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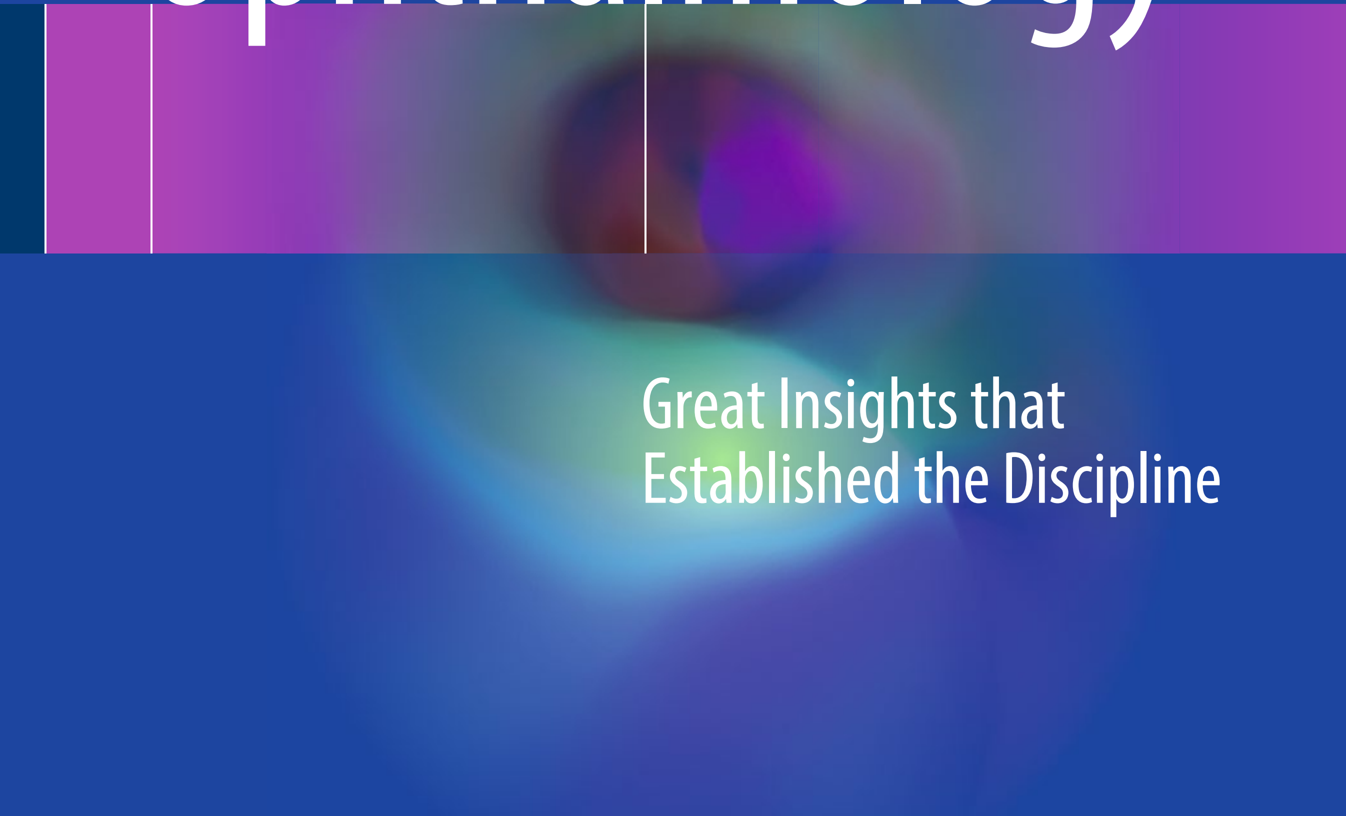
Daniel M. Albert
Editors

Foundations of Ophthalmology



Great Insights that Established the Discipline

Springer

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Preface

The acclaimed medical historian and bibliographer Fielding H. Garrison noted that the history of medicine “may be treated variously as a pageant, an array of books, a procession of characters, a succession of the theories, an exposition of human ineptitudes, or as the very bone and marrow of cultural history.” Ophthalmic history is a microcosm of medical history, and this observation applies to it as well.

One of us (MFM) organized a symposium in 2015 at the annual meeting of the American Academy Ophthalmology, under the auspices of the Museum of Vision, to present some of the great insights that have formed the foundation of ophthalmic science. The intent was to present the people responsible, and the story of how their ideas evolved, rather than a list of their accomplishments. This proved to be informative and interesting to many of the attendees, and the editors were encouraged by Rebekah Amos Collins (Springer Editor for Clinical Medicine) to expand the symposium concept into a book.

The editors thank Jenny Benjamin, Director of the Museum of Vision, for her vital role in organizing the original symposium. We appreciate the efforts of all of the contributing authors (some of whom spoke in the symposium) not only for excellent chapters, but also for their willingness to work with us in achieving a consistent approach to the material in the book. We thank Gina Kahn for editorial assistance and of course the Springer Publishing Company for its effort and support in publication. We are especially grateful to Rebekah Amos Collins (also the project editor) with whom it has been a great pleasure to work.

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Johannes Kepler and René Descartes: A Retinal Image is Transmitted to the Brain

Ronald S. Fishman

> *Nature tells us one secret in terms of another, and she may refuse to disclose one secret until another has been laid bare.*
>
> T.S. Kuhn [1]

Introduction

Our modern appreciation of how the eye and brain are related was the work of two men in the first half of the seventeenth century: Johannes Kepler (1571–1630) and René Descartes (1596–1650). Kepler solved the problem of how the optics of the eye produced an image on the retina; Descartes then conceived of sensory projection from the eye to a specific location in the brain.

The Elegant Construction of a Retinal Image

The book was a small one, with the disarmingly modest title *Supplements to Witelo on the Optical Part of Astronomy* (*Ad vitellionem paralipomena quibus astronomiae pars optica traditur*) (Witelo was a thirteenth century writer on optics) [2–7]. This book of 1604 is the first one of modern optics. No one today can read any of the optical theorists that came before Johannes Kepler (Fig. 1) and understand them without reconstructing optical ideas that are largely antique and obsolete.

In a way, what Kepler did was simple, yet it had profound effects. He had been busy throughout 1603 with calculations that would eventually show the orbit of Mars to be elliptical, the first of his laws of planetary motion. This involved reams of arithmetical calculations in which he had to be aware of how the atmosphere's refraction of starlight affected the observed star positions. Since he was so much involved with the errors created by refraction, for some reason (probably pure obsessiveness) he decided to study the refraction of light in the eye. He followed light going through the transparent media of the eye and followed where it led him, and it led him to the retina. He thus accomplished what Witelo and a host of others could not quite manage. He took what was then only a vague and tentative idea, that the retina was the true photoreceptor, and established the first convincing idea of a retinal image.

In 1583, the Swiss anatomist Felix Platter, in *De Corporis Humani Structura*, approached the problem of the eye as an anatomist and for the first time explicitly made the retina, as the expansion of

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Fig. 1 Johannes Kepler (1571–1630). "The way in which this image … is put together by the spiritual principles of vision residing in the retina and the nerves … [It belongs] to natural philosophy and the study of the wonderful" [2]. (This reproduces Fig. 29 of the University of Chicago Press publication, The Vertebrate Visual System by S. Polyak. 1957. That image in turn reproduced an image from a 1925 British publication. Permission was obtained in 1972 from the U of Chicago Press to reproduce the image in a paper of mine published in the Archives of Ophthalmology in 1973)

the optic nerve, the eye's essential light transducer. Gone was the traditional assumption that the lens, with its unique structure, was the essential element in vision. Now it was simply 'the internal looking glass' of the retina [7]. Platter made no effort to solve the geometrical problems of image formation and did not mention the inverted image produced in this scheme. He ignored it. But that problem had nonplussed prior optical theorists (including Leonardo da Vinci) and it had to be faced if the intraocular refraction was to be properly appreciated. That is what Kepler did. He confronted the problem and solved it. In a model of concision, Kepler wrote: "Thus vision is brought about by a picture of the thing seen being formed on the concave surface of the retina. That which is to the right outside is depicted on the left on the retina, that to the left on the right, that above below, and that below above" [2]. This gives us the retinal image, clearly enunciated for the first time.

Kepler's image has "elegance," that particular quality that Judson [8] ascribes to the double helix: "Structure and … function are united in DNA with such ingenious parsimony that one smiles with the delight of perceiving it." The retinal image is an elegant construction. Structure (the transparent media, the lens, the hemispheric retina) and function (the focusing of light on the retina) are united in the eye with such ingenious parsimony that one smiles with the delight of perceiving it.

Why did Kepler succeed where his predecessors had failed? He was well aware of Galen's ideas and those of the medieval optical theorists before him [2, 7]. He had, however, the advantage of not being wedded to them. When he approached the problem of how light behaved in the eye, as an astronomer he saw it in a different way. He made the strategic decision to treat the eye as an optical instrument, pure and simple. He traced light refracting through the transparent optical media of the eye and its projection as a real image onto the retina. The inverted and reversed image is a faithful representation of the outside world because its details bear the same geometrical relationship to each other as the details of the object do. It is not the insuperable obstacle to seeing things right side up that previous writers had thought it was. Kepler could afford to treat the inverted image and the other features of perception *as a different problem*, a problem whose time for solution had not yet come. This is still a critical factor in determining the success of any scientific enterprise today. Kepler's judgment here was as astute as any displayed in the astronomical discoveries for which he is famous. With admirable directness, Kepler wrote:

> I leave it to natural philosophers to discuss the way in which this image … is put together by the spiritual principles of vision residing in the retina and the nerves … For by the laws of optics, what can be said about this hidden motion, which, since it takes place through opaque and hence dark parts and is brought about by spirits that differ in every respect from the humours of the eye and other transparent things, immediately puts itself outside the field of optical laws? … [It belongs] to natural philosophy and the study of the wonderful. [2].

Very simple, and very elegant.

At this point there was a problem. Kepler's retinal image was a geometrical representation of the outside world *inside the body*. The requirements of optical theory and the constraints implicit in the rectilinear propagation of light in the formation of images ensured that for each point in the external world, there existed a corresponding point in the retinal image that bore the same relative positioning to other points as they did “out there.” The retinal image was only two-dimensional and thus was by no means an actual replica of the object. Its geometry was far more convincing than Alhazen’s quasi-optical constructions on the lens surface [7]. It thus was a powerful argument that however the soul gained understanding from the image, *its organization would be crucial*.

However, Galen’s concept of the brain, still largely accepted at the time, was of a mostly undifferentiated gland producing the animating principle, the “pneuma” or “spirit” of the nerves. What room was there in such a tradition for Kepler’s retinal image? Was Kepler’s representation of the outside world so carefully constructed on the retina only to be lost in its passage to the brain? *No*, thought Rene Descartes, *it is not lost*. It is preserved in a direct projection of retinal points to corresponding points in the brain (Fig. 2) [2, 7, 9–13]. In one stroke, Descartes invented sensory projection and brought the physiology of sensation into the modern age. There is nowhere in all of the history of science a better example of how one man’s seminal insight led directly to the equally brilliant and powerful insight of another. For Descartes, Kepler’s image became the key to the brain.

Fig. 2 René Descartes (1596–1650). “It is not immediately the movements which occur in the eye, but those that occur in the brain which represent the object to the soul” [7]. (Photo courtesy of Ronald Fishman).

Descartes Extended Kepler’s Retinal Image to the Brain

Descartes wrote about the eye and brain mainly in two works, *Dioptrique* (*Optics*), published in 1637 and *Traite de l’homme* (*Treatise on Man*), written in 1632 and published posthumously in 1662 in Latin (*De Homine)* and in 1664 in French (*L’Homme*) [13, 14]. *Dioptrique* is one of three works published together and meant to illustrate his primary effort, the *Discourse on the Method of Rightly Directing the Reason, and Searching for Truth in the Sciences*, the other essays concerning meteorology and geometry (in which Descartes formulated analytical geometry). Posterity pays most attention to the *Discourse of Method* (1637), but the three essays themselves are all substantial affairs. *Dioptrique* consists of ten chapters dealing with the nature of light, its refraction (enunciating the sine law, probably independently from Snell [15]), the anatomy of the eye, the nature of sensation and vision, and the operation of lenses in general. It even concludes with suggestions on how to fabricate new types of lenses for telescopes, the exciting new invention of the time. Descartes’ discussion of vision outlines his main ideas on the eye and the brain, which are elaborated further in *Traite de l’homme.*

Traite de l’homme purports to describe general physiology, but it deals largely with what we now call the central nervous system. The work includes some material on hearing and smell, but the principal discussion concerns vision. It is lavishly illustrated, though its posthumous publication probably means that Descartes never saw or approved of the actual illustrations. Of 54 diagrams in the book, more than half depict the eye or the eye and brain together. Kepler’s optics is dealt with in detail.

But, unconscionable as it is to the modern reader, Kepler's name is never mentioned.

Descartes consistently earns poor marks in the etiquette of attribution. This failing was less egregious in the custom of the time than it is now, but raises the legitimate question of whether Descartes actually knew of Kepler's work. Hall [16] acknowledges that "Descartes created a problem for historians by generally omitting any reference to his sources" and Scott [17] also notes that Descartes.

> … scornfully repudiates the suggestion that he received any hint for his ellipses or his hyperbolas from Kepler. Consequently, the uncritical reader is prone to accept many of Descartes' observations as his own, an assumption which is usually far from accurate.

This mention of hyperbolas refers to Kepler's 1611 text *Dioptrice*, which was written in a flurry of enthusiasm when he had just heard of Galileo's amazing observations with the telescope [2, 3]. In this text, Kepler suggested the use of elliptical or hyperbolic lenses to decrease the spherical aberrations that limited Galileo's observations. But *Dioptrice* was more than that. It was Kepler's attempt to systematize his understanding of optics, at which he had only hinted in the *Supplements to Witelo*. All the basic concepts of modern image theory are there: real, virtual, upright, and inverted images; reduced and magnified images; the crucial relationship between the distance of object and image; refraction in 1-, 2-, and 3-lens systems; the double convex lens system for an astronomical (Keplerian) telescope; and the convex-concave lens (Galilean) telescope. Kepler also coined the words *focus* and *dioptrics*.

Not only did Descartes have no compunction in using the word *dioptrics* for his own essay on optics, but the essay contains internal evidence that he had carefully read Kepler. For instance, like Kepler, Descartes used the word *painted* (or rather the Latin or French equivalent) to describe the action of light in forming the retinal image: "[A] picture can easily stimulate our minds to conceive the object painted there" [14] (Kepler: "The retina is painted with the colored rays of visible things" [2]). More than that, Kepler's *Dioptrice* was the reigning optics text in the period before Christopher Scheiner's *Oculus, hoc est.: Fundamentum Opticum* appeared in 1619. Scheiner (1573–1650) extended Kepler's retinal image by actually demonstrating the real inverted image formed on the retina in his famous experiment in which he directly viewed the image on the translucent retina of an enucleated eye [9]. Descartes referred to Scheiner in his correspondence [18] and illustrated the experiment in *Dioptrique* (without attribution) (Fig. 3). If Descartes was aware of Scheiner, it stretches

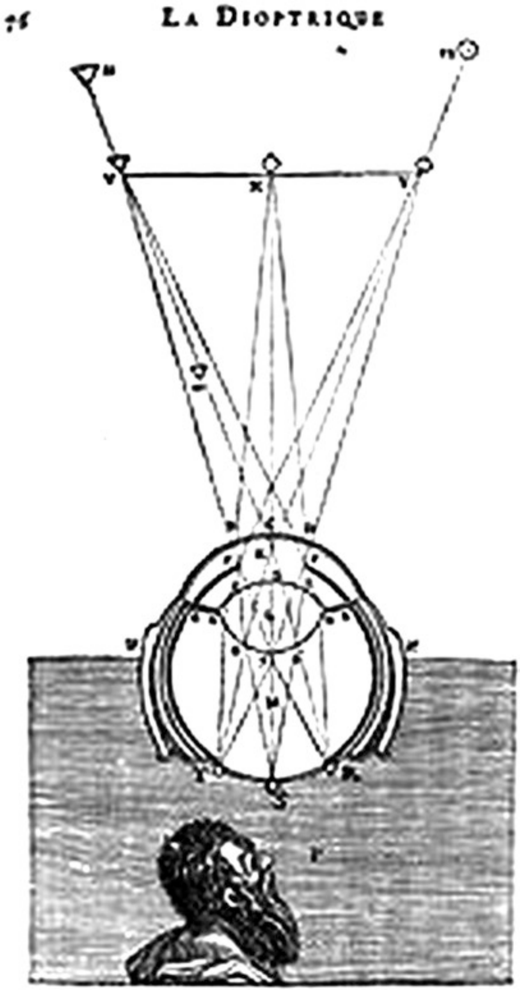

Fig. 3 Johannes Kepler's inverted retinal image as depicted in René Descartes' La Dioptrique (1637), illustrating Christopher Scheiner's experiment of observing the retinal image on the translucent retina of a freshly enucleated animal or human eye from which the back of the sclera had been removed [1]. (Photo courtesy of taken from a seventeenth century. tome at the National Library of Medicine; no permission needed)

credence to suppose that he was unfamiliar with Kepler's *Dioptrice*, if not the *Supplements to Witelo*. Descartes may not have acknowledged it, may not have even consciously recognized it, but Kepler was leading him into the brain.

At any rate, Descartes makes two significant improvements over Kepler in dealing with the intraocular refraction of light. Having by now the sine law of refraction, which Kepler did not have [15], Descartes realizes that the cornea must contribute to the overall refraction as much as, if not more than, the lens itself. Also, in changing its refractive capacity for the requirements of forming an image of a near object, the eye, according to Kepler, changed the relative position of the lens. Descartes proposes a change in the shape of the lens as being a more feasible alternative [2, 14]. (Some vertebrates, especially fish, do use Keplerian accommodation.)

In binocular vision, the image rests on corresponding points in the two eyes (the first such clear idea of binocular correspondence) (Fig. 4a). Each stimulated point on the retina exerts pressure on a fiber that runs back in the optic nerve past an uncrossed chiasm and ends on the internal surface of the ventricles. The interstices between

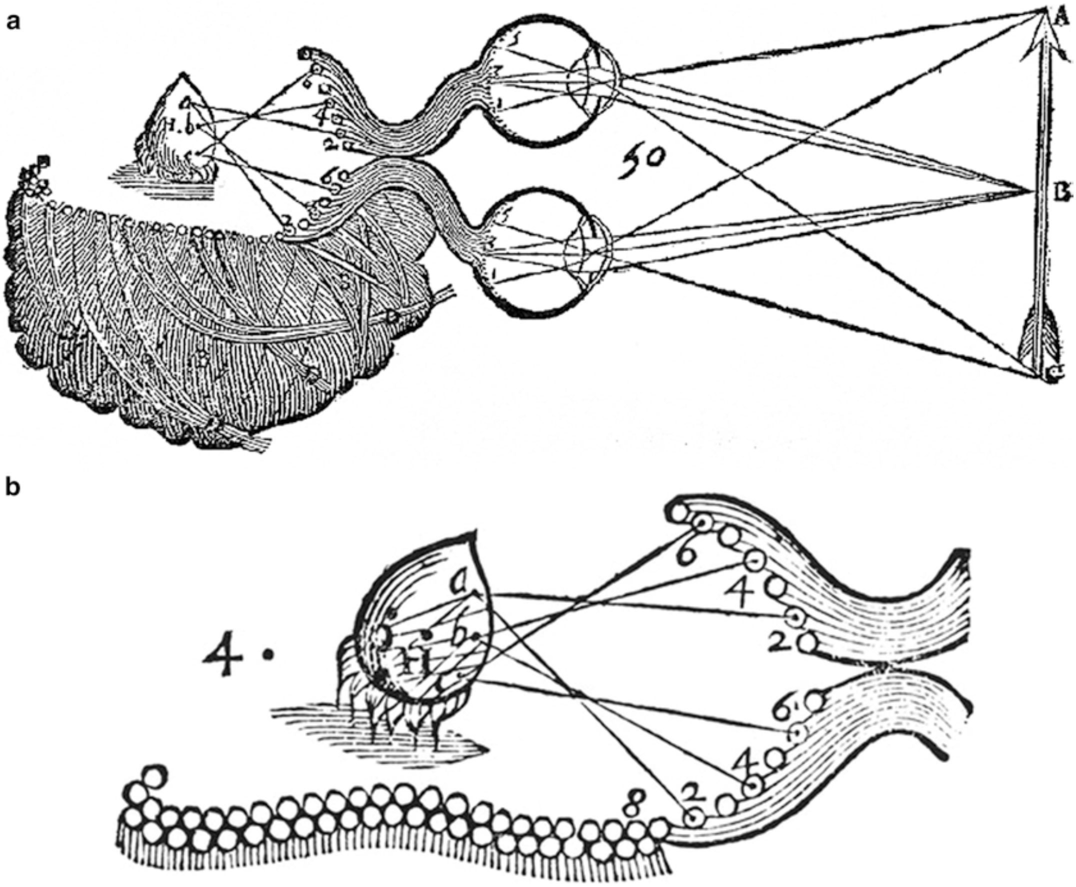

Fig. 4 (**a**) René Descartes' concept of points in the retinal image of one eye corresponding to points in the other eye, and each set of points projecting in turn to other corresponding points on the wall of the ventricles. (**b**) The corresponding points on the ventricle surface in turn correspond with points on the surface of the pineal, yielding single binocular vision. The pattern of points on the surface of the pineal gland from which the "spirit" comes corresponds to the pattern of pores on the ventricle surface. Because point A on the pineal surface serves point 2 from each eye, etc., single binocular vision becomes possible. From Descartes' Traite de l'homme. (Photo courtesy of taken from a seventeenth century. tome at the National Library of Medicine; no permission needed)

Fig. 5 According to René Descartes, by shifting its orientation, the pineal gland converts sensory information into motor instructions to the muscles so that the finger moves from one point to the other. From Descartes' Traite de l'homme. (Photo courtesy of taken from a seventeenth century. tome at the National Library of Medicine; no permission needed)

the mass of fibers on that surface can be considered a system of openings or pores. The sensory fiber controls the relative orientation of a particular pore and the degree to which it is open. This then controls the ease with which the intraventricular spirit or fluid can enter the nerve.

At this point, Descartes knows he must account for single binocular vision in particular and—in general—for the single idea generated by paired sense organs when they are stimulated simultaneously. Galen already had the blood vessels around the pineal gland as the brain's chief source of animal spirits. In a brain that seems to be bilaterally symmetrical with paired structures, the pineal gland was conspicuous as single, central, and unpaired. So Descartes selects the pineal gland as the central structure that allows the "soul," acting through the pineal gland, to obtain a unified sensation. This selection, *sui generis* in this context and unutterably quaint and wrong-headed to us, was logical to Descartes but was going to bring continuing grief to his ideas on the brain.

When the retinal image stimulates the optic nerve fibers, these fibers in turn tug on corresponding points on the ventricle surface (Fig. 4b). This opens the associated pores. There is now a lessened resistance to flow toward the open pores for the spirit emanating from the surface of the pineal gland. Therefore, the pineal gland leans toward these open pores. Certain points on the pineal surface now become apposed to the open pores and there is a gush of spirit off the pineal gland into the open pores. This, so to speak, completes the circuit and vision (in humans, at least) is made conscious.

Consciousness is a manifestation of the human's God-given immortal soul and distinguishes us from animals, which are mere automatons without souls. The immaterial soul is not strictly localizable, but interacts with the body at the pineal. The conscious mind is made aware of the retinal pattern by the pattern of the spirit as it leaves the pineal surface. The conscious idea is accurate because there is a point-to-point correspondence between the patterns on the retina, the ventricle, and the pineal gland [2, 13].

In modern parlance, this correspondence is "topographical mapping," but its configuration bears no other physical resemblance to the object. "Correspondence" effectively buries any persisting echoes of the ancient Greek idea of some tangible replica of the object entering the eye to effect vision. It guides the appropriate response to the visual input by determining how the pineal activates the motor system (Fig. 5).

The Crucial Points about Descartes' Brain

Certainly this is very odd anatomy. It is, in fact, quite literally fantastic—a fantasy springing out of Descartes' imagination. Voltaire called it a "novel of the soul" [18]. But if we let the anatomy distract us, we will miss the point. Something else comes through all of this: Descartes' single-minded, determined, relentless insistence on treating the brain as a complex mechanism. The following is the crux of Descartes' idea of the brain [11]:

1. The brain has an intricate structure.
2. Important elements of this structure are on a level too minute to be seen, but are located in specific locations that have specific functions.
3. The elements interact with each other in such a way as to form a model of the external world within the brain.
4. This model then actuates the motor system in an organized way so as to deal with that external reality.
5. Consciousness is closely related to this process.

The French Jesuit philosopher Nicolas Malebranche later wrote that when he first read Descartes, he was forced by palpitations of the heart to put the book down for awhile, as he realized the implications of the brain as a maker and manipulator of symbols [2].

It is true that we get impatient with Descartes for what Hall [16] called his "gratuitous precision" in constructing the body, describing things we know he could not have seen. We do know that Descartes dissected animal parts, including sheep brains, obtained from his neighborhood butcher [18]. When a visitor to his bachelor quarters asked to see his library, Descartes pointed to a leg of veal he was dissecting at the time.

Then we realize that Descartes is being coy in his biological writings. He explicitly tells us that he is not actually describing the body but rather a machine that could *simulate* all the activities of the body. In effect he is proposing *a hypothetical model*, a technique still useful in modern science. He seems to realize that biology is not about to yield to his method of deducing laws of nature from a few basic axioms. Life is too diverse, too complex.

Descartes lived at a time when the established wisdom was Aristotle's idea of the soul, and Aristotle's soul, after all, at one time encompassed the whole body. It was the all-pervading activating feature of all body functions, of all life. [19, 20]. Modern reductionist physiology—physical, chemical, molecular physiology—would have been impossible under it. From Descartes on, Aristotle's soul began to wither away. "There is a mask of theory over the whole face of nature," said the nineteenth century philosopher of science William Whewell [21]. Now the mask was changing. The terms of the problem were being redefined.

Descartes' great ambition was to create a new universal philosophical system. He felt that of all the traditional schemes of thought, only mathematics seemed to remain valid. Perhaps his greatest talent was in mathematics; his creation of analytical geometry was a great achievement. When it came to applying mathematics to physical phenomena, he found optics to be an effective way to do it, and in applying mathematics to physiology, he found optics by far the best approach. It led him directly to a theory of sensation and of the brain.

Our present understanding of the brain has many roots and no one can say the brain was "discovered" by a given person at a given time. But to what extent was Descartes' complex brain a departure from the models of prior writers? Pre-Vesalian anatomists, including even Leonardo da Vinci, had drawn pictures of the brain localizing three attributes—sensation, memory, and judgment—in three spherical ventricles [10, 12, 19, 22, 23]. This localization is so uncertain, so ill-defined and nebulous that it belongs to an entirely different class from Descartes' model. It is a poetic metaphor rather than serious anatomy. Vesalius himself, famous for breaking Galen's hold on anatomy, agrees with him most of the time on brain physiology:

> I … ascribe no more to the ventricles than that they are cavities and spaces in which the inhaled air, added to the vital spirit from the heart, is, by power of the peculiar substance of the brain, transformed into animal spirit. This [animal spirit] is presently distributed through the nerves to the organs of sensation and motion, so that these organs … perform their office. [24]

This brain is an enigma. All these men faced a common problem when they thought about the nervous system. They recognized that it constituted a ramified network similar to that of the heart, arteries and veins. Such a network meant something was transmitted or distributed. For the blood vessels, the blood was the obvious medium and the flow of a fluid could be readily understood. But no fluid was evident in the nerves except in the ventricles and enclosing sheathes (the reason why the ventricles had such prominence in these schemes). Hence the fluid must be "rarified"—too subtle to be visible. At the time this was a speculation based only on analogy with blood. Descartes' novel proposition was to make the transmission similar to the bell-pull to servants in Victorian mansions—a physical continuity that acted as a valve controlling the flow of fluid. The corresponding points in the retinal image constituted a symphony of such bell-pulls—a cerebral symphony. As a hypothetical model, this was a conceivable notion at a time when Galvani and his twitching frog legs were more than a century away. It proved to be wrong, but shows Descartes' determination to rely on mechanistic explanations. It is hard to overestimate the effect of this attitude on later anatomists and physiologists [2]. When the time came, they were ready to accept biological electricity as the activating medium they were searching for. All in all, Descartes gives us the impression that he would not be disconcerted in the least if one were to sit down with him in a quiet cafe with a bottle of good French wine and discuss neurons and synapses. When Descartes deals with the central nervous system, he has a recognizably modern sensibility.

To what extent did Descartes' model actually influence others? Thomas Willis (1621–1675) took some delight in pointing out how prominent the pineal gland was in supposedly soulless animals, like sheep. (Dog-loving Englishmen probably took special umbrage at the Cartesian denial of a soul to animals.) Willis then speculated on functions for specific brain parts himself and is often regarded as the author of functional localization [12, 25]. Willis' *De Cerebri Anatome* was published in 1664, 2 years after Descartes' *Traite de l'homme* was printed in Latin, some 30 years after *Traite de l'homme* was actually written. In a contest, Descartes should be given priority, though of course Willis' anatomy was far superior. What is more, Willis was impressed by Descartes' use of visual optics. In his *De anima brutorum* of 1672, he used optical metaphors himself:

> It is possible to conceive of a middle part of the brain, a kind of interior chamber of the soul equipped with dioptric mirrors; in the innermost of which images or representations of all sensible things, sent in through the passages of the nerves, like tubes or narrow openings, first pass through the corpora striata as through a lens; then they are revealed upon the corpus callosum [i.e., the entire white matter] as if on a white wall, and so induce perception and at the same time a certain imagination of the things sensed. [25]

This scheme caused a contemporary of Willis to criticize his "Cartesian temerity" [26].

