinal vessels are also present within the nerve fiber layer in the vicinity of the optic nerve head.

[13]The participants recruited for this study provided written informed consent, in accordance with a protocol approved by the Institutional Review Board of the University of California, Davis.

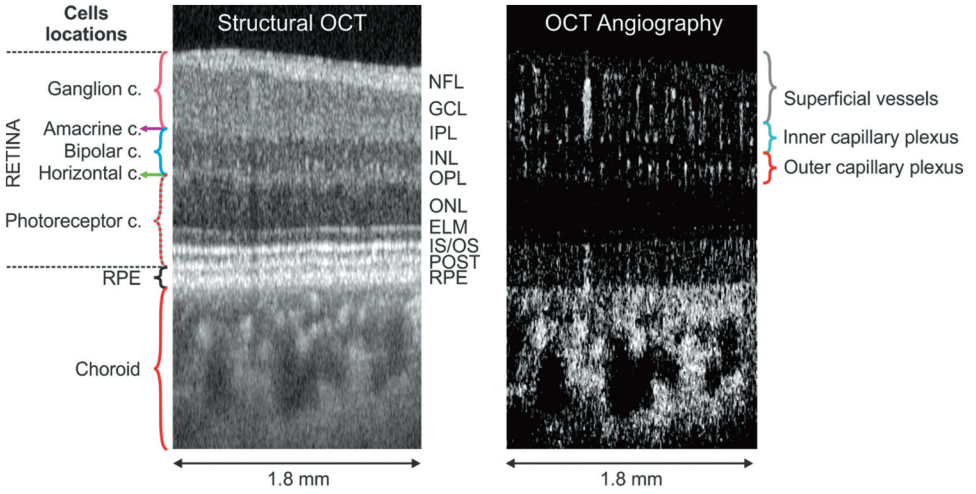


Figure 4.1. Cross-sectional OCT and OCT angiography images of a healthy human retina (location 6° nasal, 4° inferior from the fovea, age 63). Locations of cell types known to Müller's contemporaries are shown on the left of the structural OCT image (c. is abbreviation for cells). To the right of the structural image, retinal layers typically identified in OCT are denoted: NFL – nerve fiber layer; GCL – ganglion cell layer; IPL – inner plexiform layer; INL – inner nuclear layer (dark band); OPL – outer plexiform layer; ONL – outer nuclear layer (dark band); ELM – external limiting membrane; IS/OS – photoreceptor inner/outer segment junction; POST – photoreceptor outer segment tips; RPE – retinal pigment epithelium. Photoreceptor inner segments are visible as dark bands between the ELM and IS/OS junction. Photoreceptor outer segments, where photo-sensitive pigments are located, are visible as dark bands between IS/OS and POST. Locations of the retinal vascular layers are indicated to the right of the OCT angiography image, which was obtained from the same data set as the structural OCT image.

Figure 4.3 shows an *en face* projection of retinal vasculature of the living eye with color depth-encoded vascular layers for comparison with Müller's entoptic measurements. He found that the mean distance between the retinal vessels and the cells initiating vision was 0.233 mm (233 μm), with a range from 0.17 to 0.305 mm. In the subject whose OCT angiography images are shown here as examples (Figures 4.1 and Figure 4.2), the mean distances between the photoreceptor outer segments and the retinal vascular layers are as follows:

- superficial vessels: 262 μm (from 205 μm to 319 μm),
- inner capillary plexus: 175 μm (from 145 μm to 205 μm), and
- outer capillary plexus: 120 μm (from 95 μm to 145 μm).

The OCT angiography images provide information about locations of vascular layers in relation to the anatomical layers visible in structural OCT images. Inferences about typical distances between the photoreceptor outer segments and the three vascular layers can therefore be made directly from the structural OCT images in which numerical algorithms have been implemented to segment out retinal layers and measure their thicknesses. Such studies show that the distances to the layers containing the three vascular plexuses vary depending on the location in the eye (e.g., Kafieh et al. 2015) and also with age or gender (e.g., Palazon-Cabanes et al. 2020). From the data presented by Kafieh et al. (2015), in which