The Cartesian model became part of the intellectual matrix of the time, usually unacknowledged or forgotten, wrong in the details but still a program for thinking about the brain. The implicit promise was that if the brain only could be broken down into all its constituent parts, it could be understood in its entirety. In a field still bubbling with controversy, there is a consensus that Descartes' ideas had great influence on the development of physiology and psychology [27].

The Kepler-Descartes Linkage is One of the Best Examples of Synergism in the History of Science

Histories of neurophysiology and psychology have largely given their attention to Descartes' ideas of involuntary movements and reflex action and to his use of the pineal gland to solve the mind-body problem. Few writers recognize Descartes' projection of the retina to the brain as the departure it was. Even when Descartes' intricate, organized brain is acknowledged [24, 28–31], Kepler's crucial influence is almost always unappreciated.

Would Descartes have developed his ideas about the body-as-mechanism without Kepler? Probably. Would he have solved the retinal image problem without Kepler? Perhaps. Would he have conceived of the brain as he did without visual optics to guide him? Probably not.

Kepler's influence on Descartes was too significant to remain so little known, and Descartes' brain was a revolutionary idea. What we have been doing since then is changing the details. Let us allow Kepler his stopping at the retina, and allow Descartes his pineal gland. We recognize them as colleagues, avid to understand vision, engaged in a search we are still bound on, for answers that still elude us.

This chapter has been adapted from an earlier essay published in the ARCHIVES OF OPHTHALMOLOGY in 2008 [Reference 6].

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Jacques Daviel: The Invention of Modern Cataract Surgery

2

Daniel M. Albert

Introduction

Jacques Daviel's development of cataract extraction was the culmination of observations and insights by others that spanned many centuries. The location of the lens in the eye and the function of the lens in vision puzzled the physicians and scholars of antiquity and medieval times. Even more elusive was an understanding of the true identity of the lens's dark twin, the cataract. It was not until these mysteries were finally resolved in the seventeenth and eighteenth centuries that a reasonably safe and effective solution to cure the vision loss caused by cataract could be sought. This, in turn, required a surgeon with unique knowledge, experience, skill and ingenuity. These traits were found in the French surgeon Jacques Daviel (1693–1762) (Fig. 1), who, in a landmark advance in the history of ophthalmology, presented his new method of cataract extraction to the French Academy of Surgery on the 13th of April, 1752.

Understanding the Anatomy of the eye

According to Stephen L. Polyak, a prominent neuroanatomist and fine historian [1], the first authentic scientific description of the eye dates back to the Hellenistic period (323–212 BCE) and is attributed to Herophilos (344–280 BCE) [2]. Polyak states that Hippocrates (460–377 BCE) did not know of the existence of the lens. Aristotle (c.384–322 BCE) concluded that the lens was a postmortem artifact resulting from the accumulation of phlegm [3]. Celsus (first century A.D.) describes the crystalline lens as consisting of a 'humor' or liquid, resembling the white of an egg with an anterior space ('locus vacuus') between its front surface and the pupil [4] and labelled it the vital organ of vision. This latter concept persisted until the seventeenth century when the Swiss physician, Felix Plater (1536–1614) and subsequently the German mathematician and astronomer, Johannes Kepler (1571–1630) demonstrated that the lens served to refract light, and that the essential sensitive organ of vision was the retina.

Appreciating the True Nature of the Cataract

The physicians and surgeons of antiquity labored under the misconception that a cataract was a veil or humor that flowed down into the space between

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Fig. 1 The standard portrait of Jacques Daviel at the height of his fame. Taken from: Albert DM, Edwards DD, eds. History of Ophthalmology Cambridge, Mass., Blackwell Science, 1996

the lens and the pupil, where it solidified, forming a suffusion or cataract. Jacques Daviel vividly described the consequences of this mistaken concept: "The ancients who had always considered the cataract as a membrane, devised means of removing it that conformed to their opinions. Some used round needles to roll up this imaginary membrane like a ribbon; others invented extremely pointed needles so as to cause less damage to the sclera; some used cutting needles to sever the threads they believed attached the cataract to the ciliary processes; finally, Freytagius (town surgeon of Zurich) devised a kind of spring forceps terminating in needles, with which he proposed to extract the membranous cataract from the eye" [5].

The ancients, likely going back to the Babylonians and the Code of Hammurabi (1800 BCE); Suśruta (about 600 BCE) and early Chinese, also knew how to "couch" or decline cataracts (Fig. 2). Galen recorded that a Greek physician, "dislodged the cataract into another place where it was less disturbing [6]". During the middle ages, various Arabian oculists used a hollow needle to aspirate the soft congenital cataract [7], but couching remained for centuries the principal surgical treatment of cataracts.

The realization that the cataract was in fact the clouded or opaque lens did not occur until the seventeenth century when the first post-mortem examinations of cataractous lenses were performed, by Werner Rolfink (1599–1673) in 1656, and Michel Brisseau (1676–1743) in 1707, a half century later [8]. Brisseau, in the preface of his book, *Traite de la Cataracte et du Glaucoma* (Paris, Houry, p.v), described a soldier whose cataract he couched. The soldier subsequently died and Brisseau dissected his eye and extracted the lens, giving conclusive proof of the true nature of cataract. In 1707, Antoine Maitre Jan (1650–1725) independently published his findings of examination of the lens from a deceased cataract patient in his *Traite des Maladies des Yeux* and he also discovered the onion-like layered structure of the lens.

Soon after, there appeared reports on three successful lens extractions in living patients whose lenses were subluxed into the anterior chamber: two operations by Charles de St. Yves (1667–1736) in 1707 and 1716 and another by the noted surgeon Jean Louis Petit (1674–1760) in 1708. The surgeon Jean Méry (1645–1723) proposed to the august Paris Academy of Science in 1707 that they sanction extraction as a method for treating cataract. "Extraction seems to be as safe as couching; it may be even less risky," Méry stated. "The aqueous reforms easily. The cornea does not have any blood vessels and therefore does not become affected with inflammations". However, the Academy showed little interest in the new procedure [9]. Thus, by the time Daviel started his studies to become a surgeon, the anatomy of the eye, the location of the lens and the true nature of the cataract were understood by the leading surgeons of France. Indeed cataract extractions *had been* performed. But as with so many other great ideas in science and medicine, cataract extraction awaited someone to "convince the world" of its value and claim the title of its inventor. Jacques Daviel was the individual destined to accomplish this.

Jacques Daviel: Early Years

Daviel was born in La Barre, Normandy, a village about 60 miles from Rouen, in August 1693, the exact day being now uncertain. It is said he

Fig. 2 Rembrandt's depiction of the scene in the Apocrypha in which Tobias, assisted by an angel, couches the cataract of his father Tobit. Courtesy of: The Cleveland Museum of Art, Cleveland, OH. (http://clemusart.com); purchase from the J. H. Wade Fund

declared his intention to be a surgeon as a boy when he assisted the village surgeon in reducing the fractured leg of a peasant. His parents were of modest means, and following the death of his father, he was apprenticed to his uncle, Dr. Sallou, a surgeon in Rouen. In 1713, when Daviel was 20 years old, he became an assistant surgeon in the French Army, stationed in military hospitals in Flanders and elsewhere, and eventually serving as an assistant to Xavier Bouquot at the Hotel-Dieu in Paris. Notable to this appointment was the fact that the Hotel-Dieu was the only public institution in Paris where the dissection of cadavers was permitted.

In 1720, the last significant outbreak of bubonic plague in Europe, occurred in southern France and killed approximately 100,000 people in Marseille (Fig. 3) and the surrounding provinces [10]. In October of that year, Daviel, who was still in the military, volunteered to join a team of Parisian physicians as an "epidemic surgeon" and served in Salon-de-Provence. The discovery of plague bacillus was still 74 years in the future. To Daviel's credit, in addition to his courage, energy and compassion in treating infected patients, Daviel oversaw the isolation of these patients and used an aromatic antiseptic agent, with which he attempted to suppress the spread of the fleas carried by rats that are the vector of the disease. For his efforts Daviel gained recognition as a local hero and that appreciation eventually extended to the regents ruling France in the name of Louis XV (Fig. 4), then still a child. Daviel was awarded the Cross of Saint Roch and

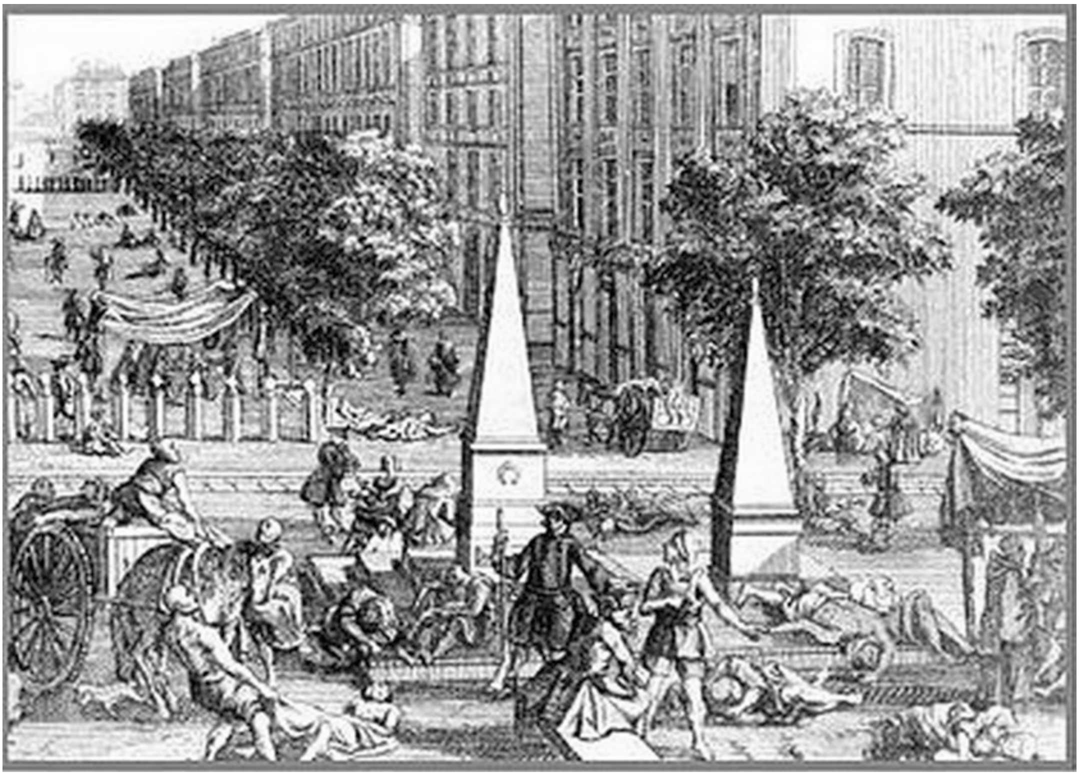


Fig. 3 Marseille at the time of the plague. Taken from: https://en.wikipedia.org/wiki/Great_Plague_of_Marseille#/media/File:Gravure_peste_-_Quartier_Belsunce.JPG

other honors from the city of Marseille, and this distinction and respect served him well for the rest of his career and, as will be seen, facilitated his work on cataract extraction.

Two years into his service in the Marseilles area, he met and married Annette, the daughter of a prominent "master surgeon", Dr. Joseph Felix, and the "several thousand pounds worth of gold Louis (French coins)" included in the bride's dowry gave Daviel a degree of independence that allowed him to concentrate on areas of surgery of particular interest [11].

In 1722, the city officials in Marseilles appointed Daviel to the rank of master surgeon. Sixteen years later (1738), he again received royal recognition with his further elevation to Royal Demonstrator of Anatomy and Surgery at the Hotel-Dieu in Marseilles, where he taught public courses in anatomy and surgery at Marseilles' Hotel-Dieu (Fig. 5). Daviel continued to practice surgery in Marseilles until 1746, when he moved to Paris.

Daviel's Life as a Cataract Surgeon

In 1733, the 40-year-old general surgeon, Jacques Daviel, performed his first operation for cataract. It was a couching procedure and the result was excellent [12] (Fig. 6). The following year, Daviel decided to devote himself entirely to eye surgery, and the basis for this decision has been speculated on by his biographers. The consensus appears to be that a major factor in this decision was the visit to Marseilles in 1734 by the surgeon-turned-traveling oculist, the "Chevalier" John Taylor. At the time in England and the Continent, couching and other eye surgery was done both by regularly trained surgeons, but even more frequently, by irregularly trained itinerant oculists. Taylor, famed as a skilled eye surgeon, but notorious for his exaggeration and self-promotion, was the eye surgeon to George II, the Pope, and a number of European royal families. He was a charismatic and flamboyant figure, and he trav-

Fig. 4 King Louis XV of France, Daviel's patron and supporter. Taken from: https://en.wikipedia.org/wiki/Louis_XV_of_France

eled throughout Europe in a coach covered with images of eyes [13]. The two men are believed to have met, and Daviel, who was said to have been increasingly interested in eye diseases since 1728 [11], decided to follow Taylor's example of limiting his practice to the eye.

To be successful in couching cataracts demanded speed and considerable skill, and Daviel became a master of this procedure in short order. His status in Marseilles and his protection by Louis XV allowed him to circumvent the social and religious restrictions that limited the use of cadavers for practice surgery in France in the eighteenth century. By gaining his experience from cadaver surgery, Daviel avoided the necessity of learning from live patients through trial and error. His famous contemporary and rival as a cataract surgeon, Baron Michael Johann Baptist de Wenzel of Lorraine, discussed the latter method: "On being complimented for his dexterity, the celebrated de Wenzel acknowledged he had lost a hat-full of eyes before he learned to extract" [14].

For the next 13 years, from 1734 to 1747, Daviel specialized in couching cataracts and his reputation for dexterity and relative success with this procedure spread throughout Europe. In eighteenth century Europe, members of nobility, as well as other wealthy patients who needed surgery, expected the surgeon to travel to them, reflecting the relatively low status and prestige of the surgical profession. To satisfy requests for his services Daviel undertook “grand tours” through southern France, Spain and Portugal, and subsequently through Italy, Germany and Belgium. During his absences from Marseilles, his progress and successes were reported in *the Courrier D’ Avignon*, the most widely read newspaper in Provence. These appeared in the form of 29 unsigned articles, which his biographers attribute to Daviel himself, a man “far from adverse to publicity.” These articles provide details of his itineraries, time-tables, lodgings where he could be found, as well as the number and results of the surgeries he performed. In addition to the patients who previously requested his consultation and surgery, he clearly invited the public to take advantage of his availability. Thus, at the end of his initial 16 months of travel through southern France and the Iberian Peninsula, he could report (writing in the third person) in the August 1737 issue of Courrier d’ Avignon: “He had done over

Christophe MOUSTIER vidit - 2005

Fig. 5 Hotel-Dieu in Marseille

Fig. 6 Contemporary illustration of a couching procedure. Taken from: Gunz De suffusion. Natur. et curat pag. 148 Lausanne: Bousquet, 1755

2000 operations on patients 30, 40, 60 up to 90 years old, among them blind patients between 15 and 54 years of age. He even had the satisfaction of curing several persons, blind since birth, who, after the operation could discern objects shown them." Daviel was received by the King and royal family in both Spain and Portugal and operated on members of royalty, the aristocracy and on their servants [8].

By 1740, his ability as a coucher had earned him honors, among which was an appointment as a corresponding member of the Royal Academy in Paris. In 1746, at the age of 53, Daviel was selected surgeon-oculist to King Louis XV, prompting him to move to Paris. Although his reputation and success were largely based on his skill in couching cataracts, at about that time he declared, in a letter to a friend, that despite his success, he was far from satisfied with the cataract surgery of that day [12].

Daviel Describes and Promotes Extraction of Cataracts

Daviel was well acquainted with the earlier publications of Brisseau, Maitre Jan, St. Yves and Petit, relevant to cataract extraction, and also knew of Méry's unsuccessful attempt to gain the endorsement of the Paris Academy of Sciences for the operation. Yet, it was not until almost 40 years after these earlier events had transpired, that Daviel, on the basis of his own similar first-hand observations, gradually changed his orientation from couching to extraction of cataracts. Critical in bringing him to make this change were two complicated couching procedures.

In 1745, just prior to moving to Paris, Daviel performed a couching procedure on Brother Felix, a hermit in Eguilles in Provence. He engaged the lens on a sharp needle and the lens broke into fragments, several of which passed into the anterior chamber which then filled with blood. Using a semi-curved needle and a small scissor, he opened the cornea and removed the lens fragments, following the procedure Petit had described in 1708. Although Brother Felix could immediately distinguish objects presented to him, the eye soon became infected and was lost [5] (p. 339).

Daviel responded to this disaster by designing a blunt instrument—rather than the usual sharp needles—with which he continued to depress cataracts. Of greater importance was his stated resolve to bring a new "great idea" for cataract surgery he was developing to a "certainty by continuing to work daily on the eyes of cadavers" [12].

The second, but more crucial, case that brought Daviel's cataract extraction technique into existence occurred 2 years later, on April 8, 1747. The patient was M. Garion, a wig maker, and the operation was clearly described by Daviel himself: "I begin with the left eye whose cataract seemed more mature and yet I was not able to depress it. The pupil appeared cloudy after the operation and the patient saw absolutely nothing. I then proceeded to the right eye and had just as much trouble. Having failed in every maneuver to push down the cataract in this eye, I decided to open up the cornea, as I had done with the hermit. I widened the aperture, then I raised the cornea with small forceps, inserted my small spatula through the pupil and extracted from the posterior chamber of the eye the whole lens, divided and broken into several pieces during my initial procedure. After this extraction, a part of the vitreous humor oozed out: it had been disrupted by the first operation but, despite this inconvenience, the patient discerned objects well. The operation had no harmful sequelae and, after some time, the patient was cured" [5] (p. 343). Daviel concluded "I decided henceforth to operate for cataract exclusively by the extraction of the crystalline lens" [5] (p. 343).

One may wonder why Daviel resolved to replace couching with "planned" extracapsular extraction, largely on the basis of these two complicated couching procedures. Could he not have reserved extraction for instances where the cataract was displaced into the anterior chamber, as had occurred with the hermit and the wig maker? Certainly, in the absence of anesthesia, couching was quicker and less painful. Moreover, with its small corneal opening—in the absence of asepsis—couching probably carried less risk of infection. As performed in eighteenth century France, it appears the final visual results from the two procedures were not much different, even for Daviel. Consequently, one might suspect that Daviel was influenced by the novelty and difficulty of extracting, and accepted the challenges extraction offered for him to display his great surgical virtuosity and lay claim to extraction's invention.

Shortly thereafter, Daviel carried out his first "planned" cataract extraction (Fig. 7). The patient was a woman on whom he deliberately opened the cornea and removed the cataractous lens from its normal position behind the iris. The operation went well, and "in 15 days, the patient had recovered."

In his work on both living patients and on cadavers, Daviel continued to refine his techniques and design new instruments specifically to carry out the surgical maneuvers he required (Fig. 8). By 1752, he had operated by extraction on 206 eyes with cataracts and reported good results in 182 cases—an impressive 88% success rate. This is all the more remarkable when it is considered that the surgery was done without asepsis or anesthesia in patients bound to a chair and restrained by Daviel's assistants.

Daviel was now prepared to present his new method to the Royal Academy of Surgery, a more pragmatic body than the Academy of Science, and this occurred in 1752. The Academy, as Daviel expected, carried out a thorough process of peer review, examining relevant documents, identifying patients and having local surgeons review and attest to their results. Then, the following year, three outstanding surgeons undertook Daviel's operation on 19 elderly soldiers with cataracts selected at the Hotel Royal des Invalides, the veterans' hospital in Paris. Of the 38 eyes operated on, 14 eyes had "good vision", 10 retained their previous vision, and 14 had reduced vision. While these results did not match Daviel's, they were apparently superior to what was expected with couching, and Daviel's paper was published in the Academy's proceedings [5].

Alvin A. Hubbell translated and summarized Daviel's description of his procedure as presented in Daviel's landmark 1752 paper as follows: "The operation which he [Daviel] had invented and

Fig. 7 Daviel performing cataract extraction. Taken from: http://www.daviddarling.info/encyclopedia/S/science_in_the_eighteenth_century.html

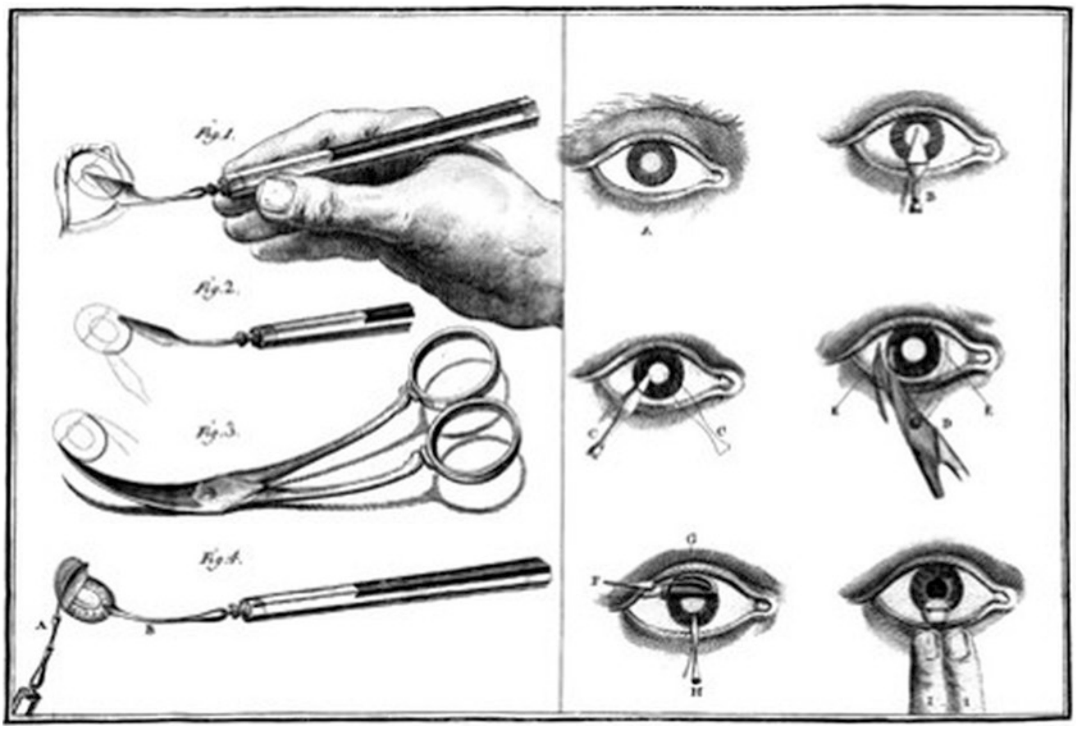
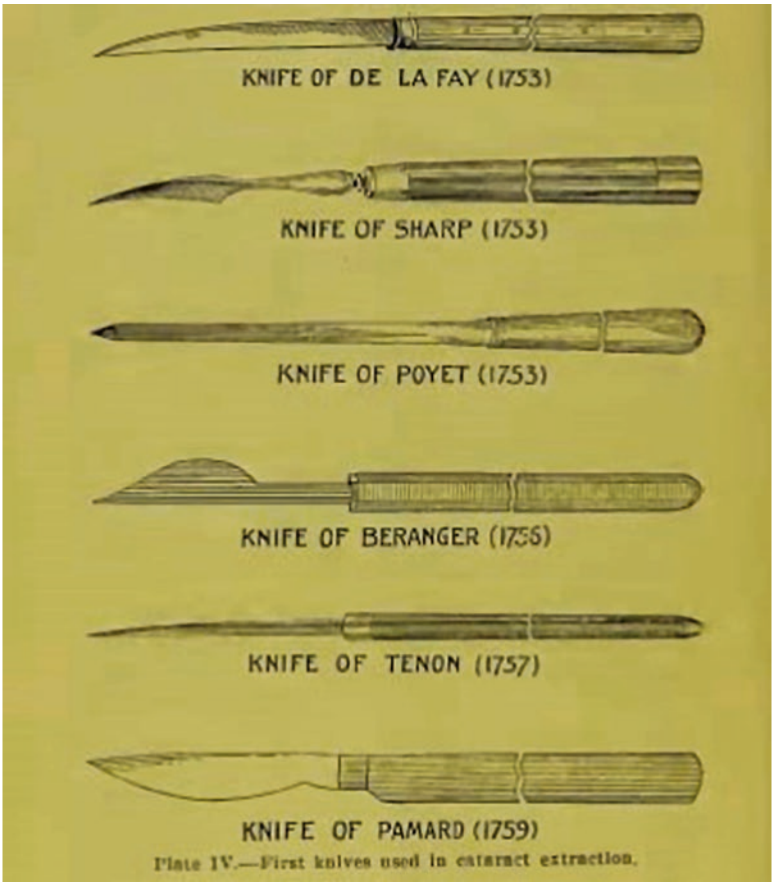


Fig. 8 Daviel’s cataract extraction technique using the instruments he designed. Taken from: Albert DM, Edwards DD, eds. History of Ophthalmology Cambridge, Mass., Blackwell Science, 1996

now made public consisted in incising the lower part of the cornea exactly at its junction with the sclera. He first made an opening into the anterior chamber at the extreme lower margin of the cornea with a myrtiform or triangular shaped knife, and then, after withdrawing this, he enlarged the incision on both sides with a narrow, blunt pointed, double-edged knife, as far as he easily could and finally when the cornea became too much relaxed to continue the incision he completed it to the extent desired with delicate scissors which were so curved on the flat and edge as to correspond to the curve of the corneo-scleral line. These, of course, were made right and left, and the blade to be introduced into the anterior chamber was blunt pointed. According to his memoir the incision was of equal extent on both sides of the cornea, and was carried to a point on each side ‘a little above the pupil’. Having completed the incision he gently lifted up the corneal flap with a small spatula and incised the anterior capsule of the lens with the sharp-edged needle. After doing this, he carried the spatula between the lens and the iris, ‘so as to entirely loosen the cataract and facilitate its tissue.’ After the cataract was delivered, the corneal flap was then allowed to fall into place. If the cataract happened to be soft and “glairy” or broken into pieces, the remnants were removed with a curette. The pupil might sometimes be disarranged by the passage of the lens, especially if it was large and hard, and it should then be readjusted. The corneal flap being accurately replaced, the eye was gently cleansed and covered with a small compress, over which plasters were applied and the whole was kept in place by a bandage without much pressure” [15]. Daviel’s procedure was basically intended to be extracapsular. The French surgeon Georges De La Faye (1699–1781), in 1752, was the first to advocate intracapsular cataract extraction.

By 1756, Daviel’s series had increased to 434 cataract procedures, of which 384 were “perfectly successful.”

Fig. 9 The Cataract Knives introduced by Jacques Daviel's rivals. Taken from: Hubbell AA. Jacques Daviel and the Beginnings of the Modern Operation of Extraction of Xataract. JAMA. 1902; XXXIX(4):177–185



Although, as the proverb states, necessity may have been the mother of invention, in the case of cataract extraction, the claimants to its paternity were many: Jean Baptiste Thurant, John Taylor, Georges de La Faye, Samuel Sharp, and others vied for credit, either personally or by proxy. However, Daviel's priority and the validity of his good results were clearly accepted by his peers.

In his later years, Daviel became increasingly intrigued by how congenitally blind persons perceived objects. He corresponded with the physiologist Albrecht von Haller regarding the subject. His findings were based on 22 cases of congenital cataract he had operated on.

Daviel staunchly defended his method of extracting cataract, and surgeons in Europe and England divided into those who preferred couching and those adapting extraction. This dispute continued until the end of the nineteenth century and was often termed the "hundred years war", by medical historians (Fig. 9).

Daviel eventually became a national hero. Louis XV took Daviel on a hunt and requested that he demonstrate his method of surgery on a slain stag. He became an internationally recognized figure and was the recipient of many additional honors, including membership in the Royal Society of London (1756) and the Royal Society of Sweden. The King created a Chair of Ophthalmology in Paris near the end of Daviel's life, unfortunately too late for Daviel to fill. In 1857, Daviel's son, Jacques Henri, training as a surgeon in Paris, published his medical thesis describing and explaining the superiority of his father's method.

Fig. 10 Daviel's Tombstone. Taken from: http://www.snof.org/encyclopedie/un-oculiste-au-si%C3%A8cle-des-lumi%C3%A8res-jacques-davielGraveyard of the parish St Hippolyte, in Grand Saconnex

Daviel's speech became impaired in 1762 and his health rapidly declined, apparently as a result of cancer of the larynx. His final paper on cataract extraction was read by a friend before the Royal Academy of Surgeons in April, 1762. Jacques Daviel died on September 30 of that year (Fig. 10).

Conclusion

Jacques Daviel had the good fortune to come into prominence as surgeon at a time when the introduction of cataract extraction was ready to be added to the eye surgeon's armamentarium. Although the idea was not original with Daviel, it required an innovative, highly skilled and prestigious surgeon to successfully convince a critical portion of the surgical world that this was an improvement on the centuries-old method of couching. Its importance in the restoration of vision, and its eventual safety as compared to couching, marked a profound advance in eye surgery. Although simple in concept, it is an operative procedure that requires considerable skill, which was possessed neither by the itinerant and irregularly trained oculist nor the regularly trained surgeons of the eighteenth century. To assure proper training, the Empress Maria Theresa established a Chair of Ophthalmology in

Fig. 11 Georg Joseph Beer of Vienna, founder of the first European program training eye surgeons. Taken from: https://en.wikipedia.org/wiki/Georg_Joseph_Beer

Vienna, filled by Joseph Beer (Fig. 11), and most major centers in Europe soon followed suit. This is thought by many to mark the start of "modern ophthalmology" on the Continent.