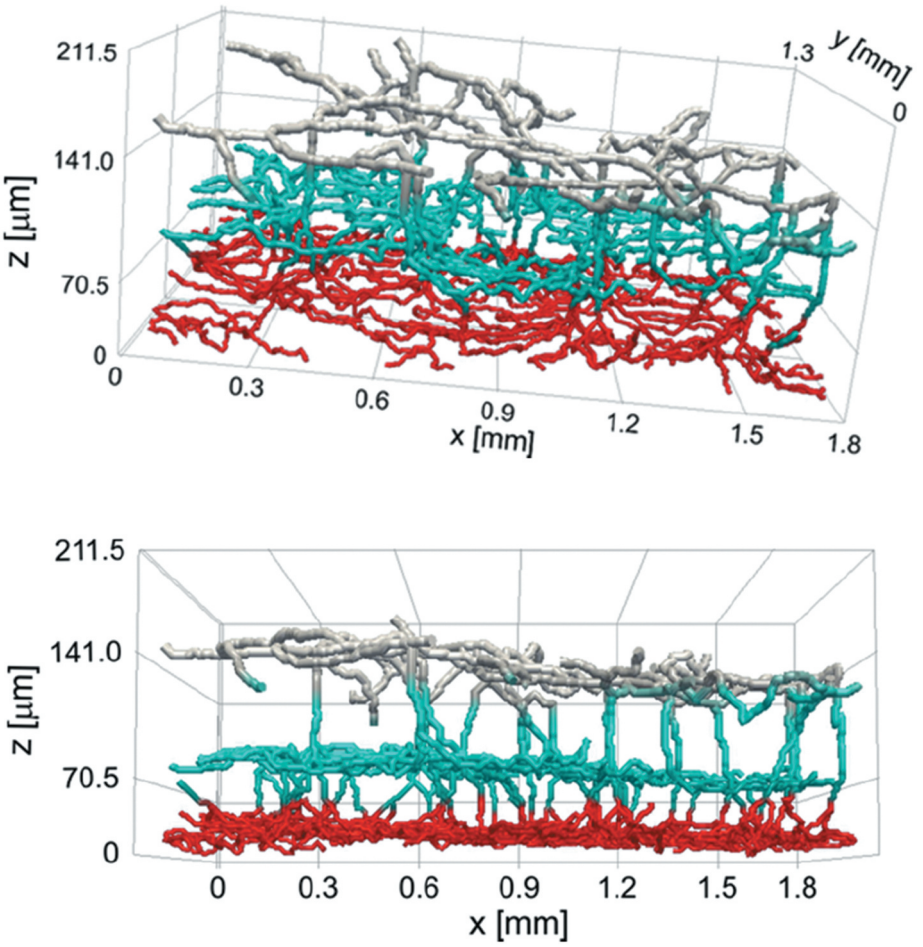


Figure 4.2. 3D skeletonization of the human retinal vasculature from OCT angiography volumetric image acquired from a 63-year-old participant with a clinically normal retina. Top and bottom images provide different perspective views. The three vascular layers and their connecting vessels are color-coded as superficial layer (gray), inner capillary plexus (cyan) and outer capillary plexus (red). Based on a video animation published by Gorczynska et al. (2016).

thicknesses of retinal layers were measured in 112 normal eyes, we have estimated the expected mean distances of vascular layers from the center of the photoreceptor outer segments, in the macular region, as follows:

- superficial vessels (from NFL to the center of IPL): 267 µm (from 220 µm to 314 µm), inner capillary plexus (from the center of IPL to the center of INL): 197 µm (174 µm to 220 µm), and outer capillary plexus (from the center of INL to the OPL, inclusive): 148 µm (123 µm to 174 µm).