Daviel's extraction of cataract continued to evolve after his death. Graefe's linear incision did not gape as Daviel's semi-circular incision tended to do, and the addition of iridectomy added to the operation's safety. With the advent of Carl Koller's cocaine anesthesia, Lister's asepsis, and Henry Williard William's corneal suture, extraction became accepted as the cataract operation of choice by the end of the nineteenth century. In more recent years, microscopic surgery, phacoemulsification, small sutureless incisions, and intraocular lenses have been important refinements. Perhaps, in this century, the next "Daviel" will be a visual scientist employing the technology of molecular biology to discover a non-surgical means to prevent or even reverse cataract formation.

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John Dalton: The Recognition of Color Deficiency

3

Michael F. Marmor

Red-green color blindness, better called color deficiency, is a relatively common genetic disorder that surely has affected humankind for many millions of years. Humans normally have three types of cone photoreceptor, S-cones, M-cones and L-cones, which have peak sensitivity respectively to short (blue), medium (green) and long (red) wavelengths of light. The balance between activation of these three cones lets us recognize all colors of the spectrum. However, prior to the time that the supercontinent pangaea split apart into Africa and the New World, all mammals had only *two* cone pigments and could recognize only the blue and yellow ends of the spectrum (Fig. 1). After the continents split apart, mutations of the L-cone pigment gene (on the X chromosome) occurred in some Old World primates who became our ancestors. The evolutionary result was two separate longer-wavelength pigments (forming M- and L-cones), which allowed full color perception.

If there is genetic loss of either the M-cone pigment or L-cone pigment in a human, which occurs occasionally, the affected person (usually male) can no longer distinguish colors between red and green. It is intriguing that this relatively common genetic variant (roughly 1.5% of males cannot tell red from green at all, and another 6–7% have intermediate levels of color confusion) was not recognized or described until the late 1700s. There is good evidence that the Florentine painter Baccio Bandinelli (1493–1560) was color deficient [1] and the French poet Charles Pierre Colardeau (1732–1776) [2, 3]. But no clinical descriptions have been found prior to 1777, although evaluation of color perception in ancient Greece, Rome and Egypt is complicated by difficulty in interpreting color names in the ancient languages. Surely there were men who found they could not see what others did, or who were ridiculed for mistakes in naming or choosing colored objects—but they must have accepted the deficit or the criticism as fate without recognition of the reason.

The first clear description of red-green color deficiency as an entity is the remarkable report by Captain Joseph Huddart (1741–1816), a man of letters and a hydrographer (Fig. 2). In 1777 Huddart described a shoemaker, Thomas Harris, who had great difficulty with colors along with two of his brothers [3, 4]. Huddart not only inquired about Harris' color difficulties, but performed color testing by showing him array of colored ribbons to characterize the abnormality. Harris had noted in childhood that, "when other children could observe cherries on a tree by some pretended difference of colour, he could only distinguish them from the leaves by their difference of size and shape." When

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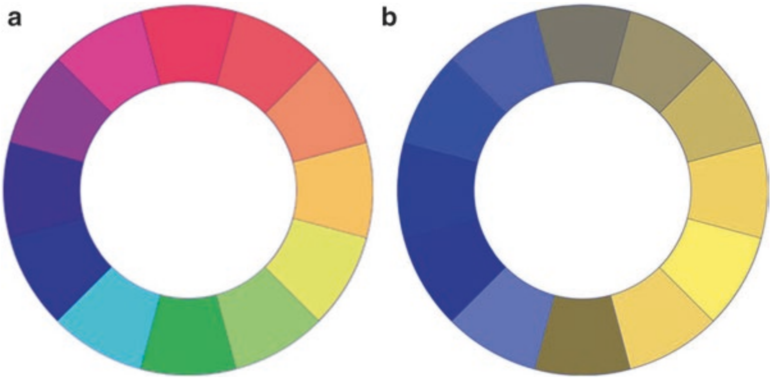


Fig. 1 (**a**) Normal (*left*) and (**b**) fully color-deficient (*right*) *color circles* (©M F Marmor). The right circle depicts loss of the M-cones (deuteranopia), which is the most common type of severe color deficiency, but the appearance would be very similar with loss of L-cones

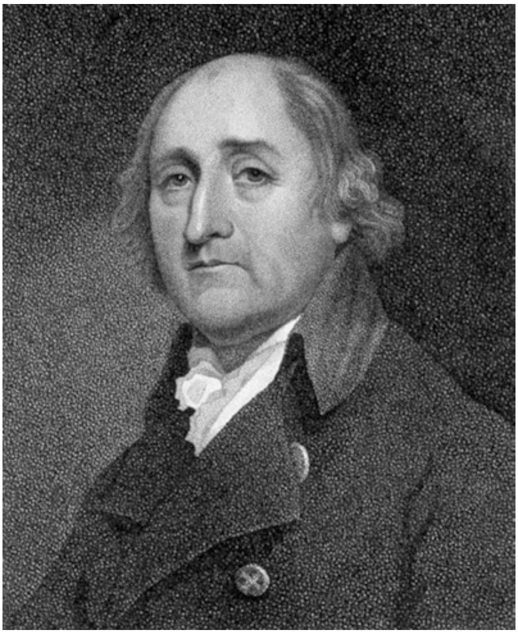


Fig. 2 Captain Joseph Huddart. Stipple engraving by T. Blood, 1811, after J. Hoppner. (From Wellcome Library, London, Wellcome Images, on Wikimedia licensed under Creative Commons)

Harris and his brother were shown colored ribbons in daylight they could recognize that there were colors, but not name them with accuracy. When one brother was shown a light green, he said, "I think that is what you call yellow". A stripe with a tinge of red was called "a sort of blue," and an orange ribbon was called "the colour of grass: this is green". Huddart published these observations as a letter to the Reverend Joseph Priestley in the Philosophical Transactions of the Royal Society of London, and a similar report by J. Scott on a different family was communicated a year later by Michael Lort [5]. However, the significance of these presentations was not widely recognized.

By 1792, the young scientist John Dalton (1766–1844) was beginning to be recognized in the fields of meteorology and chemistry (Fig. 3). He was respected as a teacher, and at the age of 26 he was appointed tutor in mathematics and natural philosophy at "New College" in Manchester, where he taught chemistry. He published a book on meteorological observations in 1793 [6], and was invited to join the Manchester Literary and Philosophical Society. For his first presentation there on October 31, 1794, he elected to report on his examination of his own color vision, which he had recently realized was quite distinct from that of most other people [7]. He took the descriptive anecdotes of Huddart and Lort to another level by critically exploring his difficulties with color using a variety of tests under different lighting conditions, and by hypothesizing about genetics and possible explanations. This was published in 1798 as “Extraordinary Facts relating to the Vision of Colours: with Observations. By Mr. John Dalton”. Perhaps because of Dalton’s reputation as a scientist, his report generated immediate and wide interest. Dalton turned out to be wrong about the mechanism of color deficiency, but his detailed study showed ways to measure color, gave estimates of genetic frequency, and provided a preliminary framework to think mechanistically about the physiology of color perception. Individuals who lived with the abnormality could now be understood and managed with compassion. Within decades, more cases were described, confirming the genetic transmission, and scientists were considering how to integrate this condition with color reception in the normal eye.

Much of the material in this chapter has been covered prior articles [8, 9], and a comprehensive book by the late Philippe Lanthony [3]. My purpose here is to focus on Dalton’s insight more than historical review.

Dalton, the man

Dalton was born of Quaker parents, and followed that discipline throughout his life [8], His parents were not well educated and his father worked as a weaver, while his mother sold paper and quills. But education was central to the Quaker ethic, and his father began his schooling before sending him to local Quaker schools [10, 11]. He was hard working and learned enough that by age 12 he was doing much of the teaching himself. He was fortunate to attract the attention of a wealthy and scholarly man, Elihu Robinson, who gave him lessons in mathematics and access to an excellent library with books

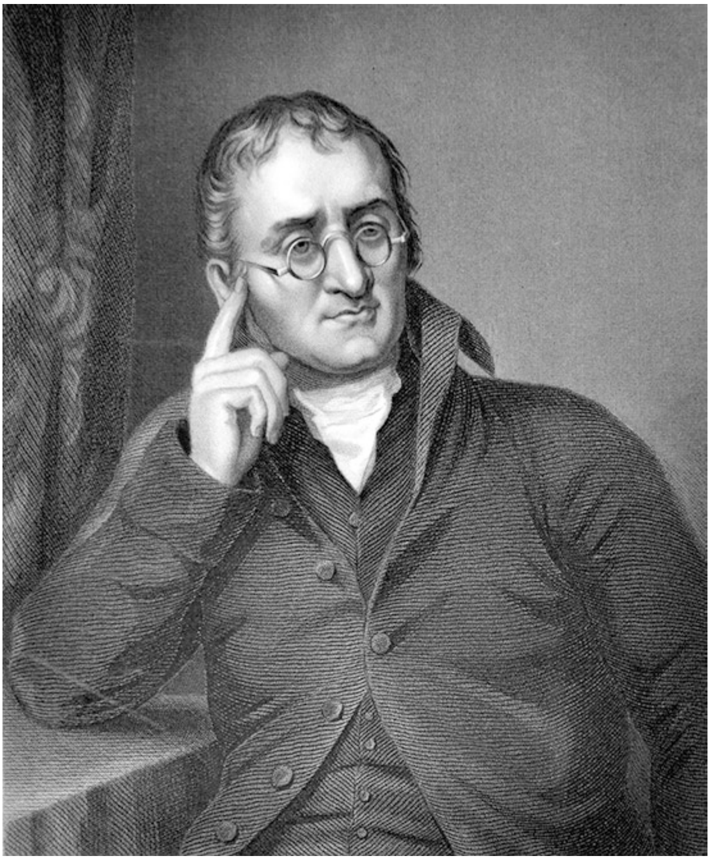


Fig. 3 John Dalton. (From Lanthony [3], and the Wayenborgh Collection, courtesy of Jean-Paul Wayenborgh)

on Greek, Latin, French and mathematics. At 15 was asked to assist his older brother in running a boarding school in a nearby town, Kendal. The brothers were considered severe disciplinarians but good teachers, and eventually John supplemented his income with subscription lectures on natural philosophy. He met a brilliant blind philosopher, John Gough (1757–1825), who tutored many students for the university and took Dalton under his wing to teach him a variety of subjects including meteorology and advanced mathematics. Dalton began keeping meteorological records, and he continued this practice right up to the time of his death. However, the provincial school provided little income, and after a dozen years Dalton began to think about greater options. He considered law or medicine, but these would be difficult since "dissenters", as Quakers were called, were not allowed in the English universities, and he lacked money to pay for such education. In 1792 he saw an advertisement for a teacher in Mathematics and Philosophy in the "New College" in Manchester, a school that was open to dissenters, and he accepted the position.

At Manchester, he began teaching a variety of topics, including natural philosophy and chemistry, and was well respected [10, 11]. His book of meteorological observations had been published, and he became friends with a wealthy cotton manufacturer and social reformer Robert Owen (1771–1858), with whom he had long discussions about broad interests including the seeds of Dalton's eventual atomic theory. Owen introduced him to the Manchester Literary and Philosophical Society, which he joined in 1794, making his first presentation on October 31 about his systematic study of his own color vision. However, this topic was a sideline to his other intellectual endeavors, and in the next year he presented on meteorological phenomena and eventually much more on his chemical theories. As his teaching gained respect, and because the school salary was low, he left the New College in 1798 to do private tutoring (which earned better income), and to have time for chemical research. He kept broad interests in and out of science, and in 1801 he published a textbook on English grammar (a subject for which he felt there was no suitable book) that was popular in schools for a number of years. He never pursued color vision further after his Manchester report, but worked with growing intensity on chemistry. And he is justly famous for innovating the concept of atomic theory.

It is hard to get a clear picture of Dalton's character [10]. He was industrious as a youngster, obviously brilliant, a hard taskmaster to his students, driven to record celestial events, always the first up hills on treks to gather samples of air, and yet relatively diffident about social affairs. He was endearing to friends, known for warm humor, loyal to youthful friends and patrons, gentle in spirit. But he could be gruff and terse with visiting scientists, while being cheerful among small groups of friends. He never married, but is said to have had a fond eye for women and to have made several unrequited proposals as a young man. When asked once why he had not married, he replied "Oh! I never had time" [8]. He lived alone, but for much of his life in the spare bedroom of a couple he knew from New College. He always respected his roots in a country upbringing, and when presented as a famous man to King William IV, who asked how he was getting on in Manchester, he replied simply "Well, I don't know, just middlin' I think" [10]. A friend told him "Why, John, thou hardly showed court manners in addressing the King in such common parlance", to which John replied in broad Cumberland dialect: "Mebby sae, but what can you say to sae like fowk?" He refused to be knighted, declaring that he would not bow to any man on earth, neither King nor potentate, for an earthly honor [10].

Dalton suffered a mild stroke in 1837, which temporarily affected the right side of his body, and his speech. He recovered quite well, but by 1838 was loosing strength and needed both physical and secretarial assistance [10], although he continued to work. He had a slight fit in May of 1844, received an acclamation for his 200,000 meteorological observations in early July, and was found dead in his room on July 27.

Dalton's Observations

Dalton undoubtedly knew that his color vision disagreed with that of others for many years, and perhaps in childhood. There are unsubstantiated anecdotes that he mistook the color of bright red clothing, which was not permitted to Quakers [3]. His report in Manchester [7] does not recount any examples of early difficulty, except to say that he had been of the opinion "that several colours were injudiciously named". Then an event changed his mind: "I was never convinced of a peculiarity in my vision, till I accidentally observed the colour of the flower of the *Geranium zonale* (Fig. 4) by candle-light, in the Autumn of 1792."

This flower, which is called pink by most observers always appeared sky-blue to Dalton (as it appears in a deuteranopic simulation)—but when he saw it by candlelight it was to him a strong red! He had dismissed his usual perception of the flower in daylight to issues of naming, which he recognized were subjective. But when all of his friends (except his brother!) stated that the candlelight had no effect on the color of the flower, it was clear to Dalton that "my vision was not like that of other persons."

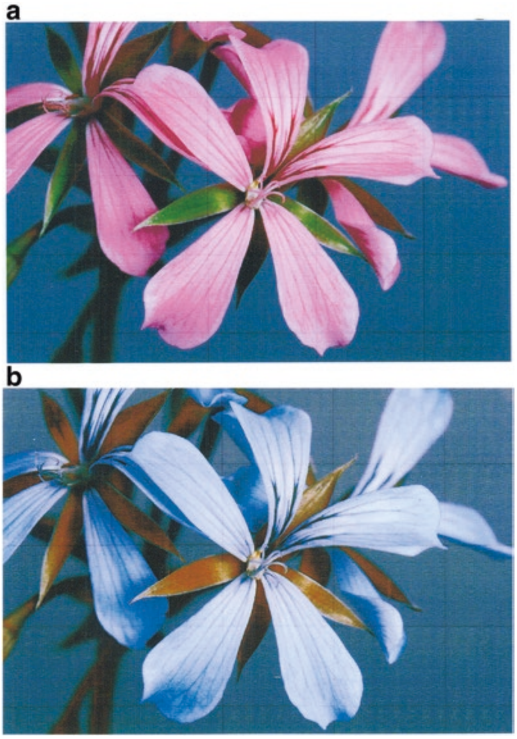


Fig. 4 *Geranium zonale* flowers. (**a**): Appearance to a normal observer. (**b**): Simulated appearance to a color-deficient (deuteranopic) observer. Created by Francois Gonnet. (From Lanthony [3], courtesy of Jean-Paul Wayenborgh)

Dalton studied his own perceptions with a variety of colored objects and under different types of lighting. However, his descriptions are not always easy to interpret as many dyes and natural substances have complex colors that mix many wavelengths, and he is using words for colors that have no precise definition for those with normal vision let alone someone with defective color vision. Dalton commented on the light coming out of a prism, which was typically described as having six colors (red, orange, yellow, green, blue, and purple) [7]. He said "To me it is quite otherwise:--I see only *two* or at most *three* distinctions. These I should call *yellow* and *blue;* or *yellow, blue,* and *purple.* My yellow comprehends the *red, orange, yellow,* and *green* of others; and my *blue* and *purple* coincide with theirs". These descriptions do match the spectral appearance in deuteranopia (lack of effective M-cone pigment), which is simulated in Fig. 1. However, Dalton then added "That part of the image, which others call red, appear to me little more than a shade, or defect of light", a statement which led some to conclude that he was predominantly red-blind (protanopia, lacking L-cone pigment). The point was controversial, as Dalton's observations with a prism seemed also to show that he could perceive red light quite well. He recognized red clothing as being colored (although he could not distinguish it from green or perhaps "mud,"), and he described distinct perceptions of crimson (which appeared blue by daylight, yellow-red by candlelight) and scarlet (which to him had no blue in it all and was a more vivid red by candlelight).

Dalton went on to compare a range of natural materials and colored objects under different colors of lighting such as blue-white daylight and yellowish candlelight [7]. Some of his notebooks with colored yarns or ribbons have been preserved (Fig. 5), and show that he perceived cer-

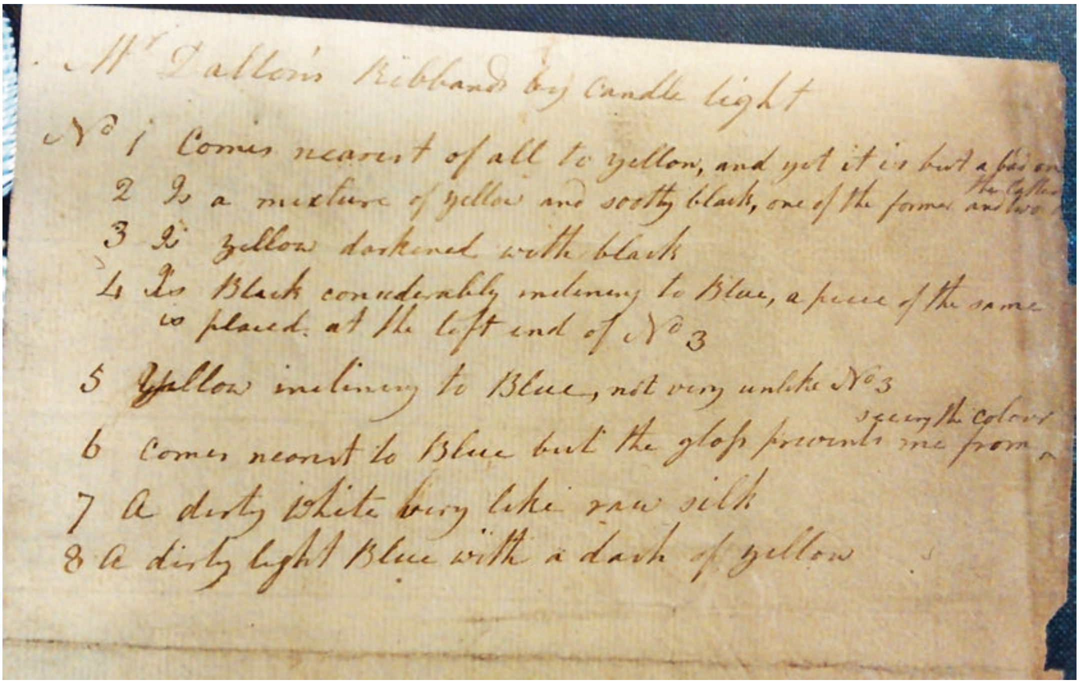
Day light	Candle light
1 Blue or lilack	1 Light blue or lilack
2 Faint blue with a tinge of yellow	2 Delicate pale red.
3 Blue	3 Light red
4 Blue, but not so bright a colour as 3.	4 Blue, nearly allied to 1.

Day light	Candle light
1 Brown.	1 Blue, not vivid.
2 & 3 brown, & nearly alike; the 1st rather brighter than 2 & 3d.	2 Red, rather dull.
	3 Red brown
4 & 5 dark blue, & nearly alike, the [illegible] rather more vivid.	4 & 5 Same as by Day light.

Fig. 5 Notebook pages (**a** and **b**) from Dalton's papers showing colored yarns or ribbons, with notes on their appearance in daylight vs. candlelight. Note in (**a**) that the pink bundles labeled 2 and 3 are perceived to shift from blue to red like Dalton's perception of the geranium. (©Science and Society Picture Library, London; used by permission)

tain colors to shift from “blue” to “red” between daylight and candlelight like the color of the geranium (tufts 2 and 3 in Fig. 5a). He also wrote that grass appeared the same color to what he called red, and he could distinguish many varieties of green as distinct from one another. However, light green on paper or silk appeared white. Browns had an affinity to green, but were diverse and often just dark. Being intrigued by the blues that he perceived in daylight but not in candlelight, he tried viewing these colors by candlelight through a sky-blue transparent liquid. This made the appearance equivalent to that in daylight! Overall, he observed that the differences between his perception and naming of colors, relative to others, were “much less by candle-light than by day-light.”

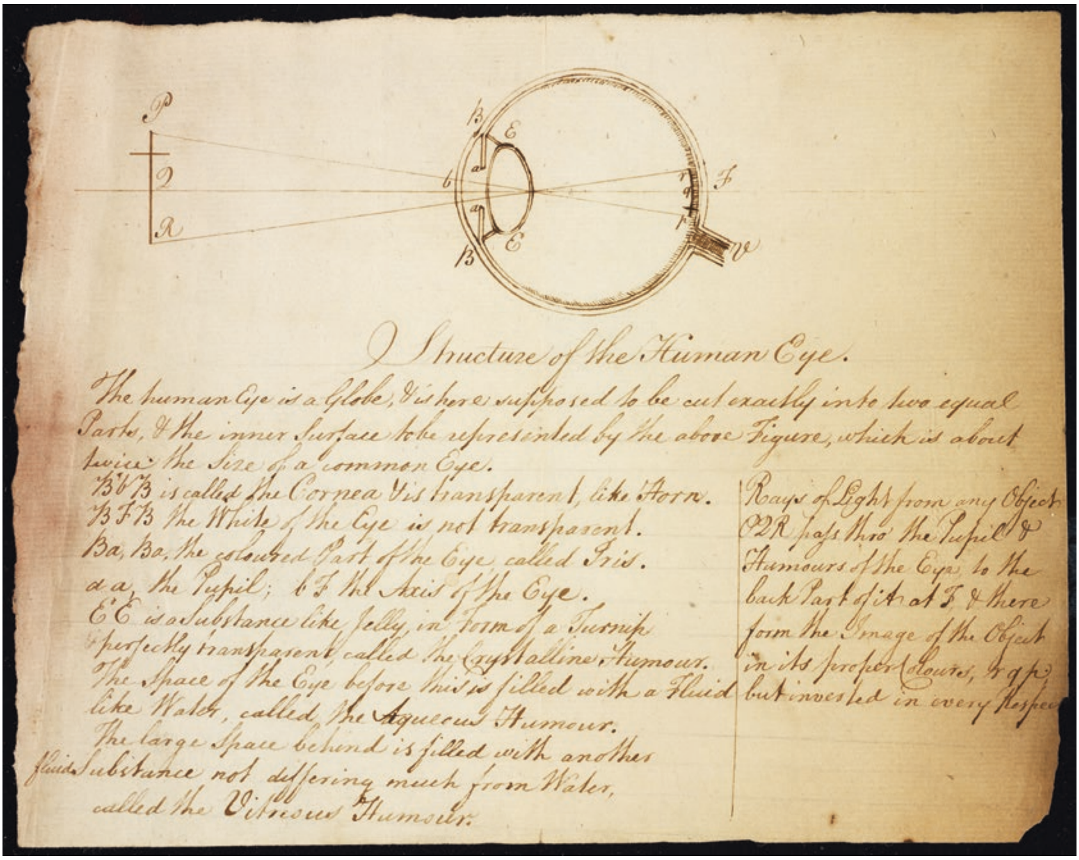
Dalton might have let this be, as a curious phenomenon but he was aware of Huddart’s account [4] 15 years earlier of Mr. Harris who “could not distinguish colors”. At first Dalton thought that anomaly was different from his own, given the way it was described by Huddart, but he tracked down one of Harris’ brothers and sent him a set of colored ribbons with instructions to view them in day-light and candle-light. The responses turned out to match his self-examination and suggested to him that, “a considerable number of individuals might be found whose vision differed from that of the generality, but at the same time agreed with my own” [7]. With investigation he found a number of additional people with the same problem, and documented their response to different colored ribbons or threads. Figure 6 shows a document from Dalton’s papers that may represent one of these inquiries, as it is not in Dalton’s handwriting and is titled “Mr. Dalton’s Ribbands by Candle light”. Dalton recognized an unusual family pattern for the color defect. He wrote, “I do not find that the parents or children in any of the instances have been [affected]”, and adding, “It is remarkable that I have not heard of one female subject to this peculiarity” [7].



Mr Dalton's Ribbands by Candle light

No 1 Comes nearest of all to yellow, and yet it is but a fai on
2 Is a mixture of yellow and sooty black, one of the former and two the latter
3 Is yellow darkened with black
4 Is Black considerably inclining to Blue, a piece of the same is placed at the left end of No 3
5 Yellow inclining to Blue, not very unlike No 3
6 Comes nearest to Blue but the gloss prevents me from seeing the colours
7 A dirty White very like raw silk
8 A dirty light Blue with a dash of yellow

Fig. 6 Description of “Dr. Dalton’s Ribbands” in candle-light. (Photographed from a display at the John Rylands Library, Manchester. ©Lucy Burscough, 2014; used by permission). The handwriting looks different from Dalton’s refined script (see other figures) and these may be observations of test objects by one of his color-deficient subjects



Structure of the Human Eye.

The human Eye is a Globe, & is here supposed to be cut exactly into two equal Parts, & the inner Surface to be represented by the above Figure, which is about twice the Size of a common Eye.

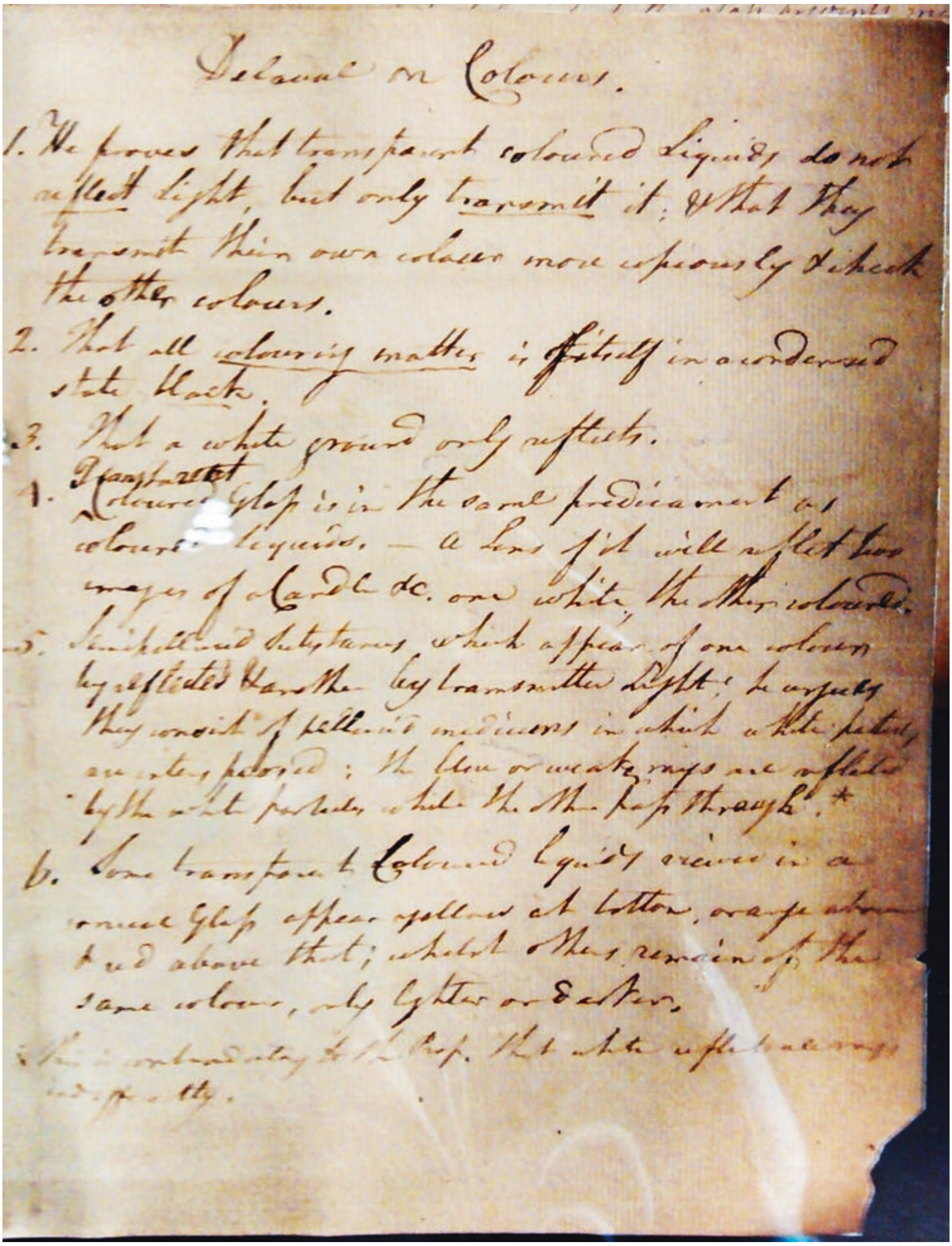
BbB is called the Cornea & is transparent, like Horn.
BFB the White of the Eye is not transparent.
Ba, Ba, the coloured Part of the Eye called Iris.
aa, the Pupil; bF the Axis of the Eye.
EE is a Substance like Jelly, in Form of a Turnip & perfectly transparent, called the Crystalline Humour.
The Space of the Eye before this is filled with a Fluid like Water, called the Aqueous Humour.
The large Space behind is filled with another fluid Substance not differing much from Water, called the Vitreous Humour.