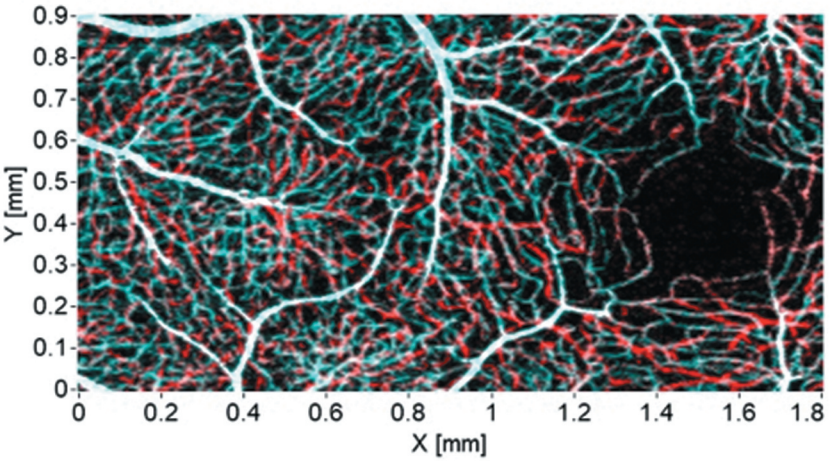


Figure 4.3. Retinal vasculature (1.8 × .9 mm) from the fovea (avascular zone) to 3.5° nasal of a healthy 39-year-old. The vessels are color coded according to their depth. At this retinal location: gray denotes the superficial vessels (~213–275 μm from the photoreceptors (inner/outer segment junction); cyan shows the intermediate layer (~174 μm from the photoreceptors); red is the deep vascular plexus (~122 μm from the photoreceptors). The size of the foveal avascular zone is ~0.32 × 0.32 mm, which is ~0.08 mm smaller than estimated entoptically by Müller. Original image from the Vision Science and Advanced Retinal Imaging Lab, UC Davis.

Although we cannot be certain as to which vascular layers the entoptic images used by Müller belonged, it is clear that his measurements are well within the range of values measured using today's advanced imaging techniques. Given the subjective methods of measurement and possible sources of errors, which he acknowledged himself, Müller's results are incredibly accurate.

The comparison of Müller's measurements of the distance between the vascular layers and the cells initiating vision is remarkably similar to measurements more than 160 years later, using modern imaging techniques that permit three-dimensional visualization of the laminar structure of the retina and the locations of the blood vessels in relation to other cell layers. Indeed, Müller found that the mean distance between the retinal vessels and the cells initiating vision was 0.233 mm (233 μm), with a range from 0.17 to 0.305 mm. Assuming Müller's entoptic visualization was based on the largest and most superficial vessels (vessels coded as gray in the preceding figures), his measurements of the distance from the photoreceptors were astonishingly accurate. Müller's entoptic visualizations are within 0.01 mm of the median OCT angiography data derived from the most superficial vascular layer (Gorczynska et al. 2016). These results attest to the validity of entoptic methods and confirm Müller's remarkable discovery of the cellular layer where human vision is initiated.

Acknowledgments

We thank John Mollon, Ivan Schwab, Nicholas J. Wade, and Heinz Wässle for helpful comments. We thank Susan Garcia, Christina Gerth-Kahlert, and Brennan Marsh-Armstrong for contributions to early versions of the translation.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This research was supported by the National Institutes of Health (NEI R01 EY 024239).

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References

Adams D. L., and J. C. Horton. 2003. The representation of retinal blood vessels in primate striate cortex. *The Journal of Neuroscience* 23:5984–97. 1.1523/JNEUROSCI.23-14-05984.2003 .

Becker O. 1872. *Heinrich Müller's gesammelte und hinterlassene Schriften zur Anatomie und Physiologie des Auges* [Heinrich Müller's collected and left behind papers on the anatomy and physiology of the eye]. Leipzig: Engelmann.

Becker O. 1881. Die Gefässe der menschlichen Macula lutea, abgebildet nach einem Injectionspräparate von Heinrich Müller [The vessels of the human macula lutea, shown after an injection preparation by Heinrich Müller]. *Albrecht von Graefes Archiv für Ophthalmologie* 27:1–20. doi:1.1007/BF01695448 .

Bird A. C., and R. A. Weale. 1974. On the retinal vasculature of the human fovea. *Experimental Eye Research* 19:409–17. 1.1016/0014-4835(74)90050-5 .

Boll F. 1876. Zur Anatomie und Physiologie der Retina [On the anatomy and physiology of the retina]. *Monatsbericht der Königlichen Preussischen Akademie der Wissenschaften zu Berlin*: 783-7. (Trans. R. Hubbard (1977). *Vision Research* 17:1253–65.

Bradley A., H. Zhang, R. A. Applegate, L. N. Thibos, and A. E. Elsner. 1998. Entoptic image quality of the retinal vasculature. *Vision Research* 38:2685–96. 1.1016/S0042-6989(97)00345-3 .

[C.W]. 1830. Contributions to the physiology of vision. No I. *Journal of the Royal Institution of Great Britain* 1:101–17.

Coppola D., and D. Purves. 1996. The extraordinarily rapid disappearance of entoptic images. *Proceedings of the National Academy of Sciences USA* 93:8001–04. 1.1073/pnas.93.15.8001 .

Cornsweet T. N. 1970 *Visual perception*. New York: Academic Press.

Gloesmann M., B. Hermann, C. Schubert, H. Sattmann, P. K. Ahnelt, and W. Drexler. 2003. Histologic correlation of pig retina radial stratification with ultrahigh-resolution optical coherence tomography. *Investigative Ophthalmology & Visual Science* 44:1696–703. 1.1167/iovs.02-0654 .

Gorczynska I., J. V. Migacz, R. J. Zawadzki, A. G. Capps, and J. S. Werner. 2016. Comparison of amplitude-decorrelation, speckle-variance and phase-variance OCT angiography methods for imaging the human retina and choroid. *Biomedical Optics Express* 7:911–42. 1.1364/BOE.7.000911 .

Hirschberg J. 1919. *Geschichte der Augenheilkunde* [History of ophthalmology]. Berlin: Springer Verlag.

Hirschberg J. 1992. *The history of ophthalmology, 11, Part 1-b: The reform of ophthalmology*. Trans. F. C. Blodi. Bonn: JP Wayenborgh Verlag.

Horner W. G. 1834. XLVI. On the autoptic spectrum of certain vessels within the eye, as delineated in the shadow on the retina. *The London, Edinburgh, and Dublin Philosophical Magazine and Journal of Science* 4:262–71. 1.1080/14786443408648324 .

Huang D., E. A. Swanson, C. P. Lin, J. Schuman, W. Stinson, W. Chang, M. Hee, T. Flotte, K. Gregory, C. Puliafito, et al. 1991. Optical coherence tomography. *Science* 254:1178–81. 1.1126/science.1957169 .

Hubbard R. 1977. Preface to the English translation of Boll's *On the anatomy and physiology of the retina* and of Kühne's *Chemical processes in the retina*. *Vision Research* 17:1247–48. 1.1016/0042-6989(77)90111- .

Jonnal R. S., I. Gorczynska, J. V. Migacz, M. Azimipour, R. J. Zawadzki, and J. S. Werner. 2017. The properties of outer retinal band three investigated with adaptive-optics optical coherence tomography. *Investigative Ophthalmology & Visual Science* 58:4559–68. 1.1167/iovs.16-21138 .

Kafieh R., H. Rabbani, F. Hajizadeh, M. D. Abramov, and M. Sonka. 2015. Thickness mapping of eleven retinal layers segmented using the diffusion maps method in normal eyes. *Journal of Ophthalmology*:259123. 1.1155/2015/2591232 .

Kim D. Y., J. Fingler, J. S. Werner, D. M. Schwartz, S. E. Fraser, and R. J. Zawadzki. 2011. In vivo volumetric imaging of human retinal circulation with phase-variance optical coherence tomography. *Biomedical Optics Express* 2:1504–13. 1.1364/BOE.2.001504 .

Kim D. Y., J. Fingler, R. J. Zawadzki, S. S. Park, L. S. Morse, D. M. Schwartz, S. E. Fraser, and J. S. Werner. 2012. Noninvasive imaging of the foveal avascular zone with high-speed, phase-variance optical coherence tomography. *Investigative Ophthalmology & Visual Science* 53:85–92. 1.1167/iovs.11-8249 .

Kölliker A. 1867. Zur Erinnerung an Heinrich Müller [In memory of Heinrich Müller]. *Würzburger naturwissenschaftliche Zeitschrift* 66:29–41.

Kühne W. 1877. Ueber den Sehpurpur [On visual purple]. *Untersuchungen aus dem Physiologischen Institute der Universität Heidelberg* 1:15–104.