Rays of Light from any Object PQR pass thro' the Pupil & Humours of the Eye to the back Part of it at F & there form the Image of the Object in its proper Colours, &c &c but inverted in every Respec

Fig. 7 Structure of the Eye lecture notes, from Dalton's papers. Transmission of light to the retina is described in the lower right corner. (Image from the Centre for Heritage Imaging and Collection Care, Manchester.©The University of Manchester; used by permission)

Dalton was still not satisfied, as he wished to understand *why* his vision was different from others and *why* it changed between daylight and candlelight [7]. Although not a visual scientist, he was not naïve about the subject, noting that "I became pretty well acquainted with the theory of light and colours before I was apprized of any peculiarity in my vision". The structure of the eye had been accurately described by Dalton's time, and among his papers are apparent lecture notes that begin with a careful drawing of the eye (Fig. 7). In his description of the posterior of the eye, he notes that "Rays of Light from any Object… pass thro' the Pupil & Humours of the Eye to the back part of it… & there form the Image of the Object in its proper Colours, … but inverted in every Respect". He is also known to have studied a 1785 book by Edward Hussey Delaval (1729–1814) entitled *An Experimental Inquiry into the Cause of the Permanent Colours of Opake Bodies* [12]. Hussey distinguished between solid bodies that reflected colors and dyes that stained a liquid. Dalton's notes from this book (Fig. 8) begin "He proved that transparent coloured Liquids do not reflect light, but only transmit it; & that they transmit their own colour more copiously". These concepts may have influenced his thinking with respect to his own vitreous body.

Dalton observed that a sky-blue liquid corrected the effects of candlelight, and wrote "I was led to conjecture that one of the humours of my eye must be a transparent, but *coloured*, medium, so constituted as to absorb *red* and *green* rays principally … I suppose it must be the



Delaval on Colours.

1. He proves that transparent coloured liquids do not reflect light, but only transmit it; & that they transmit their own colour more copiously & check the other colours.
2. That all colouring matter is of itself in a condensed state black.
3. That a white ground only reflects.
4. ~~Transparent~~ Coloured Glass is in the same predicament as coloured liquids. — a Lens of it will reflect two images of a Candle &c. one white, the other coloured.
5. Semi-pellucid substances, which appear of one colour by reflected & another by transmitted light; he supposes they consist of pellucid mediums in which white particles are interspersed; the blue or weaker rays are reflected by the white particles, while the others pass through.*
6. Some transparent Coloured liquids viewed in a conical Glass appear yellow at bottom, orange above & red above that; whilst others remain of the same colour, only lighter or darker.

* This is contrary to the Prop. that white reflects all rays indifferently.

Fig. 8 Notes from Dalton's papers on the writings of another scientist, Edward Hussey Delaval, highlighting color transmission through clear liquids. (Photographed from a display at the John Rylands Library, Manchester. ©Lucy Burscough 2014; used by permission)

vitreous humor" [7]. He then goes on to explain why this theory would explain his observations. He defines pink (and also crimson) as a mixture of red and blue, which would then more bluish in daylight, and the blue would be less reflected by candle-light. Red and scarlet lack blue and thus do not change color. He was bothered by greens, which often appeared bluish even in candlelight. Still, it is notable that he describes very clearly that most solid bodies are not perfectly reflective of any single wavelength, so that the perceived color will always be a balance of the relative reflectivity for different colors and the composition of the incident light. He wrote, speaking of color-deficient eyes, “it is evident, that our eyes admit blue rays in greater proportion than those of other people; therefore when any kind of light is less abundant in blue, as is the case with candle-light compared to day-light, our eyes serve to some degree to temper that light, so as to reduce it nearly to the common standard” [7]. This was the first analysis of how color-blindness might occur, even if Dalton himself would posthumously prove it wrong.

Legacy and Denouement

Dalton intrigued and challenged scientists of his day, for he not only proposed a hereditary abnormality of vision, but also a potential explanation. Even if he did not pursue this work, he challenged those with more direct interest in color and visual perception to think about his experiments and the implications for visual physiology. The concept of three receptors tuned to the primary visual colors of long, middle and short wavelengths was not described clearly until a report by Thomas Young (1773–1829) in 1802 [13], so that Dalton did not have these ideas at his disposal when he described his own color deficit. However, Young’s paper came out not long after his Dalton’s, and Herschel wrote a letter to Dalton in 1833 [14] pointing out that while all wavelengths from the prism reached his retina, he was functioning as if he only had two color sensations. But, there is no evidence that he ever accepted these ideas. Dalton was famously stubborn, and felt that to resolve the question, experimental evidence was needed (that he could provide): he willed that his eyes be opened after his death to determine whether the vitreous was indeed blue.

Dalton’s physician, Dr. Joseph Ransome, opened both of his eyes and reported in some detail [14], “I sacrificed one eye to the determination of the colours of the three humours. The aqueous was collected in a watch glass… [and] found perfectly pellucid and free from colour. The vitreous humor and its envelope (the hyaloid membrane) were also perfectly colourless. The crystalline lens was slightly amber”. And “in the other eye, the posterior part being removed by a vertical section … we were able to see objects as through a lens, and thus objects of different colours … were examined without an appreciable difference. I did not omit to place scarlet and green together”. And one of the eyes was brought to a laboratory where the observations were confirmed by showing that the appearance of colored powders through the ocular media was unchanged. Clearly the hypothesis of blue-tinged media was incorrect.

The initial opinion about Dalton’s color deficit, proposed by Young, was that he was protanopic [15] because of his seeming insensitivity to red, and thus he would lack the red receptor in the retina. But as noted above, Dalton did also describe clear perceptions of red. And of course, to some degree red is a darker color to all of us since sensitivity of both L and M cones falls off beyond the yellow and orange. Two other scientists of that era, Sir John Herschel (1792–1871) and Sir David Brewster, (1781–1868) had confirmed that Dalton could in fact see the full spectrum from a prism [14, 16, 17]. A definitive answer to whether Dalton was really protanopic or deuteranopic would have to await modern genetics. The remnants of Dalton’s eyes had been preserved in a specimen jar in the Dalton Hall of the Manchester Literary and Philosophical Society (Fig. 9), and towards 1995 two small samples of tissue were removed very carefully for the amplification of cone protein genes by polymerase chain reaction (PCR) [18]. The results were definitive: only an L-pigment could be identified, thereby proving that Dalton was a deuteranope who lacked a functioning M-pigment.

Modern molecular genetics has taught us that nature of color deficiency is in fact far more complicated than Mendelian inheritance. The defects are not usually caused by the simple lack or alteration of an L or M pigment, but result from com-

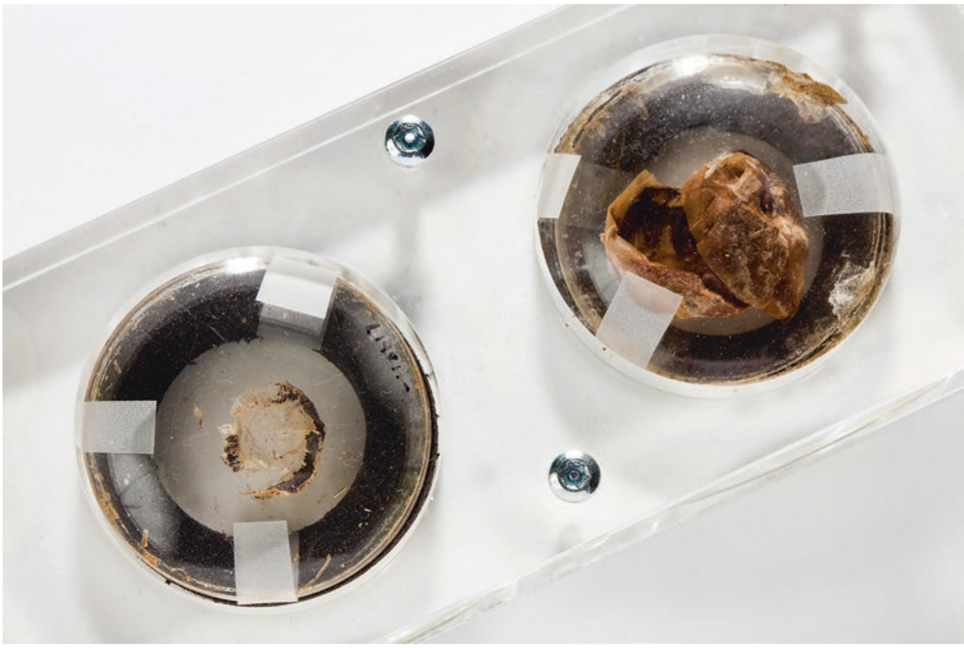


Fig. 9 Remnants of Dalton's eyes that have been preserved by the Manchester Literary and Philosophical Society. (©Science and Society Picture Library, London; used by permission)

plex recombinations of the L and M genes, which lie right next to each other on the X chromosome. [19–21] Because of these rearrangements, most people actually have several adjacent copies of the M gene in particular, and some women carry slightly altered genes on both x-chromosomes making them "tetrachromatic" (although that condition confers little visual benefit). Loss of the M pigment function on one x-chromosome through crossover is thought to be the most common cause of deuteranopia, and is consistent with Dalton's findings.

As more and more studies on color deficiency were published, the extent of the color deficiency in society became clear. Color "blindness", in the sense of complete red-green confusion (dichromacy) as Dalton had, is actually infrequent while intermediate degrees of color confusion (anomalous trichromacy) are far more common. Different authors kept inventing words for this new group of conditions, and in 1827 Pierre Prévost (1751–1839) suggested "Daltonian" [22]. This term was soon adopted by others, although it is not specific as to the type of color confusion. A number of Dalton's friends decried this term, arguing vigorously that Dalton's name should immortalize his chemistry rather than his eyes, but "Daltonism" remains in use today for color deficiency, particularly in Europe. Fortunately, Dalton is also recognized with the "dalton", a unit of molecular weight in chemistry.

Dalton died a famous man in England for his chemical researches and the concept of atomic theory (Fig. 10). Yet it was his youthful curiosity and insight that contributed to ophthalmology. He gave us early recognition of x-linked disease, made clear distinctions between individual perception and objective sensory stimulation, demonstrated the power of clinical investigation beyond mere observation, and ventured a hypothesis that helped lead others to a modern understanding of color vision. Dalton was wrong about the cause of his color confusions, but he defended his experimental approach quite literally to the death. In retrospect, he was also wrong about aspects of atomic theory as we know it today. The advancement of scientific ideas is rarely linear, given the con-

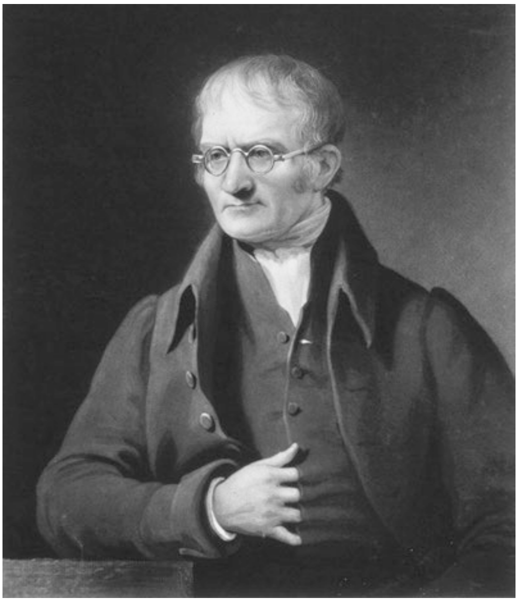


Fig. 10 John Dalton. Mezzotint, 1834, by Charles Turner after James Lonsdale. From the Library of Congress, Wikimedia)

tinual growth of knowledge. It begins with insight, persistence, and sometimes publicity. Dalton, a reserved Quaker, just beginning to explore his scientific skills, showed elements of all three. His work on color vision had a great impact, even if it was later revised and superseded. We should keep in mind that von Graefe's writings on glaucoma and other diseases helped to move ophthalmology towards a rational clinical basis, even if many of his specific concepts about pathophysiology (especially regarding glaucoma) are no longer valid.

Dalton's insight opened the eyes of ophthalmology to color testing and color perception. And his gift to society in publicizing the existence of color-deficiency is of inestimable value to affected men, including artists [23]. The skilled Renaissance artist, Baccio Bandinelli hired other artists repeatedly in the early 1500s to teach him how to paint with colors, because no matter how beautiful his designs might have been, his paintings were criticized and considered of poor quality [1]. He could never comprehend why, and he grew increasingly frustrated. His response might have been different had he been alive 250 years later.

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4

Thomas Young: The Foundations of Light, Color, and Optics

John W. Gittinger Jr.

Introduction

Named after his father, Thomas Young (Fig. 1) was born at Milverton in Somersetshire, England, on the 13th of June, 1773, the eldest of ten children. His parents were strict Quakers, and an anonymous contemporary "who had the advantage of long and intimate acquaintance with that distinguished scholar and philosopher" attributed "the power he so eminently possessed of an imperturbable resolution to effect any object on which he was engaged" to his upbringing in the Religious Society of Friends [1]. An early biographer restated this in a different way: "Nor was there anything which he thought worthy to be attempted which he was not resolved to master" [2]

His intellect was both a blessing and a curse. His perhaps overly broad interests and difficulty communicating his ideas resulted in his being underappreciated during his lifetime. He made contributions to many fields, but may be best remembered for his trichromatic theory of color vision that was expanded upon by Hermann von Helmholtz and James Clerk Maxwell decades after his death and confirmed by modern neurophysiologists. Helmholtz, the inventor of the ophthalmoscope, famously said that Young "had the misfortune to be too far in advance of his contemporaries."

Child Prodigy

To say that he showed great intellectual powers at a young age may be an understatement. He was able to "read with fluency" at age two and said he had perused the entire *Bible* twice by age four.Primarily an autodidact, he had a command of English, Latin, Greek, Italian, French, Hebrew, Chaldee (Biblical Aramaic), Persian, Syrian, and Arabic at age 14.

Accommodation

At age 19 in 1793, his paper "Observations on vision" was read by his great-uncle Richard Brocklesby M.D. F.R.S. to the Royal Society and then published in its *Philosophical Transactions* [3]. He addresses previous speculation on the mechanism of accommodation put forth by, among others, Kepler and Descartes, both of whom felt elongation of the eye explained the change in focus, then dismisses the possibility that the ciliary processes are responsible for the change in the shape of the crystalline lens. "Those who maintain that the ciliary processes flatten the crystalline, are ignorant of their structure." He does not indicate who held this opinion.

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Fig. 1 Portrait of Thomas Young by Henry P. Briggs

Based on his own dissection of an ox eye ("I have not yet had an opportunity of examining the human crystalline, but from its readily dividing into three parts, we may infer that it is similar to that of the ox"), he concludes that the crystalline lens consists of muscles and tendons and that contraction of these muscles changes the shape of the lens to produce accommodation. As for an elongation of the eye's axis, "as a bell shakes a steeple, so must the coats of the eye be affected by any change in the crystalline; but the effect of this will be very inconsiderable." He goes on to discuss what are now called phosphenes, visual phenomena produced by pressure on the eye.

Young was immediately embroiled in controversy as the eminent John Hunter F.R.S., 20 years Young's senior, claimed precedence for the idea that the lens is intrinsically muscular. There was even innuendo that Young had heard of Hunter's idea at a dinner party in 1791 at the house of Sir Joshua Reynolds. Concerned that he was being accused of plagiarism, Young wrote to those who had attended the dinner to ask if any visual researches had been discussed.

He was, however, elected to the Royal Society in 1794, the week after his 21st birthday. He wrote to his mother, "I hope I am not thoughtless enough to be dazzled with empty titles which are often conferred on weak heads and on corrupted hearts" [4]

He was to go on to demonstrate that the eye retained its ability to accommodate under water where the refractive power of the cornea is effectively neutralized. "It has been observed that the central part of the crystalline become rigid by age, and this is sufficient to account for presbyopia." He eventually was to have the personal experience of presbyopia, his eye having "lost almost the whole of its power of accommodation soon after fifty" [5]

Medical Student at Edinburgh, Göttingen, and Cambridge

Young decided to pursue a career in medicine and studied at Edinburgh and Göttingen, receiving a degree from the latter in 1796 for a thesis (in Latin) on the human voice. Because the politics of English medicine at that time required a degree from Oxford or Cambridge to obtain licensure in London from the College of Physicians, he enrolled at Emmanuel College, Cambridge, in 1797.There he acquired the sobriquet "Phaenomenon Young" as he already seemed to know what his fellow students (and tutors) were still learning. Later that same year his great-uncle and mentor, Dr. Richard Brocklesby, died, leaving him a furnished house in London and about £10,000. This assured him of a comfortable life as a gentleman scholar, which was fortunate as he never achieved great success as a practicing physician.

His tenure at Cambridge forced him to depart from his Quaker roots, as membership in the Church of England was a requirement for matriculation at either Oxford or Cambridge until late in the nineteenth century. He learned little from his tutors and fellow students, but spent much time studying and experimenting on sound and speech. In his autobiographical sketch written in 1826–1827, he speaks of himself in the third person, "His pursuits, diversified as they were, had all originated in the first instance from the study of physic: the eye and the ear lead him to the consideration of sound and of light."

He read a paper at Emmanuel in 1799 that includes the lines, "should further experiments tend to refute any opinions that I have suggested, I shall relinquish them with as much readiness as I have long since abandoned the hypothesis with I once took the liberty of submitting to the Royal Society on the functions of the crystalline lens." He appears to have temporarily abandoned his idea that the lens was a muscle that changed in shape to produce accommodation.

London and Optics

Having satisfied his required residence in Cambridge, Young moved back to London and read "On the Mechanism of the Eye" to the Royal Society in November, 1800 [6]. This long and detailed paper includes another reference to the appearance of ciliary processes upon dissection as "wholly irreconcileable [sic] with muscularity."

> Whatever their use may be, cannot easily be determined: if it were necessary to have any peculiar organs for secretion, we might call them glands, for the percolation of the aqueous humour; but there is no reason to think them requisite for this purpose.

He also seems to return to his former opinion in regards to the lens as the active structure in accommodation. He remains troubled that he cannot find any nerves going to the lens. This is also the paper where he identifies astigmatism (although he did not coin this term) by refracting his own eyes and describes a variation of an instrument called an optometer for measuring refractive error and accommodation.

He also measures his own blind spot:

> To find the place of the entrance of the optic nerve, I fix two candles at ten inches distance, retire sixteen feet, and direct my eye to a point four feet to the right or left of the middle of the space between them: they are then lost in a confused spot of light; but any inclination of the eye brings one or the other of then into the field of view.

From these observations he concludes:

> … the diameter of the most insensible part of the retina,[is] one-thirteenths of an inch.

He does not make the modern distinction between optic nerve and retina, but his calculation comports well with the 1.5–2 mm. diameter of the optic nerve determined by direct measurement.

Lloyd comments that "the first reliable observations on the area of the visual field must be credited to Thomas Young, who gave the extent of the field as upwards 50°, inwards 60° and outwards 90°. Young also pointed out that 'the whole extent of perfect vision is little more than ten degrees'" [7]

Light as a Wave

One year later he returned to give another Bakerian Lecture (one of four), "On the Theory of Light and Colours" [8]. Here he refers to Newton's Theory of Light and states that, because of the "stupendous velocity it implies, has been ever thought liable to difficulties." He proposes instead "a luminiferous ether, rare and elastic in a high degree, pervades the whole universe" and that "undulations" in this ether leads to the perception of color. The fundamentals of this characterization of light as waves had been proposed by Huygens in 1678.

In 1803 Young described experiments in support of his wave theory of light [9]. He is credited with performing the "two slit experiment" in which two parallel slits illuminated by light produce the interference fringes that would be expected if light behaves as a wave. In fact the paper generally cited for this experiment, his 1803 Bakerian Lecture published in 1804 makes no mention of slits. It does describe fringes produced by a needle hole in a "piece of thick paper" and a previously described observation by Grimaldi (no reference given) of fringes "formed by an object which has a rectangular termination." There are no diagrams associated with this lecture.

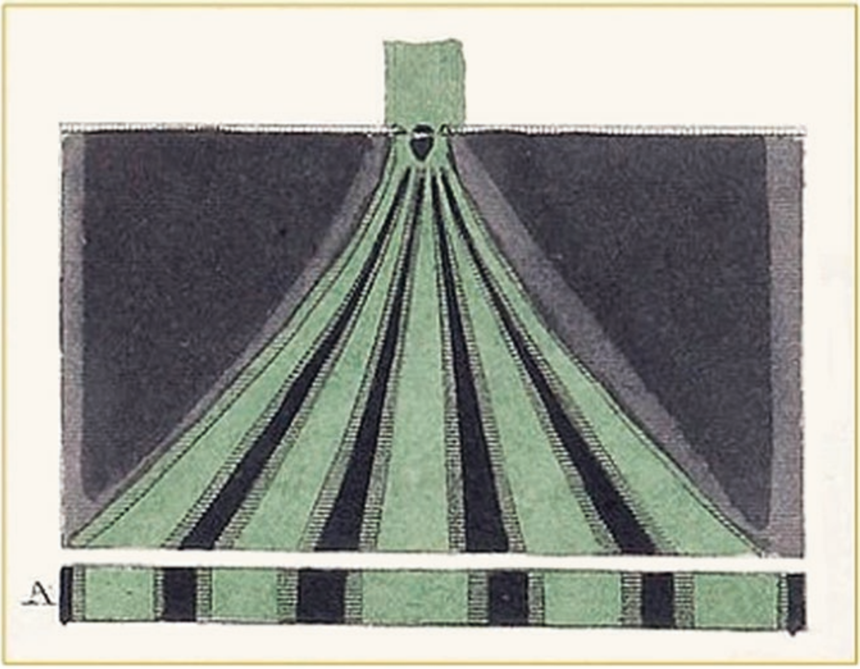

Fig. 2 Young's diagram of what is now known as the two slit experiment. His caption: "The manner in which two portions of colored light, admitted through two small apertures, produce light and dark stripes or fringes by their interference, proceeding in the form of hyperbolas; the middle ones are however usually a little dilated, as at A"

He did describe and diagram an experiment (Fig. 2) in his *Lectures on Natural Philosophy* published in 1807 [10], but he refers to "small apertures" and not slits. There is some doubt whether Young actually performed the two slit experiment. Modern historians of science point out that he does not specify the light source used or other experimental conditions, nor does he provide specific measurements as he usually did [11]. He never returned to this experiment in his subsequent publications.

In any event, even if this were a thought experiment, it has been performed and confirmed many times by others (Fig. 3).

Young had generalized from sound waves to light waves—in distinction from Newton's prior characterization of light as corpuscular (particles). Robinson characterizes him as *"The Anonymous Polymath Who Proved Newton Wrong,"* [12] but Young expressed great admiration for Newton and goes on at length to explain why various optical phenomena can only be explained if light behaves as a wave. Actually, modern physicists consider both Young and Newton correct; light behaves as particles in some situations and as waves in others—the "wave-particle duality of light."

Color Vision

The insight in his 1801 Bakerian lecture that has had the most lasting effect was Young's postulation that the undulations of red, yellow, and blue were related to each other "in magnitude as the numbers 8, 7, and 6" and that these "primitive" colors combined to produce other color sensations. Young later changed the "principal pure colours" to red, green, and violet in his essay on "Chromatics" in the 1817 *Supplement* to the *Encyclopedia Britannica*—one of his more than 60 contributions to this work on a wide variety of subjects (When the sensitivities of cones could actually be measured in the twentieth century, their peak wavelengths are nearer red, green, and blue.)

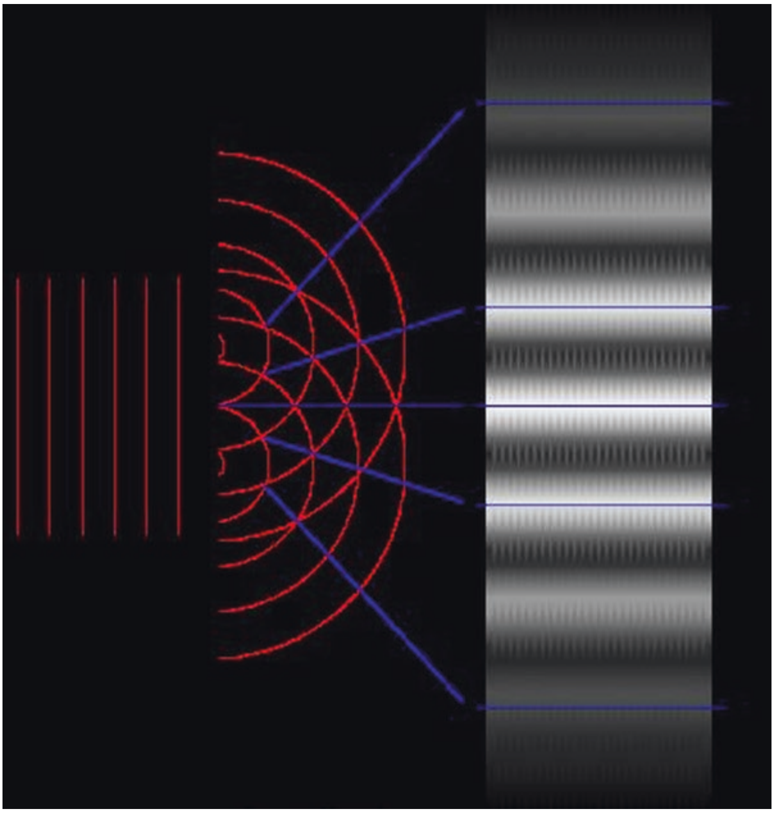

Fig. 3 A modern diagram of the two slit experiment. From http://www.shmoop.com/optics/young-double-slit.html, https://upload.wikimedia.org/wikipedia/commons/thumb/8/8b/Two-Slit_Experiment_Light.svg/2000px-Two-Slit_Experiment_Light.svg.png

In "Chromatics" he more clearly states his theory: [13]

> If we seek for the simplest arrangement, which would enable it [the eye] to receive and discriminate the impressions of the different parts of the spectrum, we may suppose three distinct sensations only to be excited by the rays of the three principal pure colours, falling on any given point of the retina, the red, the green, and the violet; while the rays occupying the intermediate spaces are capable of producing mixed sensation, the yellow those which belong to the red and green, and the blue those which belong to the green and violet.

Professor at the Royal Institution

Young was appointed Professor of Natural Philosophy in the Royal Institution, which had been founded in 1799 and given its Royal Charter in 1800. Officially the Royal Institution of Great Britain and still in existence at its original location on Albemarle Street in London, this ambitious and quintessentially British undertaking was to include, "an industrial school for artisans; a collection of models of fireplaces, grates, stoves, steam engine, spinning wheels, etc.; a professor was to be appointed and provided with a well-equipped lecture room; and a convenient club with a restaurant and school of cookery…" [14]. From its outset the Royal Institution has as one of its primary goals attempted to expose the general public to the ideas and discoveries of science.

Young gave a series of lectures there in 1802–1803 that, according to his own assessment, were "never either very popular or very fluent." His anonymous, but sympathetic, biographer comments, "As a lecturer at the Royal Institution, Dr. Young was apt, in no small degree, to pass the capacities of his audience…. His style was compressed and laconic; he…gave more matter than it would perhaps have been possible for persons really scientific to have followed at the moment without considerable difficulty."

Fig. 4 A satiric view of a lecture at the Royal Institution. "Scientific Researches! New Discoveries in PNEUMATICKS-or-an Experimental Lecture on the Powers of Air" (1802). Sir Humphry Davy (discoverer of sodium and potassium) to the right with bellows. In the center is Thomas Young experimenting on Sir John Hippisley (farting). Note the heterogeneity of the audience

These lectures did not do much to enhance Young's reputation (Fig. 4). His more serious efforts were met with a barrage of criticism. An unsigned review, but known to be written by Henry Peter Brougham (who would eventually become Lord Chancellor) in the recently established *Edinburgh Review* of "On the Mechanism of the Eye" states, "As this paper contains nothing which deserves the name, either of experiment or discovery, and, as it is in fact destitute of every species of merit…Has the Royal Society degraded it publication into bulletins of new and fashionable theories for the ladies who attend the Royal Institution?" [15] Brougham had reason to resent Young, who had previously savaged his work, "such an author appears to be confined in his conception of the most elementary doctrines, and that he fancies he has made an improvement of consequence, when, in fact, he is only viewing an old object in a new disguise" [16]

Physician in London

He finally received his M.D. from Cambridge in 1808 and became a Fellow of the Royal College of Physicians in 1809. He eventually obtained an appointment at St. George's Hospital in 1811.