Migacz J. V., I. Gorczynska, M. Azimipour, R. Jonnal, R. J. Zawadzki, and J. S. Werner. 2019. Megahertz-rate optical coherence tomography angiography improves the contrast of the choriocapillaris and choroid in human retinal imaging. *Biomedical Optics Express* 10:50–65. 1.1364/BOE.1.00005 .

Müller H. 1851. Zur Histologie der Netzhaut [On the histology of the retina]. *Zeitschrift für Wissenschaft und. Zoologie* 3:234–37.

Müller H. 1855. Ueber die entoptische Wahrnehmung der Netzhautgefässe, insbesondere als Beweismittel für die Lichtperception durch die nach hinten gelegenen Netzhautelemente [On the entoptic perception of retinal vessels, particularly as evidence for the light perception through the distally located retinal elements]. *Verhandlungen. Physikalisch-Medizinische Gesellschaft in Würzburg* 5:411–47.

Palazon-Cabanes A., B. Palazon-Cabanes, E. Rubio-Velazquez, M. D. Lopez-Bernal, J. J. Garcia-Medina, and M. P. Villegas-Perez. 2020. Normative database for all retinal layer thicknesses using SD-OCT posterior pole algorithm and the effects of age, gender and axial length. *Journal of Clinical Medicine* 9(10):3317. doi:10.3390/jcm9103317.

Purkinje J. 1819. *Beiträge zur Kenntniss des Sehens in subjectiver Hinsicht* [Contributions to the knowledge of vision in its subjective aspect]. Prague: Johann Gottfried Calve.

Ratliff F. 1971. On the objective study of subjective phenomena: The Purkyne tree. In *Jan Evangelista Purkyně, Centenary Symposium*. Brno: Universita Jana Evangelisty Purkyně.

Remky A., E. Beausencourt, and A. E. Elsner. 1996. Angioscotometry with the scanning laser ophthalmoscope. *Investigative Ophthalmology & Visual Science* 37:2350–55.

Riggs L. A., F. Ratliff, J. C. Cornsweet, and T. N. Cornsweet. 1953. The disappearance of steadily fixated visual test objects. *Journal of the Optical Society of America* 43:495–501. 1.1364/JOSA.43.000495 .

Snodderly D. M., W. P. Leung, G. T. Timberlake, and P. S. Smith. 1977. Mapping retinal features in a freely moving eye with precise control of retinal stimulus position. In *Frontiers in Visual Science*, ed. S. J. Cool and E. L. Smith III, 79–92. New York: Springer-Verlag.

Troxler D. 1804. Ueber das Verschwinden gegebner Gegenstände innerhalb unseres Gesichtskreises [On the disappearance of given objects within our field of vision]. Himly, K. and J.A. Schmidt (Eds.). *Ophthalmologische Bibliothek* 2:1–53.

von Helmholtz H. 1867. *Handbuch der Physiologischen Optik* [Handbook of physiological optics]. Leipzig: Leopold Voss.

von Helmholtz H. 1924. *Helmholtz's treatise on physiological optics*, ed. J. P. C. Southall. Trans. from the 3rd German ed. New York, NY: Dover Publications, Inc.

Wade N. J., and J. Brožek. 2001. *Purkinje's vision: The dawning of neuroscience*. Mahwah, New Jersey: Lawrence Erlbaum Associates.

Wald G. 1937. Photo-labile pigments of the chicken retina. *Nature* 140:545–46. 1.1038/140545a .

Weale R. A. 1969. Physiologist and patriot. *New Scientist*, July 24: 188–89.

Werner J. S. 1998. Aging through the eyes of Monet. In *Color vision: Perspectives from different disciplines*, ed. W. G. K. Backhaus, R. Kliegl, and J. S. Werner, 3–41. Berlin: Walter de Gruyter & Co.

Xie W., M. Zhao, S. H. Tsai, W. L. Burkes, L. B. Potts, W. Xu, H. R. Payne, T. W. Hein, L. Kuo, R. H. Rosa, et al. 2018. Correlation of spectral domain optical coherence tomography with histology and electron microscopy in the porcine retina. *Experimental Eye Research* 177:181–9. 1.1016/j.exer.2018.08.003.