Sir Benjamin Brodie, who was at St. George's with Young and later became the first surgeon to be president of the Royal Society, said of him, "The students at the hospital complained that they learned nothing from him. I never could discern that he kept any written notes of cases, and I doubt whether he ever thought of his cases in the hospital after he had left the wards. His medical writings were little more than compilations from books, with no indication of original research. I offer these observations as a matter of justice to others, and not in depreciation of Dr Young, whose great original genius displayed in other ways, place him in the

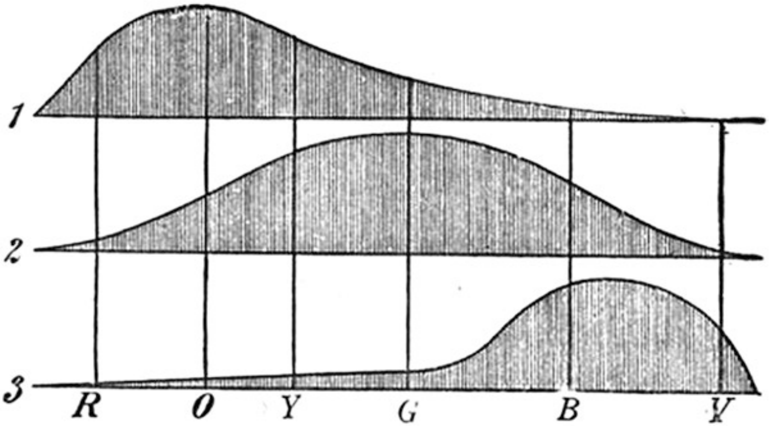

Fig. 5 Helmholtz's response curves for the three color receptors from his 1860 *Handbuch der Physiologicschen Optik*

foremost rank of those whose names adorn the annals of our country" [17]

He delivered the Croonian Lecture to the Royal Society in 1808. He applied hydraulic principles to the circulation of blood and argued against the then popular idea that peristaltic contraction of the larger arteries was a major factor in blood flow [18].

Young returned to an old pattern in 1809 for a lecture series published as *A Syllabus of a Course of Lectures on the Elements of the Medical Science*. He admitted "they were little frequented, on account of the usual miscalculation of the Lecturer, who gave his audience more information in a given time, than it was in their power to follow." As his biographer Robinson correctly observed, "Great thinkers do not always make great lecturers."

His 1813 *An Introduction to Medical Literature, Including a System of Practical Nosology* did not sell well, but he prepared a second edition (1823). He published *A Practical and Historical Treatise on Consumptive Diseases* in 1815 and was disappointed that it did not attract more patients with these disorders to his practice.

Young's Legacy

Young's failure to remain focused on one field and his inability to explain his ideas more clearly served to diminish his impact on scientific thinking during his lifetime. It remained for subsequent generations to mine his voluminous works and ensure his reputation as an innovator.

Long after Young's death at age 55 in 1829 (His choice for his epitaph, "He may be said to have been born old, and to have died young") Hermann von Helmholtz and James Clerk Maxwell, working in the 1850s, resurrected the three retinal receptor explanation of color vision that Young had implied. Heesen asserts that Maxwell deserves precedence for the concept of "coterminal response curves" (i.e. that each of the three receptors is sensitive to overlapping spectra) (Figs. 5 and 6) that explains how just three retinal receptors could account for the perception of multiple colors and argues that the Young-Helmholtz theory of color vision would more properly be called the Young-Maxwell theory or at least the Young-Helmholtz-Maxwell theory [19] (A small irony: Maxwell was also Young's wife maiden name).

Whatever his faults as a lecturer and writer (One tutor at Emmanuel commented "He was… worse calculated than any man I ever knew for the communication of knowledge"), he was a towering intellect. Fonda catalogues Young's contributions to optics: mechanism of accommodation by the lens, exposition of the phenomenon of interference of light waves, calculation of the wave lengths of seven colors in the spectrum, the first measurement of astigmatism, the first measurement of the field of vision and size of the

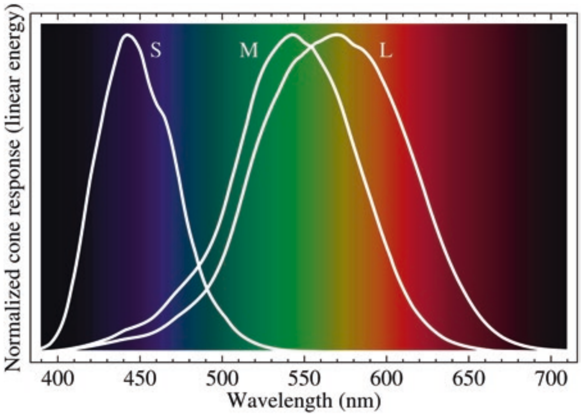

Fig. 6 A modern diagram of cone responses. The cones are designated S for short wavelengths, M for medium wavelengths, and L for long wavelengths, rather than by color. Note that the modern diagram reverses Helmholtz's color order. From https://commons.wikimedia.org/wiki/File:Cone-fundamentals-with-srgb-spectrum.svg (I, the copyright holder of this work, release this work into the public domain. This applies worldwide. In some countries this may not be legally possible; if so: I grant anyone the right to use this work for any purpose, without any conditions, unless such conditions are required by law

blind spot [20]. (Actually, Edme Mariotte "was the very first to try to determine the size of the blind spot" in 1717—which is why it has been called the "Blind Spot of Mariotte" [21])

In addition to his eponymous theory of color vision, there is the Young modulus for elasticity, the Young-Laplace equation for capillary pressure, the Young–Dupré equation for surface free energy, and the Young temperament for the tuning of musical instruments. He also found time to be Secretary of the Board of Longitude and Superintendent of the *Nautical Almanac* and serve as actuary for the Palladium Insurance Company while simultaneously attempting to translate hieroglyphics using the Rosetta Stone. Concerned that his attention to so many fields would reflect poorly on his ability to practice medicine, he published many of his papers anonymously, which probably also diminished his reputation among fellow "natural philosophers," as they were then known (The term *scientist* wasn't coined until after Young's death).

Young felt that his work on light and colors, "though it did not occupy a large portion of my time, I conceived to be of more importance than all that I have ever done, or ever shall do besides" [22]. In his own lecture at the Royal Institution, Maxwell stated, "So far as I know, Thomas Young was the first who, starting from the well-known fact that there are three primary colours, sought for the answer to this fact, not in the nature of light, but in the constitution of man" [23]

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5

Valentin Haüy and Louis Braille: Enabling Education for the Blind

Alan R. Morse

For most of history, blindness has condemned those afflicted to lives of misery. People who were blind, like those with other disabilities, rarely were integrated into society. The stigma of blindness came from the "implication that an 'uncured' disability somehow represented shameful incompleteness." [1] (p. 20) Scott [2] presents a modern perspective: *The various attitudes and patterns of behavior that characterize people who are blind are not inherent in their condition but, rather, are acquired through ordinary processes of social learning…Blind men are made, and by the same processes of socialization that have made us all.* (p. 14) Unlike modern disability rights, the historic struggle to advance the blind was largely exogenous and driven by people with sight and foresight. Because the blind were marginalized and disrespected, change in their societal status would have to come from sighted society.

This chapter describes developments that played a seminal role in the transformation of individuals with vision loss to active, productive members of society. We consider three philosophers and several of their contemporaries whose thinking set the stage for an intellectual awakening to the capabilities of the blind and two individuals whose role was transformative in changing societal perceptions and practical realities for the blind—Valentin Haüy and Louis Braille (Figs. 1 and 2).

Rejected by society, those born blind were deprived and destitute. Many blind infants were abandoned at birth and left to die, an acceptable practice of the times because their plight was hopeless. Moreover, because those who were blind were assumed ignorant and incapable of learning, methods for teaching the blind were unfathomable and their fate became self-fulfilling. Uneducated and unskilled, they generally were condemned to a life of ignorance and poverty as beggars or street musicians. Cardano, an Italian physician with a deaf son, understood disability and was not content to consign the blind to a life of abject poverty, but he also understood the enormity of the burden of blindness and stated *"[n]*ext. to death, blindness is the worst misfortune that could befall any person*"* [3]. However, he believed that education was the key to social transformation. Cardano was prescient in proposing that by tracing the outline of letters engraved on a metal plate and learning how to identify them by touch, the blind would be able to read. However, one more step would be necessary to enable to write because Cardano had not developed a method to teach writing with letter or line spacing [4]. Moreover, even if writing were possible, there was nothing for them to read.

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Fig. 1 Giromolo Cardano

In the next century, the Jesuit priest Francesco Lana de Terzi, devoted a chapter in his *Prodromo* [5] to writing, reading and other issues of blindness and helped to lighten the burden of blindness by offering hope. For de Terzi, like Cardano, to consider education represented significant change in attitudes that had stubbornly persisted since the beginning of recorded time.

Lana de Terzi proposed an entirely new alphabet for blind people of his own invention. Unlike previous writing systems for the blind, Lana de Terzi's alphabet was not based on replicating the handwritten or printed letters used by those with sight; rather, he used a series of raised dashes that could be recognized by the touch of one's fingers. Had de Terzi continued his work developing a reading and writing system, he may have brought education to the blind 150 years before Haüy and Braille. However, he was an inventor not an educator and his interests quickly changed. His method of writing did not fail, de Terzi simply abandoned it and no one else continued his work. His focus changed towards establishing a theory of aerial navigation that could be verified by mathematics; he was successful and is known as the Father of Aeronautics. Nevertheless, de Terzi's insight that an alphabet for the blind does not have to replicate the alphabet for the sighted in its appearance, coupled with the concept of reading by touch represented fundamental change and would contribute significantly towards advancing the progress of blind individuals in society.

The seventeenth century marked the start of the scientific revolution and the Age of Enlightenment. Three philosophers, Descartes, Locke and Diderot, are especially noteworthy and established foundations that ultimately would be transformative for individuals who were blind (Figs. 3, 4, and 5). Their thinking would lead to the development of educational institutions for the blind, set the stage for the development of Braille and establish the begin-

HIER. CARDANI
DE VTILITATE
ex adverſis capienda
LIBRI IV.

FRANIKERÆ
Excudit IDZARDVS BALCK, Illuſtrium
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Anno Typographus *1648*

Fig. 2 Cover of Cardano’s De Utilitate ex Adversis Capienda ning of rights, i.e., disability rights, and societal inclusion for individuals without sight.

Descartes was fascinated by vision and knowledge acquisition; all knowledge was either primary, i.e., derived directly from the senses or secondary, derivative and developed through reasoning but not directly grounded in sense perception. If a sense is lacking, knowledge normally obtained through that sense exclusively, i.e., primary knowledge, therefore, can never be obtained. In the case of sight, for example, unless one can see a color, knowledge of that color can never be acquired. How can red or blue be explained to, or by, someone who is blind? And, while all senses are important for knowledge and understanding, he considered none more important than sight. At the start of his *Treatise on Light, Discourse One*, Descartes asserts the primacy of vision among the senses.

> *The conduct of our life depends entirely our senses, and … sight is the noblest … No doubt you have had the experience of walking at night over rough ground without a light, and finding it necessary to use a stick to guide yourself … this kind of sensation is somewhat confused …But consider it in those born blind who have made use of it all their lives: with them, you will find, it is so perfect and so exact that one might almost say that they see with their hands* [6] (p. 57).

That phrase, ‘see with their hands’, equates sense perception through touch to sense perception by sight in those who are blind, a theme that portends the development of Braille and also comports with current theories of neuroplasticity. Decartes’s insights provided an understanding of what it means to be without sight and how other senses could accomodate to create a sense of the real world.

Fig. 3 Rene Descartes. Artist unknown

Fig. 4 John Locke, from an engraving of a painting by Godfrey Kneller

Fig. 5 Denis Diderot, oil painting by Louis-Michel van Loo, 1767; in the Louvre, Paris

Continuing in the inquiring tradition of Descartes, the Irish philosopher and scientist William Molyneaux, whose wife had become blind during their first year of marriage thus stimulating his interest about blindness, wrote to his friend John Locke in 1688 [7] positing a question that has become known *Molyneaux's Problem*: If a man born blind and taught by touch to distinguish between two shapes of the same material, a cube and a sphere, is then made to see, could he by his sight alone distinguish them and tell which is the cube and which is the sphere? Molyneaux and Locke agreed the answer was no, because although the man had obtained the experience of how the objects felt to his sense of touch, he had not yet experienced how those same objects appeared to his sense of his sight; experience was considered essential element of knowing and learning required sense experience [8]. In 1728, the English surgeon William Cheselden performed a cataract operation and an iridotomy that gave sight to a 13 year-old boy born with congenital cataracts. This provided fodder for further thinking about sense perception after sight acquisition and knowledge. After surgery, even the simplest visual tasks were a challenge: *When he first saw, he was so far from making any judgment of distances … and thought no object so agreeable as those, which were smooth and regular, though he could form no judgment of their shape* [9] (pp. 447–450), confirming Molyneaux and Locke.

In his *Letter on the Blind for the Usage of Those who can See* [10], Diderot called further attention to the blind using a fictional conversation between a narrator and an unidentified woman, known only as Madame. As with Descartes and Locke, Diderot's interest was the relationship of knowledge to sense perception. In *Letter on the Blind*, however, he aimed to affect broad societal change and used the treatment of the blind to underscore the need to recognize the dignity and potential of all human beings. Diderot believed that everyone should become literate and learn how read, write and count. Using a discussion with a blind man he had visited in the town of Puisseaux, Descartes asked if gaining sight would be a joyful and overwhelming experience. The blind man answered:

> *If I wasn't so curious, I would just as soon have long arms: it seems that my hands would tell me more about what happens on the moon than you can find out with your eyes and your telescopes; and besides, eyes cease to see sooner than hands to touch. I would be as well off if I perfected the organ I possess, as if I obtained the organ which I am deprived of* [11].

Diderot's letter provided strong stimulus for robust societal discussion and was the first time that a blind man was portrayed in literature as able to contribute to society [12, 13]. By showing that a blind person's mind can be as rational and subject to study as that of the seeing, he sought to bring and end to "a [pernicious] tradition that had prevailed for almost the whole duration of European culture" [14] (p. 157): blind people are different from the sighted only in their loss of vision, not in their humanity.

Particularly stimulating, although not in a helpful way, was Diderot's attribution to Nicholas Saunderson, the Lucasian professor of mathematics at Cambridge University, the most preeminent position in mathematics, the belief that for him as a blind man to believe in the reality of God, he would have to be able to touch him. Blinded by smallpox since early childhood, Saunderson taught himself to read from tombstomes and learned basic arithmetic from his father. In 1711, the year he ascended to the Lucasian chair, Saunderson developed a method of teaching arithmatic by touch, asserting that since knowledge derives from the senses, mathematics is the only knowledge that can be equally accessible to sighted and blind individuals. His *palpable arithmetic* was an advance, but an abacus, developed millenia before, could have been readily utilized by blind people but was not because of widespread beliefs about their limited intellectual capacity [15]. By the middle of the eighteenth century, the stage was set for a blind revolution.

Valentin Haüy (1745–1822) was born in the village of Saint-Just-en Chaussée, in northern France. His father was a weaver and his upbringing, modest. His father also rang the Angelus bells, morning, noon and night at the local abbey run by Catholic monks and Valentin often accompanied his father to the abbey. He became known to the monks who took time to educate him and he became a skilled linguist fluent in ten extant languages as well as ancient Greek and Hebrew. As his linguistic abilities developed, he gained the title interpreter to King Louis XVI, as well as to the Admiralty and was a gifted teacher. Although not born of high birth, his literacy and teaching skills propelled him forward in French society. He had been a professional translator since 1769 and understood nuances of language and how dependent individuals were on those who interpreted for them, if they were themselves unable to read or write (Fig. 6).

1771 was a watershed and marked the beginning of Haüy's desire and commitment to help the blind. At lunch in a cafe on the Place de la Concorde during Saint Ovid's Festival, a religious street fair, the 25 year-old Haüy witnessed a 'concert' by nine men from the Quinze-Vingts Hospice for the Blind, being mocked (see Fig. 8a). Dressed in long robes with high pointed hats like dunce caps and oversized cardboard glasses, they obviously were unable to read the music in front of them. Nevertheless, they played their instruments, resulting in a cacophony. The crowd was amused, but witnessing the ridicule of the blind 'musicians', Haüy was struck with quite a different emotion:

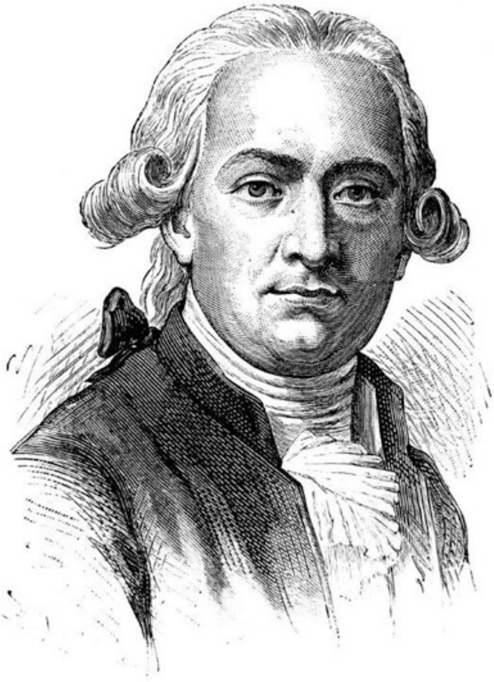


Fig. 6 Valentin Haüy

> *We conceived, at that very instant, of the possibility of realizing, to the advantage of those unfortunates, the means of which they had only an apparent and ridiculous enjoyment … Yes, I said to myself, seized with a noble enthusiasm, 'I will replace this ridiculous fable with the truth. I will make the blind read … they will trace letters and read their own writing. I will even have them give harmonious concerts'* [16].

On the day of Saint Ovid's in 1771, Haüy imagined, the use of embossed letters to teach reading and writing for the blind and a method of reproducing text so that they could read books [17]. It is with this method that Louis Braille would ultimately learn to read and write. Haüy later credited Diderot's depictions of the blind man of Puisseaux, competent in all ways and of Saunderson teaching at England's most esteemed university, to embolden him to dare to experiment [18]. Haüy also had a role model, the Abbé de l'Épée, who achieving fame as an educator of deaf mutes, basing his educational methods on the belief that deaf mutes learn through their eyes what others learn through their ears (Fig. 7). While the Abbé did not invent sign language, he improved it substantially and made his new educational methods widely known so that others could use them, removing the cloak of parochialism that had characterized 'special' education.

Following the St. Ovid's spectacle, Haüy spent the next 12 years continuing to teach, contemplating a school for the blind and saving money for its creation. In a popular retelling of the story, as Haüy left church he gave a few coins to the blind beggars who waited patiently on the church steps. Pope Clement had institutionalized begging by the blind in France since 1265 with the key spots for beggars going to those who resided in the Quinze-Vingt Hospice for the Blind that had been established in 1256 by King Louis IX, later known as Saint Louis. The positions at the top of the church stairs were particularly prized. As was his habit, Haüy gave some coins,

Fig. 7 Concert extraordinaire at the Cafe of the Blind, St. Ovid's fair 1771

Fig. 8 Statute of Valentin Haüy and François Le Sueur outside the Institut National des Jeunes Aveugles in Paris

a few *sous*, to each blind beggar he encountered. Slightly less than 25 *sous* equaled 1 *franc* and a *franc* equaled about 20 cents in US currency; a few sous was indeed meager. A few feet from the bottom of the church steps, Haüy he gave a coin to a young blind boy. The boy called out the denomination, believing Haüy had accidentally given him too large a sum; obviously able to read the coin by touch, he realized it was more than the usual few *sous*. Haüy immediately recognized the significance of this chance encounter and galvanized his belief that the blind could learn to read: Haüy knew he had found his perfect student [19]. Haüy convinced the beggar, François LeSueur, to become his student, inducing him by offering to pay as much as LeSueur earned by begging, after watching LeSueur's skill in reading the value of coins by touch. LeSueur was no ordinary beggar. He wanted to better his life and that of his five siblings. He had approached the Philanthropic Society a few months before his encounter with Haüy, but at age 17, LeSueur was too old for the 'pension' they created for blind youths and, in addition, each of 12 of their allotted slots for blind youths were filled.

After watching LeSueur, Haüy knew instantly that his earlier speculation about raised letters was correct and asked rhetorically, 'why couldn't entire books be written with the letters raised so that people who could not see with their eyes could read with their fingers'? His ideas validated by LeSueur's identification of the coin, Haüy immediately went to work educating his new student. To teach LeSueur the alphabet, Haüy began with wooden blocks, each with a carved letter. Serendipitously, a printed funeral notice stimulated the next breakthrough. When LeSueur felt the notice—a piece of newspaper—he asked if the letter he was feeling was an 'O'? It was. The force of the printing press had embossed some of the letters and Haüy then recognized that by deliberately embossing letters, the blind could be taught to identify letters them by touch and read. Using thick paper, moistened to make it more susceptible to the force of the printing press, Haüy created his technique for printing so that the blind could read. However, by inking the letters the embossed characters could also easily be read by those with sight. Haüy's technique for printing for the blind and his Haüy Noire technique blackening the letters to be read by those with sight as well as by touch by the blind were created.

Within 3 months, LeSueur learned to read and write using an embossed book made with Haüy's technique. Haüy's success with LeSueur, coupled with his credentials as a royal interpreter, gave him a broad audience catapulting Haüy and his methods forward [20]. Haüy presented his plan to educate the blind to the French Philanthropic Society and his time meditating and contemplating every detail was rewarded. In the *Journal de Paris*, September 16, 1784, the Society announced its intention to fund the project that Haüy had designed [21]. He also had LeSueur demonstrate his newly learned abilities to the Bureau of Academic Writing on November 18, 1784.

At the meeting of the Writing Bureau meeting, Haüy read his "*Memoir on the Education of the Blind*," [22] detailing plans for the school. Numerous French dignitaries were present, giving him the widest possible exposure. Not content to present to only one segment of French intellectualism, Haüy also presented his plan to the elite Royal Academy of Science, no doubt buoyed by his success with the Writing Bureau and the knowledge that his brother, Rene Just Haüy, had recently been elected a member of the Academy. At least there would be a friendly face in the audience although no doubt by now Haüy knew many others of that august group since they traveled in the same social circles. He made his presentation on December 22, 1784 and on December 26, the secretary of the Philanthropic Society wrote to the *Journal de Paris* indicating that the Society would expand the number of pensions for those born blind by 6–18 effective January 1, 1785.

LeSueur's demonstration of his abilities to read and write were so impressive that he no longer would be a student, he would now be a teacher and the teaching would be of students in groups, boys and girls together. Haüy had an almost intuitive understanding of the need for companionship and relationships of 'his' blind children, no doubt due to their solitary upbringing. Having a blind teacher like LeSueur would give them a role model like themselves, blind since early childhood, who would be empathic but also demanding in his expectations. Moreover, all students, regardless of their social background, would be taught together just as the Abbé de L'Épée had prescribed for those who were deaf mutes: "Among our children, there are noble and rich deaf-mutes just as there are those who are poor and from the dregs of society …Be they rich or poor, they must learn language in its entirety, or not be taught at all." [23], in Weygand, p. 105. The presentations had gone well and to assure continued acceptance of his efforts, Haüy had the students give twice-weekly public demonstrations of their abilities focusing on their public relations value and, of course, the generous contributions often made by those who stopped by to see the students' achievements. The *Journal de Paris* regularly reported on Hauy's activities and, following each report, was a request for donations. On January 7, 1786, the very positive review of Haüy's methods by the Royal Academy of Sciences was complete and reported. Haüy's publication, *Essai sur l'éducation des Aveugles* (*An Essay of the Education of the Blind),* was produced under subscription with the King and and many others paying generously for its publication.

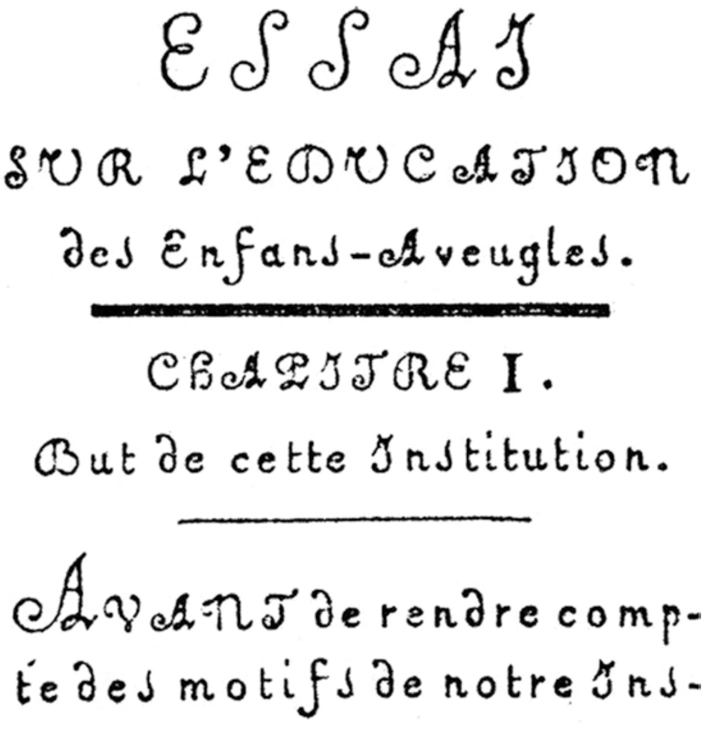
One innovation rapidly followed another. Patience, one of Haüy's great virtues, was finally rewarded. He thought, "[t]welve years of meditation followed the conception of this project until the moment I executed it." [24] When the school opened, it had three books, each made by Haüy's method of embossing heavy moist paper with letters formed from copper. The first book embossed by Haüy's technique, the first book for the blind, was his *Essai sur l'éducation des Aveugles*, dedicated to the King of France. Printed on one side of the page to preserve the relief of the letters, the work for the book was done by blind children of the school under the direct supervision of the Royal court printer. It was a laborious process but the book enabled the blind to read and represented a significant step forward. Haüy's skills as an educator were equaled by his skills as an engineer; there were enormous technical problems to solve in modifying printing presses to accommodate Haüy's printing methods, from increasing the pressure exerted by the printing presses to setting the type as 'right-reading' while normal print is set in 'mirror-image' or 'wrong-reading' to finding the right weight and strength of paper, and of course, Haüy Noire made by inking the surface of the raised letters so that what was readable by touch could also be read by sight. Each of these challenges he addressed with alacrity (Fig. 8).

Describing his efforts and techniques, Haüy wrote:

> W*e ordered typographical characters to be cast of the form in which their impression strikes our eyes, and by applying to these a paper wet, as the printers do, we produced the first exemplar which had till then appeared of letters whose elevation renders them obvious to the origin of a library for the use of the blind* [25] (p. 12).

For Haüy, the way to teach the blind to read and write was the same as teaching anyone else only the blind would learn by touch. It was essential that books could be created so that libraries for the blind could be established and it that was in that way that the blind could rise above their meager place in society (Fig. 9).

Haüy's efforts created the first school for the blind; in 1784, *the Institut National des Jeunes Aveugles* (the National Institute for Blind Youth), later renamed the Royal Institute for the Blind, was established. Before the end of the eighteenth century, schools for the blind were established in Liverpool (1791), Edinburgh (1793), Bristol (1793) and London (1799), followed by expansion throughout Europe. During Haüy's lifetime, schools for blind children were established in England, Austria, Germany, Holland, Russia, Switzerland, and Denmark. The blind education movement then spread to the United States, where the first school for the Blind was established in 1829 in Boston. Originally known as the New England Asylum for the Blind, it is now the Perkins School. The New York Institution for the Blind was established in 1831 followed a year later by The Pennsylvania Institution for the Instruction of the Blind in Philadelphia, now the Overbrook School for the Blind.



ESSAI
SUR L'EDUCATION
des Enfans-Aveugles.

CHAPITRE I.
But de cette Institution.

Avant de rendre compte des motifs de notre Ins-

Fig. 9 Cover of Haüy's Essai sur l'éducation des Aveugles

On September 28, 1791, during the French Revolution, the Royal Institute was taken over by the State and became the National Institute of Blind Workers. Haüy was dismissed and forced to retire in 1802; the school was relocated to a Celestine monastery and placed under the direction of Sébastien Guillié. Because of his royal connections he was in constant danger of arrest despite his progressive support of the revolution, Haüy fled France. While travelling east through Germany, because word of his success in Paris had spread, he was invited to a royal audience with King Fredrick and importuned him to help establish the first school for the blind in Germany. He then accepted an invitation from Czar Alexander I to establish Russia's first school for the blind at St. Petersburg. Valentin Haüy did not return to Paris until 1817. He was old, infirm and all but forgotten. On August 21, 1821, at the invitation of Dr. Pignier, the director of the Institute, Haüy returned for a visit to the school he founded. There is no record that he met one of their star pupils, Louis Braille. He died in 1822, 3 years after Louis Braille first entered the Institute as a student.

Louis Braille (1809–1852) was born in Coupvray, a small town about twenty miles east of Paris, which had a population of about 600 when he was born. Louis was the fourth child, and second son, of Simon-Rene and Monique Braille. Simon-Rene was a harness maker, working with leather and well known for his fine workmanship. Louis, intelligent and inquisitive, followed his father everywhere, often spending time in Simon-Rene's workshop watching and mimicking his father's harness making efforts. When Louis was 3 years old, he was playing by himself in the workshop with a curved awl-like tool with a cutting edge and imitating his father's movements to cut fine strips of leather. The tool slipped and gouged deeply into his eye leaving him blind in that eye. History is unclear as to whether because of an infection that spread to his other eye or due to *sympathetic ophthalmia, but* before his fifth birthday, Louis Braille was completely blind.

Although his parents were not wealthy, they were educated—both Simon-Rene and Monique Braille could read and write, something quite unusual for their social class and they wanted their children to learn and be educated, as well. Louis‘blindness presented an enormous challenge. Simon-Rene used upholstery tacks with rounded heads hammered into wood strips to form the letters of the alphabet and allow Louis to feel the shape of each letter. Each strip contained tenletters. Each day, Louis worked for hours to learn the shape and name of each letter. Unlike *Haüy's* method of single letter on each block developed more than 40 years earlier, which was, unknown to Simon-Rene, the strips allowed Louis learn letters quickly by touch, but would make learning to spells words harder since the raised letters on strips couldn‘t be separated. Louis then learned to write and to carefully and accurately form each letter and link letters into words. While Simon-Rene was motivated, he was not an educator and unable to challenge Louis' intelligence and inquisitiveness. Coupvray had a small school and the local priest helped Louis join with the other children in the one-room classroom. Although the only blind child, Louis was able to keep up and often surpass his sighted classmates. While he was able to write, thanks to his father's teaching, albeit slowly, there was nothing for him to read [26]. His learning was limited to what he could memorize. His memory was prodigous, but not without limits. Louis remained living at home with his parents, attending the local public school. The same local priest who helped Louis enroll in the small school helped him take the next step in his education. Louis' father received a letter from Sébastien Guille, Director of the Royal Institute for Young Blind, that a place was available for Louis at the Institute. The only requirement that Louis had to meet was obtaining a Certificate of Poverty from the Mayor of Coupvray that would allow Louis' education to be provided by the government. At age ten, Louis left for Paris with his father. When Louis enrolled in the Royal Institute, the school was already well established. On January 15, 1819, Louis Braille's name was entered on the school's registration log and on February 15, 1819, at age ten, he became student number 70, the youngest enrolled at the Institute.

Louis enjoyed school. The work he had done with his father to learn the alphabet and spelling by touch coupled with his industrious and inquisitive nature made him stand out. Later, when a teacher at the Institute, he commented to his students about the good fortune,

> *… of going blind so early in life. The older you are when blindness comes, the harder it is to adjust. Being able to adapt when growing up makes being without sight more a handicap than an affliction. The spirit is not crushed as heavily as being sightless in later years. That is why knowledge is so important to us younger people. We do not want to be shut away from the world because we cannot see and so we must work and study to be equal with others, not to be despised as ignorant or objects of pity. I will do all in my power to help you all attain dignity through knowledge* [27].

Louis' blindness was acquired, but his comment was prescient and still rings true. Issues of congenital vs. adventitious blindness and understanding the importance of age at onset of blindness remain topics of considerable interest today. While the youngest at the Institute, Louis was soon identified as one of the brightest and best students. He studied and worked incessantly, not content to be idle. Two years later, in 1821, while a student, Braille learned of a communication system devised by Captain Nicolas Charles Marie Barbier de la Serre, an artillery captain in the French Army. Barbier visited the school to share his invention of “night writing,” a code of dots and dashes pressed into thick paper. Made without light and read by touch, Barbier's method let soldiers share information on the battlefield without having to use light in order to or needing to speak. Barbier's ‘letters' used combinations of raised dots arranged in a rectangle with twelve points in two vertical columns of six positions each for each character, without punctuation. Barbier's system was not used by the military for whom it was developed and he believed the system would be useful for the blind. During Barbier' visit to the Institute, there is evidence that among the students with whom he spoke was Louis Braille. Slight and young, Braille was, nevertheless, vocal about what he perceived as the system's shortcomings. Barbier made no changes to his system following his visit to the Institute and conversation with young Louis. He was pleased that the students instantly accepted his method and were excited to have a way to write and read that would allow them to take notes and communicate with one another (Fig. 10).

Louis Braille was excited too but while recognizing the potential, he saw the limitations of Barbier's system. He worked every spare moment to address the shortcomings of night writing. He knew that "there could be no emancipation for the sightless without learning through books." [28] The size of each character presented a substantial problem because it meant that a normal sized finger could not cover one character. Barbier's system was phonetic and did not provide punctuation; it was based on counting dots rather than the idea that a combination of dots that can form a 'character' that can be read by touch, much as a letter in the alphabet can be read by people with sight. Braille was intrigued by the challenge and immediately began addressing the shortcomings of Barbier's system. Although Braille was five when he lost all vision, as a child there is little doubt that he saw men playing with dominoes, a game developed in Italy but which spread quickly throughout France. History is unclear, but the similarity between the 'domino six'—the six dots on dominos—and the Braille cell is unmistakable; by reducing the number of dots from 12 to 6, Braille immediately addressed a major limitation of Barbier's method [29] (Fig. 11).

When working to improve Barbier's system, Braille had another remarkable insight: when people with sight read, the eye transmits information to the brain, which "reads" or interprets what the eye saw. It was the brain not the eye that gave meaning to what was perceived. Why couldn't the fingertips do the same thing for those who were blind and communicate with the brain through touch, just as reading by sight? The insight that fingertips could rapidly present information for the brain to interpret, and that this could be done as quickly and as instinctively as reading through sight, unlocked learning for the blind. By 1824, at age 15, Braille completed his modifications of Barbier's system simplifying its form and maximizing its efficiency (Figs. 12 and 13).

Fig. 10 Charles Barbier de La Serre

Fig. 11 Louis Braille, from a daguerreotype taken soon after his death

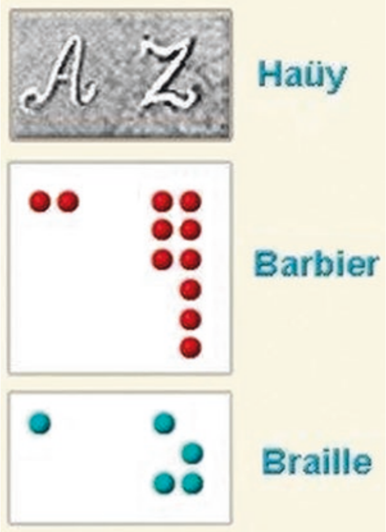


Fig. 12 Comparison letters A and Z in three forms of tactile writing

In 1829, Louis Braille published a thirty-two page monograph explaining his system for writing [30]. The modification necessary to assure success of the Braille writing system was the elimination of dashes because they were too difficult to read. Each character was composed of dots in one of six positions and it was their position rather than their shape that determined the letter or symbol the dots represented. Most importantly, by making each letter smaller than Barbier's, Braille's smaller cells composed of dots in six positions could be recognized with a single touch of a finger without the need to scan vertically. He worked with Gabriel Gauthier, a new friend from the Institute and a gifted organist, on a method to place the dots uniformly and spaced evenly and compactly, something that had eluded Cardano several centuries earlier. The Braille writing device they created in 1825, a *planchette*, was based on a slate developed by Barbier and is remarkably similar to the Braille slate that is still used. Braille included the alphabet, numbers, punctuation marks, mathematical symbols and basic notation for music so that the newly created 'Braille code' could be adapted and used for all forms of written communication [31]. The 1829 music code was elementary: there was no way to indicate the time value e.g., a half-note or quarter-note, the clef, octave or time signature. Braille excelled in playing the cello and organ and, as was true for many blind musicians, had an excellent 'ear.' On summer vacations, when he returned to Coupvray, he tuned pianos for the local residents. Within few years after arriving at the Institute, while still in his teens, Braille's musical talent led him to become the organist at L'Eglise de Saint Nicholas-des-Champs and shortly thereafter, moved to the more prominent L' Eglise Saint Vincent de Paul.

Braille's friend Gauthier no doubt provided stimulus for further development of the music Braille code. In 1837, Braille published a book in Braille [32] and presented the second edition of his monograph [33] to which he added additional symbols for math and devoted more attention to his system for music notation, addressed the shortcomings of his earlier system (Figs. 14 and 15).

Braille cells dots are arranged in two columns of three dots each, with each cell representing a letter or character or symbol. The same six dots are used for literary Braille and music Braille. In music Braille, dots 1, 2, 4 and 5 are used to indicate a musical note's pitch, e.g., the actual note 'C' or 'D' or' E', while dots three and six are used either individually or together in combination to provide time values. Each of the notes in a scale, following the French Solfège system (in English, do, re, me, fa, so, la, ti), had the same Braille notation and 'do' would be fixed at 'C' with octaves indicated by a mark or code preceding the notes. Other earlier omissions were also addressed. Blind musicians were now able to read and play music transcribed into Braille without having first having to hear the music to acquire the essential musical elements. The revised music Braille code gained instant acceptance, as it far superior to any other notation system for blind musicians. One obvious note: A blind musician may be able to read and learn a piece through Braille, but he must memorize it since instruments require two hands making it impossible to read music and play it at the same time. Over the years, there has been expansion and refinement of music Braille and these are consolidated in the Music Braille Code of 2015 [34], more than 400 pages in length, which exhaustively details the current music Braille code and is the definitive resources for state of art

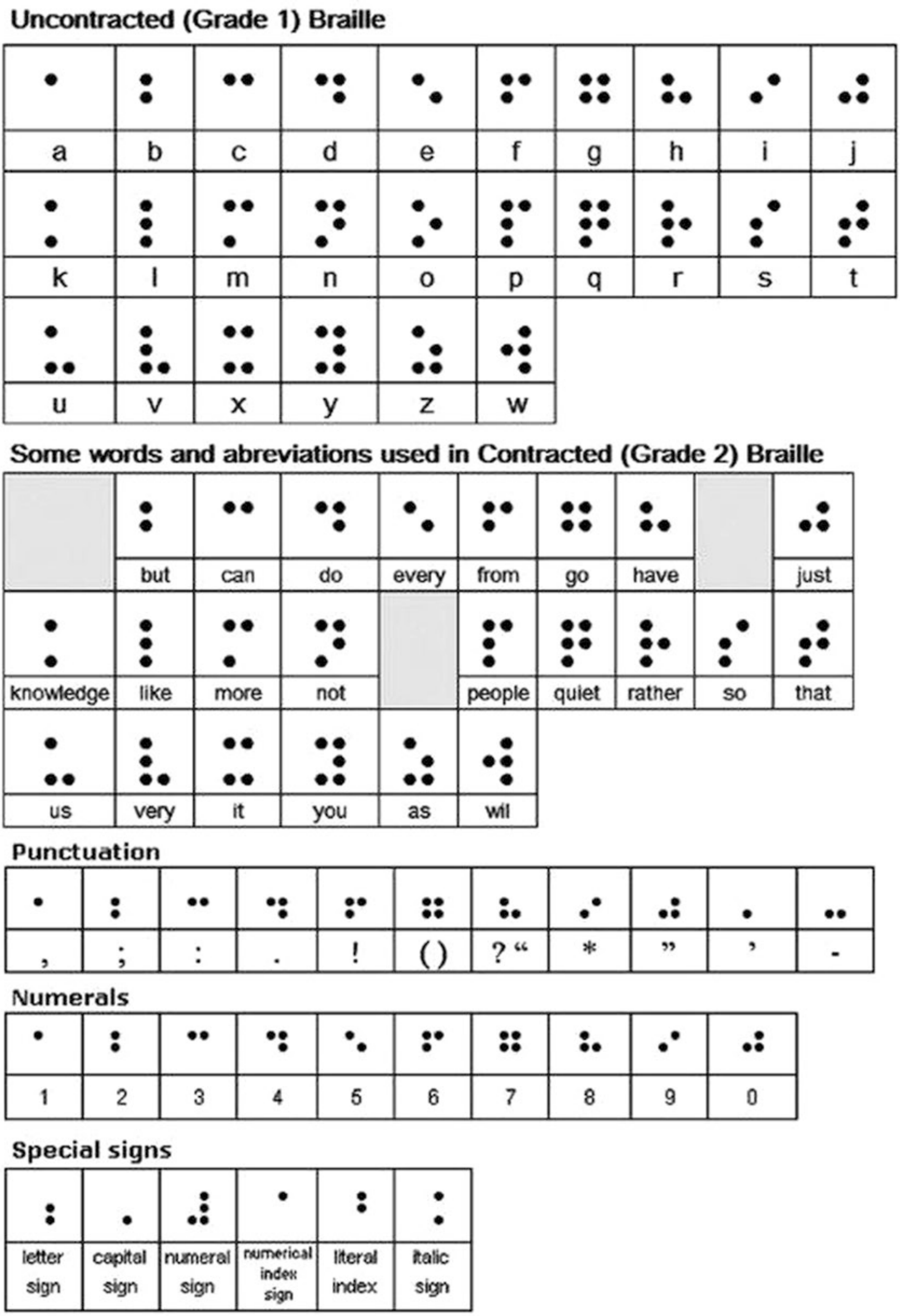


Fig. 13 Braille reference card, in English

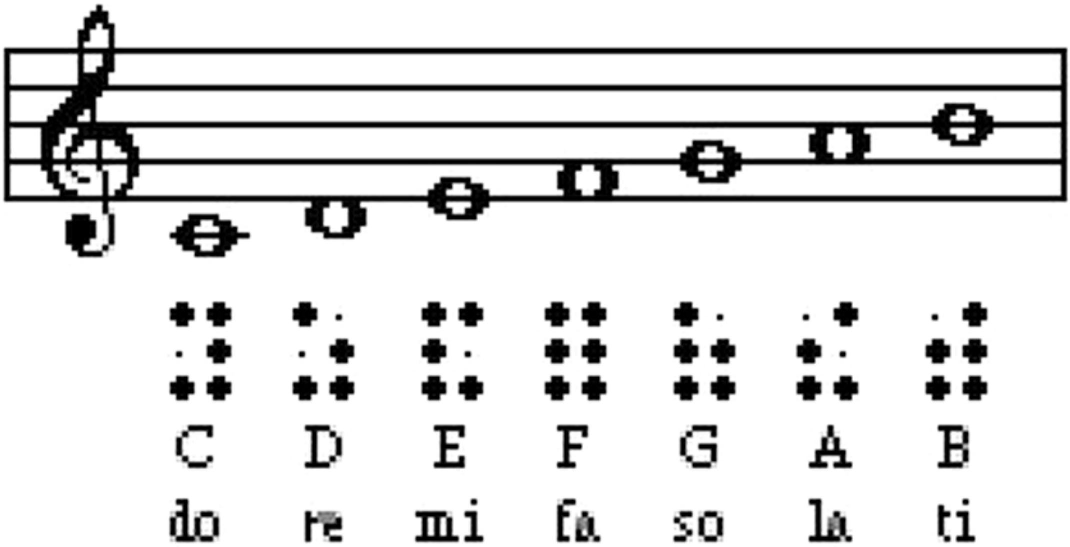


Fig. 14 Braille music note representations

Fig. 15 Braille music time values

Time Value	C	D	E	F	G	A	B
Whole or 16th	⠽	⠵	⠯	⠿	⠷	⠮	⠾
Half or 32nd	⠝	⠕	⠏	⠟	⠗	⠎	⠞
Quarter or 64th	⠹	⠱	⠫	⠻	⠳	⠪	⠺
8th or 128th	⠙	⠑	⠋	⠛	⠓	⠊	⠚

information on music Braille notation and usage. Nevertheless, today's Braille music would be readily recognizable by Louis Braille and his contemporaries.

Louis Braille understood the importance of writing and reading and he worked tirelessly to develop communication for the blind. In 1841, he commented:

> *Access to communication in the widest sense is access to knowledge, and that is vitally important for us if we are not to go on being despised or patronized by condescending sighted people. We do not need pity, nor do we need to be reminded we are vulnerable. We must be treated as equals—and communication is the way this can be brought about* [35].

The second edition (1837) of Louis Braille's system remains substantially untouched today, although enhancements have evolved to provide contractions and shorthand techniques to make reading and writing faster. His insights created not only a method for reading, writing, but also allowed blind musicians to read, learn and transcribe music. In the United States, there are no data on how many musicians use Braille's music notation system, however, 2014 data indicate that

5147 blind students use Braille as their primary reading medium [36].

Just as technology changes lives of people without vision loss, so too have technology developments changed the lives of people who are blind. Many devices and applications such as cell phones and GPS technology can be used without modification or adaptation while other devices are designed specifically as assistive technology to enhance and enable everyday functioning primarily for individuals with low vision, although increasingly, devices for individuals who are blind are emerging, as well. For example, screen readers are able to translate the contents of computer screens and change visual text to audio output, closed circuit televisions (CCTVs) can greatly magnify printed text, 'glasses' with artificial intelligence transmit images to a retinal prosthesis allowing people who are blind to see, technologies are being developed that encode visual signals and allow them to be decoded and transmitted to the brain to produce detailed cortical representations of images, computer-based tactile output devices produce 'refreshable' Braille so that a book or other text can be stored in a small book-sized device and present the material on a braille display array one line at a time and the list of advances changes almost daily. That said, while people with computers to find information—Google has become ubiquitous—books and libraries are still used, even if they are accessed via computer. Although technology may someday replace Braille, that time has not yet arrived. While as many as 70% of blind individuals in the U. S., are unemployed, of those who are employed, it is significant that 80% use Braille. Braille is accepted worldwide and, for now, remains an essential element of blind literacy, fulfilling Haüy's and Braille's dreams.

Recent research has established that cortical areas that are usually used by vision can be activated by other senses [37], and that tactile discrimination in individuals who are blind is superior to those who are sighted, something noted by Darwin:

> *When we direct our whole attention to any one sense, its acuity is increased; and the continued habit of close attention, as with blind people to that of hearing, and with the blind and deaf to that of touch, appears to improve the sense in question permanently* [38] (p. 361)

While tactile acuity is enhanced by loss of sight [39], it can be improved through training, with finger size being a limiting factor [40]. Importantly, by reducing the size of the size of the cell for each character from 12 in Barbier's system to 6 in Braille's, Braille had intuitively, without the benefit of modern neuroscience, accomplished an essential step for the universal acceptance of his code by making each cell able to be read, without scanning, by one's fingertips. That said, "[t]he neural representation of nonvisual sensory stimuli is different in blind people," [41] (p. 2230) which may be a result of cortical reorganization that follows loss of vision, but early visual experience may also play a role. The visual cortex is invoked in tactile tasks demonstrating cross-modal responses and neural plasticity [42]. Interestingly, when sighted subjects are subjected to visual deprivation over a period of time, their sense of touch improves [43]. Modern science can help to explain how Braille works, but not the insight that created it.

Haüy and Braille stood on the shoulders of giants. Cardano and de Terzi presaged the development of Braille and the need for education to fulfill the potential of individuals who are blind, while the genius of Locke, Descartes and Diderot helped create the *zeitgeist* that expanded social awareness and societal receptivity for change. Haüy established the educational environment and Louis Braille had the intelligence, insight, personal knowledge and perseverance that has changed the world for the blind. Each reflected Louis Pasteur's wisdom that fortune favors the prepared. Neither's accomplishments could have reached fruition without the other. Together they changed the meaning of what it is to be without sight in a sighted world.

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6

Jan Evangelista Purkinje: Visual Physiologist

Gerald A. Fishman and Marlene Fishman

Johann Evangelista Purkinje was an experimental physiologist whose investigations encompassed a wide radius of interests including subjective sensory phenomena, visual physiology, anatomy, and pharmacology. His prodigious scientific investigations, which, spanned a segment of the nineteenth century, left an enduring legacy of insight and innovation that, even today, inspires various subspecialties. His discoveries facilitated the development of new scientific disciplines such as the field of neuroscience and cellular physiology. He tenaciously pursued the doctrine that scientific knowledge should be predicated on experimental observations in the laboratory and not theoretical speculations. Because of his methods of investigation, he was generally considered the founder of experimental physiology. Purkinje was both a dedicated and admired teacher and an innovator in the development of original mechanical devices that facilitated new discoveries. On a personal note, he was known for his superb intellect, his excellence as a teacher, and both his kindly and generous behavior. Purkinje had a talent for music and both sang in a church choir and played the violin (Fig. 1).

Jan, or Johann, Purkinje was born on December 17, 1787 in Libochovice, a small village in northern Bohemia (then part of the Austrian-Hungarian Empire and subsequently the Czech Republic). Purkinje was the first son of Josef Purkinje and Rosalia Safranek. His father suddenly died in 1793 when Jan was only 6 years old.

In 1797, at 10 years of age, he was sent to a Piarist order monastery at Mikulov in Moravia. Their curriculum, unlike the Jesuit schools of that time, taught natural sciences including math, physics, and biology, all of which helped to prepare Purkinje for his future career. Although Purkinje's original intent was to follow the priesthood and teach, he left the Piarist order in 1807 "*to be more free and to deal more freely with science*." To satisfy this goal, he entered the Department of Physiology in Prague as a student where he developed his interest in the natural sciences. It was this interest in science that subsequently led to his acceptance in medical school in 1813 at the Charles-Ferdinand University in Prague when he was 26 years old. His doctoral thesis for graduation from medical school was defended in 1818 and published in 1819. It was entitled "Contributions to the Knowledge of Vision in its Subjective Aspects." This thesis led to the interest and support of the accomplished poet and scientist Johann Wolfgang von Goethe, who shared similar interests. After completing his MD degree in 1818, he did not consider a clinical

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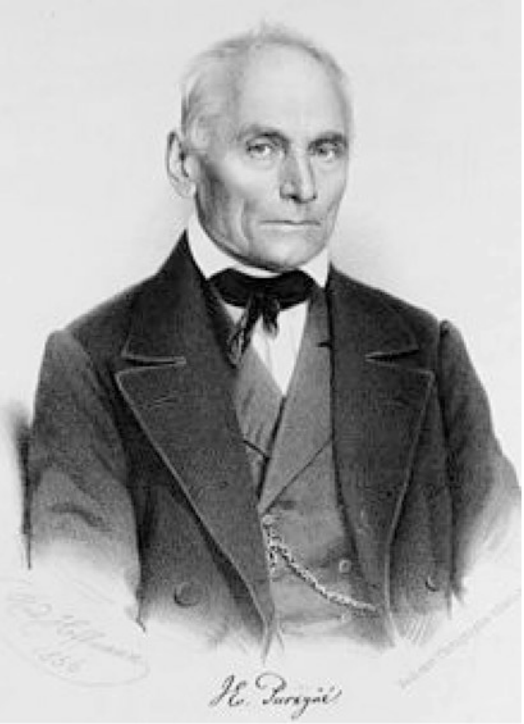

Fig. 1 Lithograph of Purkinje by Rudolph Hoffman, 1856, after a photograph by Bertsch and Aaraud in Paris. From: Wikipedia.org and monoskop.org (public domain)

medical practice but rather chose to pursue a career in experimental physiology and pharmacology. Five years later, in 1823, he accepted an appointment as Professor of Physiology and Pathology in Breslau, Prussia, where his scientific career ultimately flourished and where he founded the world's first independent, experimental, Physiological Institute in 1839 (Fig. 2).

His appointment at Breslau was contentious. With the influence of Goethe, as well as others, including his future father-in-law, Karl Asmund Rudolphĭ (1771–1832), Berlin Professor of Anatomy and Physiology, Purkinje was chosen over another candidate who was favored by the Breslau faculty. Initially Purkinje encountered appreciable resistance. As a Czech nationalist, he was an outlier in a land where Germanization of the populous was beginning to accelerate. The upper class segment of the population, such as those who were professors at the University of Breslau, were most often of German decent. Certain professors were particularly aggressive in hindering his research and adjustment to his new surroundings. In the end, Purkinje succeeded in spite of their hindrance. Nonetheless, he was often treated with

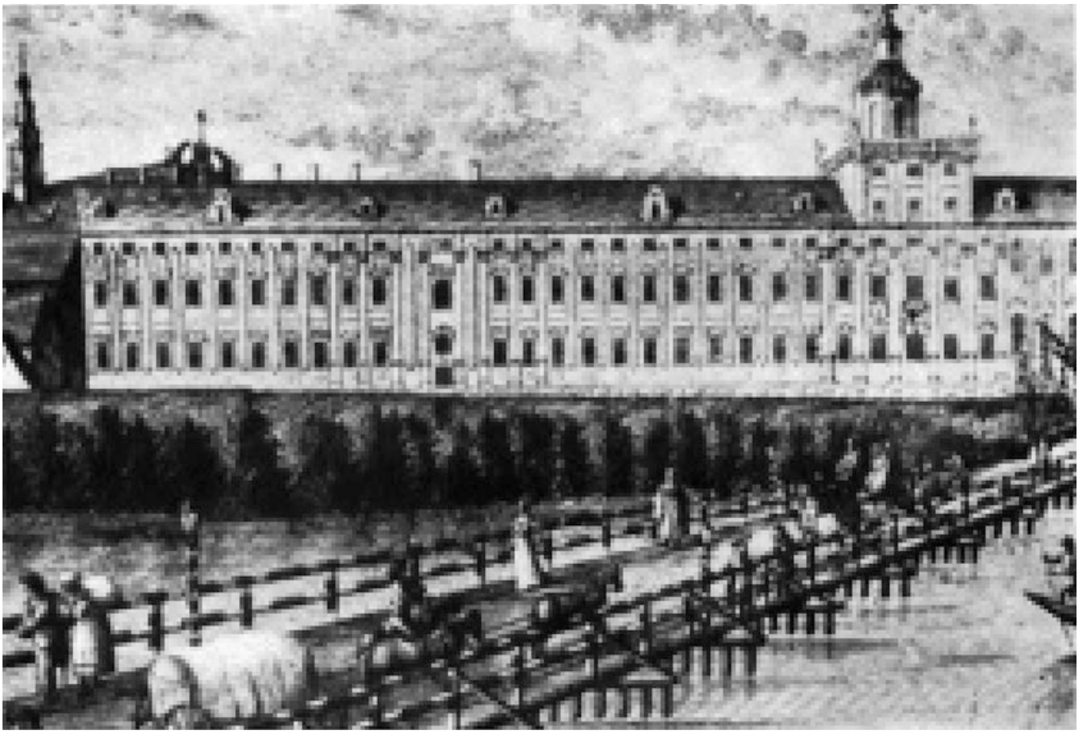

Fig. 2 University of Breslau. From: http://monskop.org/Jan_Evangelista_Purkyně (public domain)

Fig. 3 Physiological institute in Prague. From: http://monoskop.org/Jan_Evangelista_Purkyně (public domain)

suspicion and followed by the Breslau police [1]. In comparison, his devotion to this fatherland in Prague was limitless. He supported nationalistic issues aggressively. Purkinje participated in promoting Czech poetry, literature, and scientific publications so that his countrymen would be recognized and respected [1]. In April, 1850, he left Breslau and returned to Prague where he became the Chair of Physiology at the University. One of his primary goals at Prague University was to establish a physiological institute which he accomplished in October, 1851 (Fig. 3).

While Jan's native language was Czech, the scope of his linguistic talents included Latin, Greek, German, Polish, French, English, Hungarian and Italian, among others. He used the Germanic version of his name (Purkinje) while in Germany and in most of his scientific publications and the Czech version (Purkyně) in his correspondence with Czechs and subsequent to his return to Prague in 1850.

In 1827, at 40 years of age, Purkinje married his wife Julia Rudolph. They had two daughters, Rosalie and Johanka, and two sons, Karel Purkyně and Emmanuel von Purkyně. Tragically, both daughters died from cholera in 1832 during an epidemic in Breslau. In 1835, his wife Julia, died of either typhoid fever or a disease that affected her central nervous system, possible meningitis. He never remarried.

The study of overall visual function was both Purkinje's initial and his most sustained scientific interest throughout his diverse scientific pursuits. He continued his interest in various objective and subjective optical phenomena during the latter part of his career. His inaugural lecture at the University of Breslau in 1825 included discussions that related to his research on accommodation, peripheral vision, and "long and short" sightedness. Also included were topics on strabismus, the Purkinje shift, motion after images, and vertigo. While Purkinje pursued his study of vertigo in an experimental setting, the development of vertigo continues to be used as a clinical test for vestibular function. Purkinje helped to define a new era of study, that being subjective visual phenomena such as stroboscope patterns, effects of galvanic stimulation, pressure figures, visibility of retinal blood vessels and blood flow, other entoptic phenomena, and after images, among others. He was curious and highly motivated to identify the objective, physiological explanations of these subjective impressions. In so doing, he impacted upon the advancement of contemporary neuroscience (Fig. 4). Purkinje's initial studies of vision were conducted prior to when the accelerated development of various investigational instruments had occurred and thus his early experimental observations of visual phenomena were made without the use of more sophisticated laboratory equipment [2]. Nevertheless, his observations had a sizable impact on the study of sensory physiology.

Fig. 4 Portrait of Purkinje from an illustration in Posoinrěková (1955), included on page 27 in reference #2. From: http://www.pinterest.com/pin/154740937166756935/ Explore these ideas and more (public domain)

Purkinje had a notable difference in visual acuity between his two eyes, the right eye being considerably better than his left. The later was defective since childhood. It is estimated that his right eye was myopic and his left hyperopic and slightly astigmatic. In his 30s, his right eye was alleged to require four diopters of correction [2]. This ocular asymmetry in vision was a hindrance for obtaining precise measurements during various investigations as it was necessary to predominantly use his right eye. In spite of this infirmity, he was yet capable of being accurate in his experimental observations.

The scope of Purkinje's scientific interests was wide [3]. While some of his observations had also been made previously by other investigators, his investigations often resulted in more precise and comprehensive descriptions of various phenomena. In general, Purkinje's scientific interests can aptly be categorized into broad topics including investigations in subjective sensory phenomena, physiology, anatomy, and pharmacology. Within these categories reside many of Purkinje's contributions to ophthalmic science. Some of those with the strongest interest and importance are selected for further discussion. They represent only a small sample of his interests and productivity in the above topics of sensory phenomena and physiology.

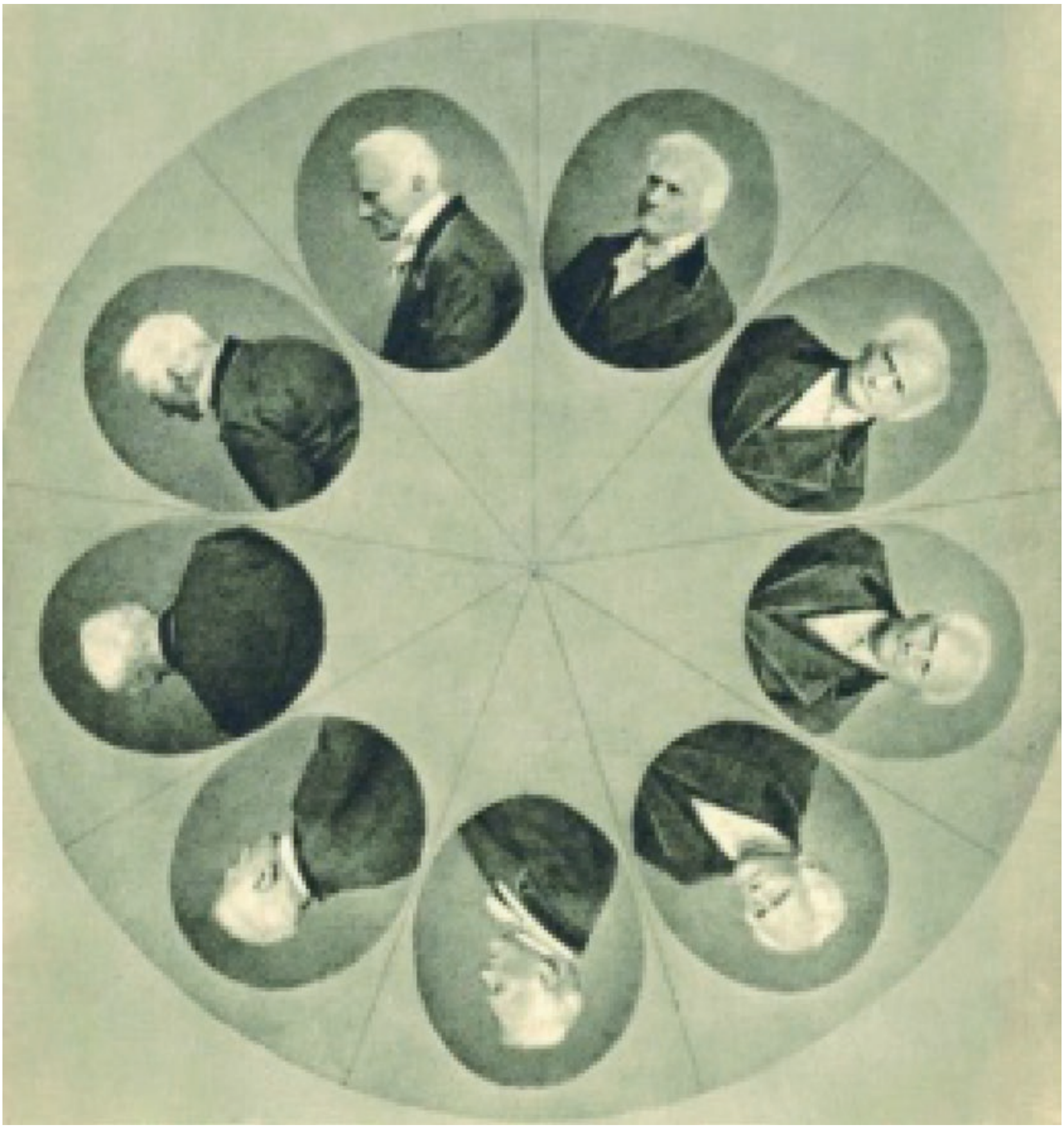

Fig. 5 Purkinje kinesiscope disc showing portraits of Purkinje, 1865. From: http://monoskop.org/Jan_Evangelista_Purkyně (public domain)

Development of the Ophthalmoscope and Other Clinical Instruments

In his 1823 academic acceptance dissertation, published while he was at Breslau, Purkinje was the first to describe a method for illuminating the interior of the eye. It was therefore Purkinje who discovered the illuminating principle ultimately used by Helmoltz in his ophthalmoscope, as well as the principles by which an ophthalmoscope operates. Using these principles, he examined the interior of the dog, cat, and human eyes. His work was published in Latin by Breslau University and preceded by 27 years, nearly three decades, Helmholtz's description of the ophthalmoscope [4, 5]. While Purkinje recommended his method for clinical use, he did not follow through with further development and promotion of his instrument. As a consequence, 24 years later, Ernest Brücke of Vienna, and E. von Erlach

[6] rediscovered the same method of illuminating the eye and provided Helmholtz the necessary information for his development of the ophthalmoscope. It is noteworthy that in an article by Thau it is cited that the word ophthalmoscope was first said to have been used by Anagnostakis who constructed an instrument with a similar purpose in 1854 [7].

Purkinje is also credited with having developed the first stroboscope and kinesiscope (Fig. 5). The stroboscope he initially constructed in the 1830s and an improved version in 1840 that he called the phorolyt. It consisted of two revolving cylindrical drums that produced moving pictures of the heart muscle and heart valves, among other images. A version of his kinesiscope was manufactured in Prague in 1860. It consisted of a rotating drum upon which drawings were placed. Purkinje used this instrument in his lectures to demonstrate animal movements. It also demonstrated the opening and closing of the heart valves in addition to the contraction of the auricles and ventricles of the heart. He was thus a pioneer of scientific cinematography.

Purkinje additionally laid the foundation for the development of an ophthalmometer, ultimately credited to Helmholtz. This instrument facilitated the measurement of changes in the curvature of the cornea as well as the anterior and posterior surfaces of the lens. This measurement helped to resolve several contradictory theories as to the process of accommodation. He also developed a simplified perimeter that facilitated a more precise estimate for the boundaries of peripheral visual fields. With this instrument, he determined the peripheral field limits of color vision and observed that yellow and blue colors were visible at slightly greater peripheral locations than were red and green and he discovered that all colors were more visible in the temporal compared to the nasal field.

Description of a Shift in Light Sensitivity of the eye during Dark-Adaptation (Purkinje Shift)

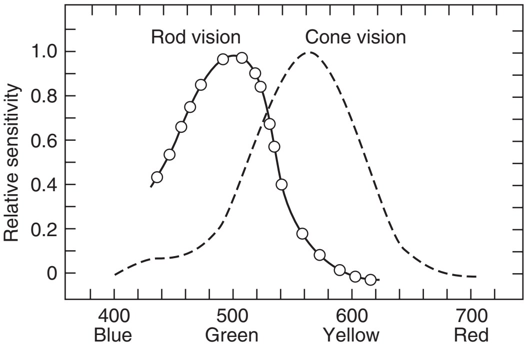

Fig. 6 Rod and cone light sensitivity curves on which the Purkinje shift is based. From: http://www.csus.edu/indiv/w/wickelgren/psyc103/classvisionone.html. The Visual System: Neuron to Higher Level Processing (public domain)

It was in 1825 that Purkinje described the effects of ambient illumination on the visibility of spectral colors and their apparent brightness which he originally published in German. The Purkinje shift, or Purkinje effect, refers to the observation that reduction in luminance from daylight (photopic) levels to night (scotopic) levels results in a measurable change in visual spectral sensitivity as blue light becomes more readily perceived than red. This observation implicated a duplex organization of the retina (Fig. 6). During daylight, vision is mediated by the cone spectral sensitivity function while night vision is mediated by the rod spectral sensitivity function [8, 9].

Purkinje himself did not attribute great significance to the phenomenon [2]. He noticed its occurrence by chance while walking in the Bohemian fields when he noticed that his favorite flowers appeared a bright red on a sunny afternoon but very dark at dawn. He surmised that the eye has two different systems for the perception of colors, one for bright intensity light, and another for dusk and dawn. The term “Purkinje phenomenon” was coined by two French physicians, J.M. de Lepinay and W. Nicati, in 1882 [10]. Earlier recognition of a similar phenomenon were said to have already been made by both Aristotle and Leonardo da Vinci, although not with the same comprehensive clarity and sophistication as defined by Purkinje [11]. Reference to this observation can also be found in the Koran where it is described that there are times when a red and subsequently a blue thread will become more visible [12]. In the earlier part of the nineteenth century, Mathias Koltz had observed a difference in color vision under different levels of illumination [13].

Description of Visual Entoptic Images

Purkinje was not the first to observe the negative shadows cast on the retina by the retinal blood vessels when elicited by a moving source of light that illuminates the retina when directed through the sclera. In 1803, Sir Charles Bell (1774–1842) realized that the shadow phenomenon was related to the retinal blood vessels. Purkinje specified the characteristics of the phenomenon in greater detail and illustrated the appearance of the blood vessel shadows [2]. As such, the phenomenon became referred to as the “Purkinje tree.”

This technique continues to have a useful application. The Purkinje test has been used to pre-operatively evaluate the visual potential for eyes undergoing surgery for a cloudy or opaque media. When a vascular pattern is observed, there is a good probability that reasonably substantial macular function is present, while if no vascular pattern is seen, it is more probable that the eye will have reduced macular function [14].

Based on personal observations with his own eyes, Purkinje also made observations referable to floaters, which were termed *mouches valantes*. He reported seeing several at the same time and described their motion as that of “falling stars.” Purkinje also described and illustrated the circulation of blood in the retinal blood vessels, previously observed in 1703 by Boerhaave and in 1789 by Robert Doiven. Purkinje, however, better described and illustrated this entoptic phenomenon [2]. His interest in entoptic phenomena lead him to investigate the findings that prolonged pressure applied to the eyeball produced small patches of light referred to as phosphenes. This phenomenon was noted even in darkness. Purkinje explained this sensation as occurring from oscillations from the interior of the eye. It had previously been described by Alemaeon approximately 2500 years earlier and by several others, such as Descartes, Newton, and Morgagni, with various interpretations as to their origin [2].

Description of Catoptric Images

In 1823 while in Breslau, with the use of the flame from a candle, Purkinje observed four reflected images from the refracting surfaces of the eye (Purkinje images). These reflections arose from the anterior and posterior surfaces of both the cornea and lens (Fig. 7). An understanding of these catoptric images contributed to the development of the keratometer. Additionally, Purkinje suggested that the reflected image from the cornea could be used to measure its curvature, a principle that was a basis for development of the ophthalmometer.

In 1837, Sanson, a Parisian oculist, without prior knowledge of Purkinje’s discovery, independently described these images. As such, there are those who prefer the term Purkinje-Sanson to describe this phenomenon. These images had previously been observed by Thomas Young (1773–1801) and, considerably later, comprehensively investigated by Helmholtz and were the basis for his investigations into the refraction of light by the eye.

Motion Aftereffects

In 1820, Purkinje reported on a type of apparent motion that was dependent on visual stimulation. It can be elicited by observing, for an extended period of time, a sequence of spatially distinct objects such as a long parade, moving water, or

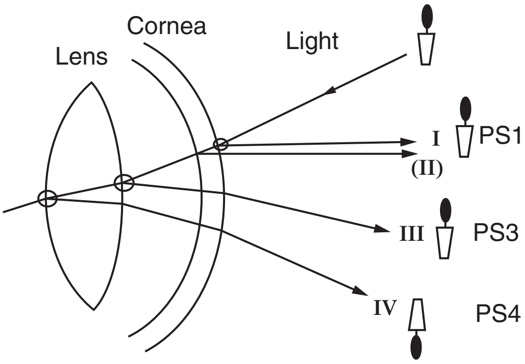

Fig. 7 Diagram illustrating the basis for the Purkinje images from the surfaces of the cornea and lens. From Internet: Purkinje Images by Kevin L. Ferguson. Typecast. How Can Film Speak of Writing? (public domain)

the spokes of a wheel not moving too quickly. When the movement of the objects stop and the observer fixates on a stationary object, this object will appear to move in the opposite direction [2].

Motion aftereffects had previously been described by both Aristotle and Lucietius. Purkinje provided an interpretation of the direction in which the aftereffect motion was observed to occur opposite to that of the prior motion. The motion aftereffect phenomenon had a subsequent impact on more modern day research relating to visual motion and as such was seen as having an impact on linking the psychology of vision to its underlying neurophysiology. Other notable nineteenth century figures in visual science, such as Müller, Helmholtz and Mach added knowledge to a better understanding of motion aftereffects [2].

Additional Contributions

In addition to contributions on ocular related investigations, Purkinje pursued an abundance of work on non-ophthalmic topics that fall under the rubric of anatomy and pharmacology. Four of these of particular interest are discussed.

Purkinje capitalized on the use of the achromatic microscope that had become available to him in 1832 over the protestations of colleagues who saw no reason why a physiologist should need such a device [15]. This instrument incorporated an achromatic lens that was added to a compound microscope notably improving its efficiency that facilitated greater visibility of small anatomical structures of both human and animal tissues. This enhanced magnification led to the identification of the Purkinje cells of the brain and Purkinje fibers of the heart. Purkinje is credited for the first lucid description of nerve cells and their processes in the brain and spinal cord. The Purkinje cells of the brain, discovered in 1837, are large neurons with branching dendrites that were identified in the cerebellar region of the brain. The Purkinje fibers or "network" identified an important intraventricular conduction system within the heart. These fibers, discovered in 1839, conduct electrical impulses from the atrioventricular node to the ventricles of the heart. Purkinje made two other meaningful contributions to the field of cardiology including the role of the heart on venous blood return and the description of the effect of digitalis on the heart in humans.

The physiological mechanism as to how digitalis blurred vision [16] was among Purkinje's extensive pharmacological studies. Following graduation from medical school, he worked for 5 years as an assistant in anatomy and physiology at the medical school in Prague. During this period he began his research activities experimenting with several medicinal substances that were in use for various conditions.

Purkinje was dissatisfied with medical research on drugs. At the time, knowledge of the effect and dosage of various drugs were in their very early stages and quite inadequate as they were all too often based on the use of experimental animals or a speculative approach rather than a rational, experimental verification basis. For these reasons, as well as his interest in the sensory and mental effects of various drugs [16, 17], Purkinje decided to experiment on himself, experiencing considerable discomfort and potential risk. Among his most noteworthy studies were his experiments with digitalis.

Over a 4 day period, Purkinje deliberately ingested an overdose of digitalis, the equivalent of nine times the lethal dose for a cat. For 15 days he experienced photopsias and black spots in his vision. His heart rate slowed and skipped beats. Purkinje also studied the effects of several extracts of ipecac (emetine). He additionally instilled drops of belladonna in his eyes and described the blurred vision that resulted. Further, he swallowed it and experienced its systemic effect [17].

In additional experiments Purkinje studied the toxic systemic effects for the self-administration of turpentine, nutmeg, ether, opium, and camphor to experience their sensory and general mental effects [2, 17]. After taking different doses of camphor, on one occasion he became totally unconscious for about half an hour. It took an additional full day before he regained his sense of time and awareness of his environment [17].

Purkinje conducted these experiments when he was a third year medical student. He visited a pharmacy in Prague owned by the father of a friend who provided him with the various substances [16, 17]. In total, he performed 35 experiments on himself [2]. His willingness to experiment on himself caused Goethe to refer to Purkinje as the martyr.

Purkinje's self-experimentation in pharmacology had lasting value beyond his various descriptions of the actions of individual drugs. He helped introduce a more sound basis for prescribing drugs and was possibly the first to describe the principle of drug interactions [17].

Although both the Babylonians and the ancient Chinese used fingerprints to sign documents, and the Chinese to identify criminals [18], Purkinje was the first to introduce a system of fingerprint classification and provided its detailed description. His systematic classification was introduced in 1823. In his system the papillary lines on the skin of the fingers were divided into nine parts based on their geometric arrangement [18]. Purkinje outlined how fingerprints could be used as a means of identifying individuals. This did not become recognized internationally for several years [18]. Nonetheless, his description and illustration of the furrows in the distal portion of the fingers subsequently led to the development of the science of dermatoglyphics.

Purkinje also conducted experiments on hearing, vertigo, made observations on the anatomy of human teeth, discovered the sweat glands in humans, studied the physiology of sleep, and developed a procedure by which, for the first time, photographic images could be obtained on microscopic material. In 1838, he observed cell division, and in the subsequent year he was the first to use the term "protoplasm" in the scientific literature. The diversity of his interests is underpinned by his additional investigations on the germinal vesicle in the yolk of birds' eggs [2]. These, and other, various investigations contributed to development of the cell theory, considered as likely one of the most important theories relevant to the rapid progress of both biology and medicine of the nineteenth century. Purkinje provided the basis upon which the cell theory would subsequently be developed [1]. The cellular theory was subsequently comprehensively formulated by Schwann and Schleiden.

Legacy

It was most unfortunate that his many investigations received less recognition than they deserved. Perhaps because of the accelerated rate and sheer volume of his productive investigations, he did not have enough time, or perhaps motivation, to adequately disseminate his observations. A likely more cogent reason is that his findings were frequently not appreciated because of the manner in which they became available. A majority of his publications were in the reports of the Silesion Society and other Czech publications. They also were contained in the Latin dissertations for the medical degrees of his pupils and in the summaries of various scientific congresses. Purkinje was continually experimenting and was seemingly not primarily motivated by personal gain or recognition [1]. He was more focused on stimulating thought and careful observation of details rather than following up on his observations. His discovery of a principle for an illumination source used for viewing the retina prior to Helmholtz and his subsequent pivotal invention of an ophthalmoscope is a vivid example [7].

Purkinje's collected works (*Opera Omnia*) have been published in 13 volumes. They are not assembled in chronological sequence. In 1918, the first portion of Purkinje's Opera Omnia was published in Latin. This volume contained his investigations relevant to ophthalmology as well as other studies [19]. The final volume appeared in 1985. These 13 volumes included Purkinje's various scientific contributions that appeared in journals and books. A list of Purkinje's scientific contributions, in addition to responses to them, was assembled by Kruta in 1969 [20].

Jan Evangelista Purkinje was a modest, inquisitive, courageous and visionary Czech physiologist whose vast interests and astute observations fostered a legacy of accomplishments that, even

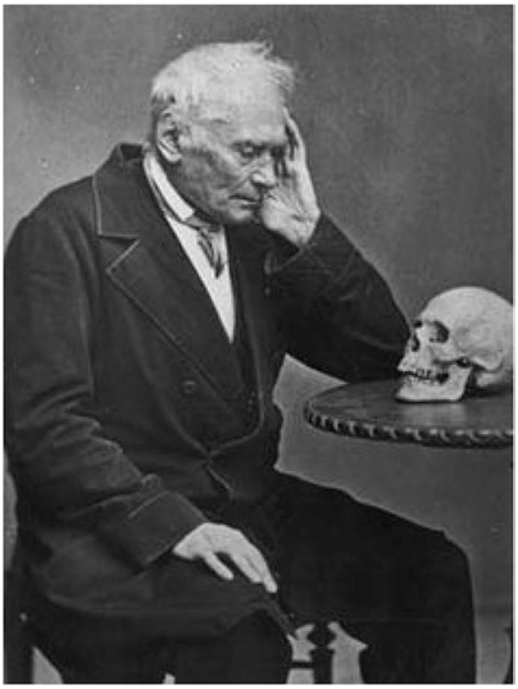

Fig. 8 Purkinje, in a reflective pose. From: http://www.pinterest.com/pin/154740937166756933/ Explore these ideas and more (public domain)

today, still impact our understanding for several aspects of visual science, general medicine, and biology (Fig. 8). It was said that "he found physiology a speculative study and left it an experimental science." [21] "Although he was not always thoroughly appreciated by his professional contemporaries, Purkinje was greatly respected, admired and loved by his Czech associates and countrymen. At his death … Purkyně was mourned by people of every class in Bohemia" [15]. It is a sad commentary that, because of limited financial means, a man such as Purkinje often could not afford to attend scientific meetings and had to work up until nearly the end of his life. He died on July 28, 1869 at age 81.

His humility and self-effacing manner are clearly in evidence in his own words, reported to have been said in 1869, just shy of 7 months before he died.

> "*I have indeed discovered various things, but, as for immortality of my name, this should not be taken literally. A hundred years hence perhaps only a few will know who Purkinje was, but that makes no difference. For indeed we do not know who discovered the plow, and yet it serves all humanity. The cause remains the same, but not the name—and that is the important thing.*" [22]

More than a century after his death, we can still appreciate the value of his substantial contributions to both visual science and clinical ophthalmology.

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7

Franciscus Donders: The Management of Anomalies of Refraction

David G. Harper

Francisciscus Cornelius Donders (Figs. 1 and 2), born on May 27, 1818 in Tilbury, Netherlands, was the youngest child and only son in a family with eight older sisters. At the young age of seven his mother enrolled him in a boarding school in Duizel where he was schooled in Dutch, French, mathematics and music. His remarkable talents already recognized by age 11, the school employed him as a tutor during the next 2 years thereby defraying some of his expenses. Transferring to the Latin School in Boxmeer at age 13, he graduated cum laude in 1835. Now 17 years old, and giving up on some earlier ideas of becoming a priest, he entered directly into the Military Medical School at Utrecht. In February 1840, he was assigned to the position of health officer in Vlissingen and in October of that year was awarded his MD degree. In 1842 Donders returned to the Utrecht Military Academy, where he taught anatomy, histology and physiology under the guidance of Gerardus Johannes Mulder (1802–1880) [1].

Donders married in 1845, and because his yearly salary of 800 guilders was insufficient to support his new family, he supplemented his income by translating Ruete's Handbook of Ophthalmology. Donders' Dutch translation was published in 1846 [2]. One year later at the age of 29, he was appointed to the special position of Professor Extraordinarius. He then added ophthalmology to his teaching duties, and according to Henry Willard Williams, MD (1821–1895), a Harvard ophthalmologist and the first American to focus his practice exclusively on Ophthalmology, Donders said, 'my teaching of ophthalmology gave a new direction to my life.' Williams commented that, "As a teacher, he was radiant; he seemed superb in the lucidity, conciseness, elegance, and adaptiveness of his style of explanations, which he often made, in several vernaculars, where he saw that he was not understood by an intelligent disciple." Donders himself said: 'To teach is as great a joy as to learn. Acquired knowledge is as a hidden treasure, which slumbers useless until it is disclosed in teaching.' Jean-Pierre Nuel (1847–1927), commenting on Donders' teaching style, stated that, "Few have equaled, none surpasses him" [3]. According to Sir William Bowman (1816–1892), Donders was, "Indefatigable in the pursuit of truth, he was as able in imparting it. Eloquence, the graces of style, and the mastery of several languages combined to make him a great teacher" [4] (Figs. 3 and 4).

Destined for a brilliant career in physiology and ophthalmology, Donders came of age during the first half of the nineteenth century when the science of refractive errors and accommodation was very poorly understood. Although, convex and concave lenses had long been used to treat

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Fig. 1 Franciscus Cornelius Donders. Photograph, 1889, Courtesy of the National Library of Medicine (public domain). Available in print quality at http://resource.nlm.nih.gov/101413833

presbyopia and myopia, the very existence of hypermetropia as a separate refractive error requiring constant accommodation to obtain clear vision at all distances, was unknown prior to the work of Donders and Helmholtz in the 1850s. Donders wrote that, "In the writings of the eighteenth century I have sought in vain for proofs that H [Hypermetropia] was observed and recognized as such, or that the existence of this anomaly of refraction was even suspected". Moving into the nineteenth century, Donders graciously credits James Ware (1756–1815) as the discoverer of Hypermetropia. In 1812 Ware read a paper before the Royal Society entitled, *Observations relative to the near and distant sight of different persons,* describing the cases of young phakic persons who required convex lenses for both distance and near in order to see clearly [5]. However, Donders admitted that Ware did not perceive "the great bearing of his discovery" And that, "With Ware our knowledge of H was lost." There were, however, throughout history, other cases of young phakic individuals noted to require convex lens to

Fig. 2 Franciscus Cornelius Donders. Photograph, Date Unknown. Courtesy of the National Library of Medicine (public domain). Available in print quality at http://resource.nlm.nih.gov/101413835

Fig. 3 Franciscus Cornelius Donders. Photograph, 1889, Contributor: Schubert, artist. Courtesy of the National Library of Medicine (public domain). Available in print quality at: http://resource.nlm.nih.gov/101413837

Fig. 4 Franciscus Cornelius Donders. Photograph, Date Unknown, Contributor: Edwards, Ernest, Courtesy of the National Library of Medicine (public domain). Available in print quality at: http://resource.nlm.nih.gov/101435075

see clearly both in the distance and near. Donders was aware that the French ophthalmologist, Janin, had probably described a similar case in 1772. A review of Jean Janin's original text shows that to be true [6]. Donders noted that the Scottish ophthalmologist Makenzie, writing in 1854, failed to understand the true nature of Ware's cases, stating that his cases seemed …"to partake more of the character of asthenopia than of presbyopia." Donders was disappointed with Mackenzie for not recognizing that …"his asthenopia might, *vice versa,* have suggested to him the idea of hypermetropia" [7].

Philip de la Hire (1640–1718) in 1694, did not believe that the eye possessed a separate focusing mechanism [8]. However, most researchers disagreed with him, and ultimately, Thomas Young, working during the last decade of the eighteenth century, proved through personal observations that the lens was the seat of accommodation. Unfortunately, he also adamantly maintained that the lens was a muscle and his work in this arena was largely ignored and forgotten [9]. Finally, anatomists and physiologists, while discounting or ignoring Young's work, settled on ciliary muscle action as at least part of the mechanism for accommodative change. Sir Phillip Crampton working in Ireland in 1813, thought that a muscle in the eyes of large birds flattened the cornea; Robert Knox in Scotland, the original discoverer of the ciliary muscle in 1823, believed it focused the eye for distance. And William C. Wallace in 1835 thought that the ciliary muscle moved the lens forward as did Donders' future friend and colleague, William Bowman, in 1849 [10].

While translating Ruete's handbook in the mid-1840s, Donders developed his own personal views regarding certain topics and became interested in ophthalmological research. He thought Ruete's belief that forward displacement of the lens brought about accommodation was incorrect and that "… Ruete tried to answer a physiological problem with a subjective opinion." In 1848, Shroeder van der Kolk (1797–1862), recognizing Donders' keen insight and inquiring mind, asked the Dutch Society of Sciences to offer a prize for the best treatise on the mechanism of accommodation. The next year, Maximillian Langenbeck began investigating reflected Purkinje images from the front surface of the lens. Although using only his naked eye to view the images, he was able to deduce a most important fact as stated by Donders: "…that *in accommodation for near objects the anterior surface of the lens becomes more convex.*" Reading Langenbeck's work, Donders stated that he was, "Struck with Langenbeck's fortunate idea…" and immediately tried to replicate his work, but was unsuccessful [7]. Donders predicted that with adequate magnification, one would see the accommodative lenticular changes noted by Langenbeck. In 1851, Donders' friend and colleague, Antoine Cramer, led by his prediction, took up the question with a microscope that he designed specifically for the purpose [11]. Donders noted that, "He comprehended its full importance, solved it in the manner pointed out by me, and so put forward his result, that its correctness was in a very short time universally admitted" [7]. Hermann von Helmholtz (1821–1894), working independently, came to the same conclusion as Cramer and published his work in Volume I of his, "Treatise on Physiological Optics" in 1856 [12]. Fortunately, Cramer's priority was established when Donders noted it in an 1853 publication, and Cramer received the 300 gilder prize money awarded by the Dutch Society of Sciences.

Travelling to London in 1851 to attend the first Great Exhibition, Donders met Sir William Bowman (1816–1892), thus beginning a lasting friendship as well as a collegial relationship that would endure to the end of Donders' life. He also met Claude Bernard (1813–1878), the founder of experimental medicine and the great Berlin ophthalmologist Albrecht von Graefe (1828–1870), who ultimately made significant advances in the treatment of glaucoma and cataract surgery. Returning home, Donders focused his clinical and research efforts on ophthalmology. Having learned about the invention of the ophthalmoscope by Helmholtz during his travels, and impatient to acquire one, he constructed a similar model himself with a concave silvered mirror in place of the glass plates used by Helmholtz. Initially, private individuals provided clinic space for Donders where he could pursue his newly chosen career path. When the clinic ultimately proved too small, his supporters raised 40,000 florins to buy a larger building. Opening in February 1859 in Utrecht with 40 beds, it soon became a teaching hospital that attracted both foreign graduates and local students [7].

Donders clinical and research efforts during the 1850s lead to the publication in 1860 of an essay in Dutch entitled, "*Ametropie en hare gevolgen* ('Ametropia and its Results')…" which, according to him "… was confined to the anomalies of refraction, and treated them exclusively from the dioptric point of view" [7]. He elaborated, writing that, "In the preface…I announced my intention of producing, subsequently to the appearance of that essay, a complete system of the anomalies of refraction and accommodation: the anomalies of refraction, including the subject of astigmatism, were to be treated also from an anatomical and practical point of view, and the anomalies of accommodation were to be developed both in their opposition to, and their connection with, the anomalies of refraction". Published in 1864 by the Sydenham Society, this grand thesis on refraction and accommodation was entitled, "On the Anomalies of Refraction and Accommodation of the Eye, with a Preliminary Essay on Physiological Dioptrics". The publication of this monumental work first in English and soon in multiple other languages introduced many new ideas and concepts to the practice of ophthalmology [7].

Helmholtz wrote about hypermetropia and accommodation in Vol. 1 of his 1866 publication [12]. However, it was Donders, devoting nearly half of his 1864 publication's total space to Hypermetropia, Accommodation and Asthenopia, who originally brought scientific understanding and clinical clarity to this new topic area. Previously, during a mutually attended meeting in Heidelberg in 1859, Donders and Helmholtz collaborated on terminology. Helmholtz suggested that the term, Hyperpresbyopia (used to describe phakic individuals who appeared to be presbyopic at a younger age than expected), be replaced by Hyperopia. Donders countered that Hypermetropia would be more consistent with the then current terminology for the other refractive states such as Ametropia and Emmetropia [7]. Both terms have survived into the twenty-first century, with Hypermetropia, as suggested by Donders, generally the more formal and preferred usage.

In Chapter II, entitled, “Defects of Refraction and Accommodation in General”, Donders stressed the “…necessity of drawing an accurate distinction between the anomalies of refraction and those of accommodation.” He was the first to state that “…whether the eye be emmetropic or ametropic, in either case it has a power of accommodation, and this may be normal or abnormal. Abnormal accommodation is, therefore, as independent of refraction as any other disease of the eye” [7]. Prior to this, investigators had no comprehension that the majority of humans with generally excellent vision had some degree of hypermetropia and required accommodative effort to achieve clear focus at all distances. It was also unknown that asthenopia with blurred vision and headache was caused by the use of excessive amounts of accommodation in uncorrected hypermetropia. To make matters worse, the use of convex lenses, which seemed to alleviate symptoms, was vigorously discouraged by many oculists as likely to lead to serious amblyopia.

Aware that he had entered the field of ophthalmology during a time when many facts and ideas were blatantly wrong, Donders addressed the issue stating, “It is not my intention to subject anew to criticism the long series of incorrect views upon the subject. I am not writing a history of errors”. However, his teaching and writings in the 1850s and 1860s did ultimately clarify many incorrect and misunderstood ideas. Donders, noted that, “Hypermetropia...once discovered and understood…speedily revealed all its mysteries, and gave us the key to a number of phenomena, whose origin had, until then, continued enigmatical: thus the source of asthenopia and of strabismus convergens was found in this anomaly” [7].

Donders’ elucidation of hypermetropia and its associated symptom complex of asthenopia brought a singularly great contribution to the science of ophthalmology of his time. Hypermetropia was, by far, the most common refractive error in the nineteenth century and before. Ware studied the incidence of myopia in several population groups and found that overall less than 10% of people were myopic. He reviewed, “three regiments of foot guards, which consist of nearly ten thousand men; and the result has been, that near sightedness, among the privates, is almost utterly unknown” [5]. Even in a population of Oxford graduates, only about 25% were myopic. The negative consequences of living with several diopters of uncorrected hypermetropia was observed in lace makers and others in occupations with equally taxing near work. After several hours, they would experience significant visual blurring and headaches. Donders called on his extensive experience to dispute the belief that correction with convex lenses lead to amblyopia, asking: “What are the results of continued excessive tension of accommodation in asthenopia?” He answered his own question by noting that he had “… never seen a diminution of the acuteness of vision arise from such a course.” He concluded with the observation that the complete relief of asthenopia by spectacles had been proven [7].

For centuries, myopia and presbyopia were thought to be opposite refractive conditions because of the blurred distance vision of myopia and blurred near vision with presbyopia. Donders pointed out “…that both in an anatomical and in a physiological point of view, myopia and presbyopia belong to very different categories. Myopia is based upon an abnormal construction of the eye; presbyopia is the normal condition of the normally constructed eye at a more advanced period of life… So little are myopia and presbyopia opposite conditions that they may both occur simultaneously in the same eye” [7]. As with many new ideas however, there wasn’t universal acceptance of this concept. The Austrian ophthalmologist, Karl Stellwag von Carion (Zeitschrift der K.K. Gessellschaft der Aerzte au Wien, 1862), for one, continued to support the idea that Presbyopia and Myopia were opposite refractive errors. Not understanding the role played by accommodation, he continued to apply the term, Hyperpresbyopia, to cases where young people required correction with convex lenses both at distance and near [7].

Myopia as a refractive error was known for centuries by the time that Donders began his studies. In discussing myopia, he found that, “Almost always the myopic presents himself before us with the statement, that he can see near objects well, while he with difficulty distinguishes at a distance, and if we place a book in his hand a book with small type, for example I or II of Snellen’s tests, the distance he chooses itself indicates about the farthest point”. Donders, by trial and error, and usually examining both eyes simultaneously, searched out the weakest concave lens that afforded the patient clear vision. He was aware that, “Many will possibly find the…directions tedious and too minute. And yet they are in many respects incomplete; so that, at the risk of incurring the displeasure of my readers, I will take leave to point out some additional sources of error.” Ever mindful of overcorrecting myopia with spectacle lenses, Donders felt that achieving a high grade accuracy in the refraction of myopes was crucial, stating that, “an incorrect determination of the degree of M [Myopia] may highly endanger the eyes”. Here, Donders reflected the fear that all ophthalmic practitioners then had concerning the correction of myopic refractive errors with glasses. Myopia in young people usually worsens over time, and the idea that the spectacle correction exacerbated this tendency was deeply entrenched. Donders did point out that low grades of myopia where progression appeared minimal were safe to correct with concave lenses on a full time basis [7].

Donders was very aware that myopia was far more prevalent in educated societies, remarking, “…on how much in the registers of my private patients (the more wealthy) the M—in those of my hospital patients, on the contrary, the H predominates”. Donders observed that, “If it were thus found—and I can scarcely doubt that it would be so, —that the M is progressive in cultivated society, this would be a very serious phenomenon, and we should earnestly think of means of arresting this progression”. Viewing myopia in very negative terms, Donders stated that, “Not only is the myope not in a condition to discharge all civil duties, not only is he limited in the choice of his position in society, but in the higher degrees M leads to disturbance of the power of vision, and threatens its subject with incurable blindness. The distribution of M, chiefly in the cultivated ranks, points directly to its principal cause: tension of the eyes for near objects. Respecting this fact there can be no doubt [7].”

In writing about astigmatism, Donders pointed to, “Mackenzie’s justly celebrated book (A Practical Treatise on the Diseases of the Eye,, London, 1854)…where…we really find almost everything comprised, which science, up to the dates of the publication of those works, possessed upon the subject under consideration.” Donders found it, “remarkable that we find the subject treated of almost exclusively in English literature.” Expanding on this note, he wrote that, “In the first place we meet with two men, of whom England may well boast: Thomas Young, who discovered normal astigmatism, and the Royal Astronomer Airy, who first recognized and described the asymmetry of his own eye as a defect.” Donders also noted that, “…we are indebted for the astigmatic lens for determining the degree of astigmatism…” to Sir George Stokes (1819–1903). News of this forerunner of the Jackson Cross Cylinder, published in, “The Report of the British Association for the Advancement of Science”, appeared in 1849 [13].

Donders began his discussion of astigmatism by restating that myopia and hypermetropia are two opposite conditions, but that, “Sometimes, however, it happens that in the several meridians of the same eye the refraction is very different”. And that, “Usually it exists in so slight a degree, that the acuteness of vision is not essentially impaired by it,” emphasizing that, “…a certain degree of regular astigmatism occurs in all eyes, and therefore cannot be considered as abnormal.” However, he noted that, “…exceptionally it becomes considerable, and occasions as aberration of the rays of light, which interferes with the sharpness of sight.” Then it, “…may be designated as *astigmatism”* [7]. Ernest

Clarke (1857–1932) noted that, “The whole subject had been very carefully and thoroughly written upon by Sturm, Fick, Helmholtz, and others when Donders published in 1862 ‘Astigmatisme en cylindrische Glazen,’ and in 1863…‘De Zitplaats van het Astigmatisme’ and added knowledge of supreme importance to the subject” [14]. Donders noted that, “The cause of regular astigmatism is to be sought partly in the cornea. Numerous measurements have shown, that the cornea in its several meridians has a different radius of curvature; and what holds good for the dioptric system of the whole eye, namely, that the maximum of curvature usually lies closer to the vertical meridian than to the horizontal, is equally applicable to the cornea, taken by itself” [7]. He thus defined “with the rule” astigmatism.

Finding irregular astigmatism to depend on the lens, Donders ascribed polyopia uniocularis to it: “The direct proof of this is furnished by the fact, that in the condition of aphakia, when the lens is wholly absent from the eye, all these phenomena of irregular astigmatism are removed” [7]. Morlet, Minassian and Dart noted in their review paper in the BJO in 2001 that, “Corneal astigmatism was characterized by Knapp and Donders in 1862 after the invention of the ophthalmometer by Helmholtz [15]. In the same year Donders also described astigmatism due to cataract surgery and soon after Herman Snellen (1834–1908) suggested that placing the incision on the steep axis would reduce the corneal astigmatism” [7]. Thus began the era of corneal refractive surgery.

Williams, the American ophthalmologist, observed in a remembrance of Donders in 1889 that, “His discovery of Hypermetropia, his explanation of Astigmatism, his indication of the relations between different forms of Strabismus and the hypermetropic or myopic conditions of refraction of the eye, were and must remain masterpieces of absolute demonstration”. He also noted that, “In 1864 appeared Donders’ monumental work on the Refraction and Accommodation of the Eye, published by the Sydenham Society at London, and soon translated into many other languages. It came to the world of Ophthalmology as a revelation—as a complete and finished creation, involving infinite labor and research—from which nothing could be retrenched without loss, and to which nothing could be added without superfluity. It created scientific ophthalmology” [3].

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8

Hermann von Helmholtz: The Power of Ophthalmoscopy

James G. Ravin

The 150th anniversary of the invention of the ophthalmoscope was celebrated in 2000. Hermann von Helmholtz (1821–1894) (Figs. 1 and 2) brought about the modern era in ophthalmology with this important invention, which, arguably, has done more to revolutionize the advancement of ophthalmology than any other invention or discovery. Before Helmholtz's instrument was available visualization of the posterior pole of the eye in a living subject was impossible. This new tool allowed observers to correlate clinical signs and symptoms with findings in the retina, vitreous, and optic nerve. The ophthalmoscope became the model for all forms of endoscopic evaluation that followed. It is comparable in importance to the telescope, a seventeenth century invention, and the stethoscope, an early nineteenth century invention.

Helmholtz was trained as a physician but spent most his career as a scientist and educator. Beginning in childhood he was interested in solving scientific problems, including optical ones. His father was a military veteran and professor of philology at the Potsdam Gymnasium, the leading secondary school in Prussia. His mother was a descendant of William Penn, the founder of Pennsylvania. Potsdam was a garrison city near Berlin that housed many elite military units and was also the formal residence of the King, Sans Souci. The family led a comfortable middle class life style but the father's income was insufficient to finance Hermann's medical education and raise six children, four of whom lived to adulthood. Hermann wanted to become a physicist or a physiologist, but a career in medicine offered him a more secure future.

Although he was a brilliant student and an affable young man, not every step along the way was easy. His initial attempt at admission to medical school at the Friedrich-Wilhelms-Institut in Berlin was rejected. He received acceptance in 1837, though, and admitted that family connections were important. A great-uncle was a leading medical figure in the Prussian army, a professor of surgery at the Charité Hospital in Berlin and a professor at the Institut. Helmholtz entered the military medical school in Berlin in 1838, where tuition was free, and passed his final examinations in 1842. He successfully defended his doctoral dissertation in Latin that same year. He did all this despite a serious episode of typhus in 1841which hospitalized him for 5 weeks at the Charité. The free tuition obligated him to 8 years of military service afterward, which he was able to shorten by

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Fig. 1 Helmholtz as a young man

Fig. 2 Helmholtz older in life

a year. A year of internship took place at the Charité in 1842–43, including a rotation in ophthalmology under Johann Christian Jungken. He obtained a coveted position as an army physician in Potsdam, where his parents lived. After fulfilling his required military service, in 1848 he taught anatomy at the Kunstakademie and served as an assistant to Johannes Muller at the Anatomisches Museum in Berlin. The following year he was appointed extraordinary professor of physiology at the University of Königsberg.

The Invention

Helmholtz invented the ophthalmoscope at the relatively young age of 29, while teaching in Königsberg. He was preparing a lecture on ocular physiology and was trying to understand why the pupil illuminated when a light was shined in and the observer was close to the light source. Previous examiners were unable to see the retina since they were too far offline or the light source was blocked. Helmholtz understood that light rays entered and left the eye taking the same pathway. It took him 8 days to answer the question and create a new instrument. By using a mirror set at an angle to the light source he solved the problem of the observer's head blocking the light source. The original mirror was made of three thin parallel sheets of glass angulated to reflect the maximum amount of light into the eye. (Figs. 3 and 4) It was difficult to use and was simplified by replacing the layers of glass with a silvered concave mirror that had a small central opening.

His first description of the ophthalmoscope took place on December 6, 1850. To establish his claim as the inventor he gave an oral presentation to a small group of scientists, the Physical Society of Berlin. He soon described the invention in a letter to his father. A feeling of pride and excitement, tempered by his Prussian sense of propriety is apparent:

"I have on the occasion of my lecture on physiology made an invention which could possibly be of considerable use to ophthalmology. Actually, this invention was obvious, did not need any more knowledge of optics than I had learned at the gymnasium. It now seems ridiculous to me that

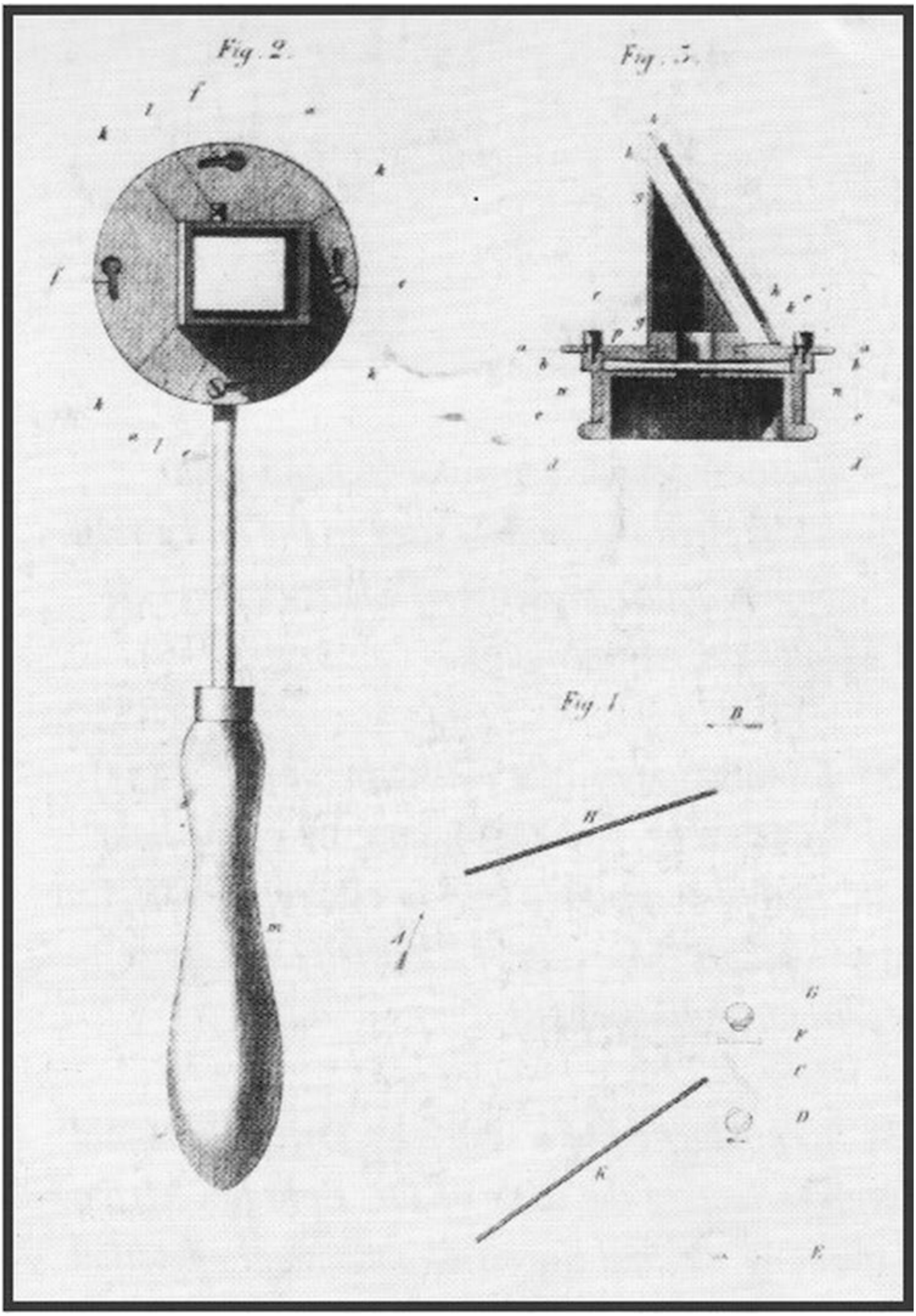
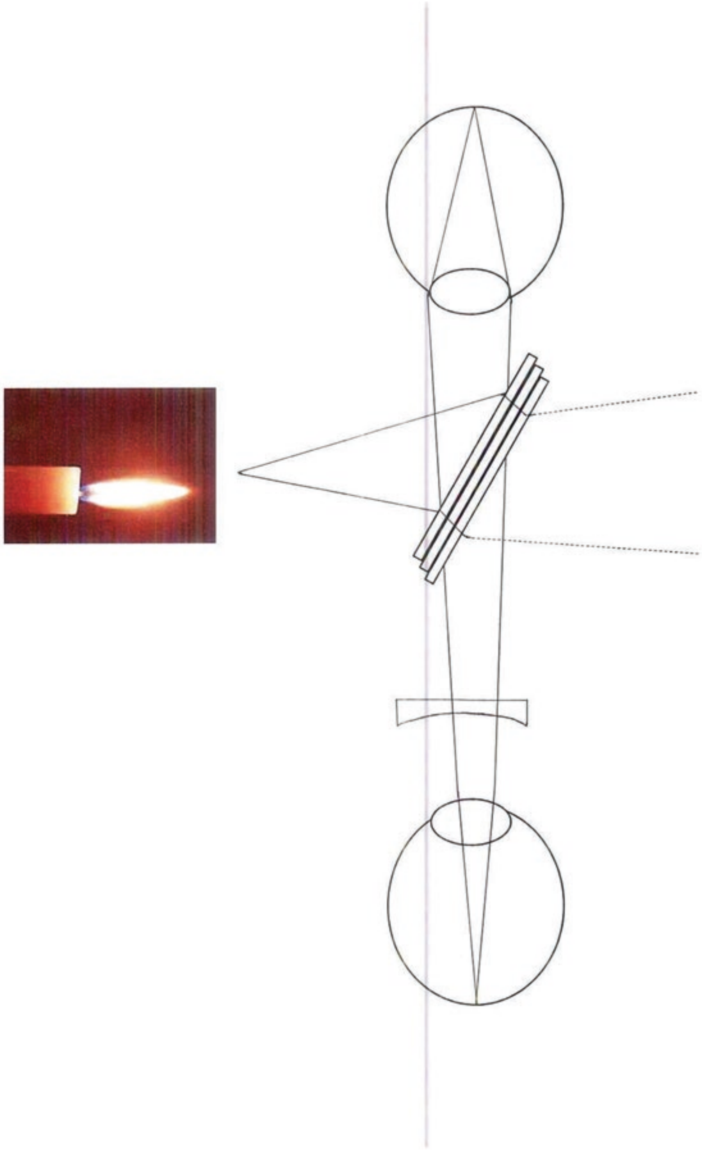


Fig. 3 Early ophthalmoscope

others and I myself could be so obtuse not to have found it earlier. It is a combination of glasses by which it is possible to illuminate the dark fundus of the eye through the pupil without using a glaring light, and at the same time to see details of the retina much more precisely than we can see the

Fig. 4 Light path for the original ophthalmoscope



external eye without magnification. The transparent parts of the eye are seen as if through a loupe of 20X magnification. One can see the blood vessels, the branches of arteries and veins, the entrance of the optic nerve head into the eye, etc. Up to now a large number of important eye diseases were lumped together under the name of "black cataract," a terra incognita, because we knew nothing about the pathologic changes in the living eye, not even after autopsy. Thanks to my invention the most detailed examination of the inner structure of the eye is possible. I have regarded this invention as an egg of Columbus to be treated cautiously. I have presented it at the Physical Society in order to protect my priority and presently I have such an instrument manufactured, which is better and handier than my preliminary design. I will then examine with the local chief ophthalmologist some patients and later publish the whole affair" [1] (p. 105).

Actually, the invention was not as self-evident as Helmholtz stated it rather modestly. The concept required a sophisticated understanding of optics and an inquisitive mind. His father wrote back, "The instrument is immediately practical and the question will arise whether you should not obtain a patent for this diagnostic instrument" [1] (p. 105). The senior Helmholtz realized that the invention might be lucrative. The inventor did not respond to his father's idea and never patented the ophthalmoscope. Although he and the family could have used the income, he preferred to have the instrument used widely to benefit humanity rather than for self-enrichment. He was not opposed to having his instrument maker earning from his work, though. Shortly after his article on the new instrument appeared in print, Helmholtz wrote his father that eighteen orders had already come in, including requests from Holland, France, and England, "so that my mechanic will make quite a profit" [1] (p. 106).

Helmholtz's first public announcement of the ophthalmoscope took place on November 11, 1851, at a meeting of the Society for Scientific Medicine of Koenigsberg. This society had been founded just a few days earlier and Helmholtz was its first president. At nearly the same time his 43-page monograph on the ophthalmoscope was published [2]. Since his first public description of the instrument and his first publication both occurred in 1851, that year is sometimes given as the date of the invention, rather than his presentation to the Physical Society of Berlin the year before.

Helmholtz understood the clinical importance of his invention: "I believe I may hold the expectation, not to be exaggerated, that all the alterations of the vitreous body and of the retina, which until now have been found in cadavers, will also be recognizable in the living eye, a possibility which appears to give promise of the greatest advances in the hitherto undeveloped pathology of these structures" [3].

A century ago the ophthalmic historian Thomas Shastid aptly wrote this is "probably the most significant sentence ever penned" by anyone working in the field of ophthalmology: "How the great man's prophecy has been fulfilled is known not merely to specialists and general practitioners, but even, in some degree, to first year medical students and the educated portion of the laity. In fact, there are just two kinds of ophthalmology, that which came before and that which followed after Helmholtz's *Beschreibung eines Augenspiegels* [*Description of an Ophthalmoscope*]" [3] (p. 29).

Helmholtz called his instrument an *Augenspiegel* (eye mirror) because the glass plates of his invention reflected light into the eye being examined. The word ophthalmoscope was introduced by Maressal de Marsilly in 1852 [4, 5]. This was a modification of an earlier word, ophthalmoscopy, which itself was a general term for examination of the eye.

Prior Observations

As early as 1703 Jean Mery in Paris, France, became the first person to observe details of the fundus in a live subject. He saw the optic nerve of a cat, but to do so he had to submerge the cat's head under water to neutralize the effect of the cornea [6]. Adolf Kussmaul, who is remembered today for his work on respiration, did animal experiments as a medical student at Heidelberg, Germany, in 1844 in an attempt to visualize the retina [7], but he did not know how to illuminate the fundus. William Cumming, working in England in 1846 and Ernst Brücke in Vienna, Austria, in 1847 were even closer. They were able to illuminate the fundus but could not visualize it. They laid the foundation for Helmholtz's work.

There is a British claim for precedence. In 1854 the ophthalmologist Thomas Wharton Jones published a report on the ophthalmoscope, writing, "It is but justice that I should here state, however, that seven years ago Mr. Babbage showed me the model of an instrument that he had contrived for the purpose of looking into the interior of the eye" [8] (p. 426). It was a mirror with a central opening. There is no other bit of information to corroborate Jones's statement. If Wharton Jones did try to see the fundus with this instrument, he may not have succeeded due to lack of focus from an uncorrected refractive error of the observer or the subject. Charles Babbage, a well-known and eccentric mathematician, is generally recognized as the father of the modern computer. Neither his autobiography [9] nor the

Fig. 5 Jaeger's Atlas. Circa 1890

Fig. 6 Jaeger's Atlas

eleven volumes of his published works [10] contain anything related to examination of the eye. Apparently Babbage kept a diary, which has been kept private by his descendants. Perhaps someday its contents will be made public. Until that time, as the eminent ophthalmic historian Julius Hirschberg has written, the retrospective claim for Babbage cannot be verified [11].

One other person may have seen the retina before Helmholtz, the Czech physiologist Jan Purkinje, who is remembered today for the catoptric images formed by reflection from the lens and cornea, for cells in the brain, and for introducing the words plasma and protoplasm [12, 13]. As a Czech nationalist he was treated roughly by German authorities when he was about to obtain a position at Breslau, Prussia. He was required to write a graduate thesis in Latin. His work on an ophthalmoscope formed a small part of the thesis and was published later in book form. Twenty-seven years before Helmholtz's first description, Purkinje made these interesting statements:

"I was also by coincidence capable of observing the interior of the eye where the vitreous is present when a suitable method is used. I examined the eye of a dog by using the spectacle lens of a myope (i.e., a concave mirror) and placing a candle behind the dog's back…I found the light as the source which is reflected from the concavity of the spectacle lens into the interior of the eye. From there it is again reflected. I immediately repeated the experiment on a human eye and found the same phenomenon" [1] (p. 102). Unfortunately, we do not know if he saw the retina or the optic nerve. There is no question that he described a functional device, as did Helmholtz later, but we do not know precisely what he did with it.

Purkinje constructed an artificial eye to verify these findings. He was still alive 20 years after Helmholtz described his ophthalmoscope and appears never to have claimed priority. The issues for us concerning Babbage and Purkinje are not only whether they saw the fundus, but that they failed to publicize it if they had. As in many other fields the credit is most often given to the person who has made the invention known.

Popularization of the Instrument

The ophthalmoscope was accepted into practice quickly by nearly every prominent European ophthalmologist [14]. One notable advocate was Albrecht von Graefe, who obtained a copy of Helmholtz's monograph shortly after it was published. Von Graefe was only 23 years of age in

1851 and Helmholtz was 30. When von Graefe first viewed the fundus with the new invention he shouted out enthusiastically, “Helmholtz has unveiled a new world to us” [15] (p. 597). He ordered several ophthalmoscopes from the manufacturer and sent one to Desmarres in Paris and another to Bowman in London. Soon there was a flood of publications describing observations using the ophthalmoscope, most notably those of Ruete, Coccius, von Graefe, Liebreich, Stellwag, Jaeger (Figs. 5 and 6), Donders, Wells, and Bowman [1] (p. 123). A further improvement, indirect ophthalmoscopy, was devised by Ruete in 1852. Elkanah Williams of Cincinnati brought ophthalmoscopy to America in 1855. He had already published one of the earliest reports [16] in English on the new instrument in 1854 while working at Moorfields Eye Hospital in London.

Often there is resistance to innovation in medicine and not surprisingly this new instrument proved to be no exception. A few ophthalmologists did not want to learn a new technique. Others were concerned about the potential for light damage to the retina, especially in a diseased eye. Ophthalmologists were well aware of the temporary blind spots and sensitivity that can be induced by light as well as the potential for permanent damage from the sun. In 1853 a British ophthalmologist made the interesting comment, “Prolonged illumination of the retina in order to draw the fundus could cause amaurosis” [17]. However, the risks of ophthalmoscopy were soon shown to be negligible and the instrument was quickly incorporated into medical practice.

Early ophthalmoscopes were not easy to use. The light source was a reflected flame that was far less intense than the bulbs used today. Glare from the cornea was an important obstacle. A small pupil increased the difficulty. Atropine was used commonly to dilate the pupil, but the long lasting mydriasis and cycloplegia from this drug were significant disadvantages. Despite the difficulties some humorous anecdotes have been passed down to us. Helmholtz received a dozen letters from one ophthalmologist who repeatedly wrote “Your ophthalmoscope is excellent, but I cannot see anything with it.” Helmholtz always answered, “Practice.” The thirteenth letter finally stated, “I can see!” [1] (p. 125) Visitors to von Graefe’s clinic in Berlin were often shown a mark on the ceiling of the darkroom used for ophthalmoscopy. Apparently it was made by an excited ophthalmologist who threw the instrument up in the air when saw the optic nerve for the first time.

Helmholtz’s Other Scientific Achievements

Helmholtz was the most famous scientist of the second half of the nineteenth century and also acted as a statesman and popularizer of science. His work cut across traditional disciplines, and included ophthalmology, otology, physiology, physics, and esthetics. His *Handbook of Physiological Optics* [18], which went through many editions in several languages, was an essential resource for generations of ophthalmologists. His ophthalmometer (keratometer) of 1851 was also important. He directed scientific institutions at several universities (Konigsberg, Bonn, Heidelberg and Berlin) and at the Physikalisch-Technische Reichanstalt in Berlin. He also spoke to the general public on science and its relationship to society.

To most of the scientific world he is best known for the law of the conservation of energy. It was not immediately accepted, however, and was initially rejected for publication in the *Annals of Physics*. The year that he created the ophthalmoscope he was able to perform a scientific feat that experts thought impossible – to measure the speed of conduction of a nerve impulse.

The major biography of Helmholtz is well over a century old is now and contains much important material [19]. However, it has not stood the test of time very well. It is very much a piece of hero-worship, not at all analytical or critical, and provides no references. Reunification of Germany has meant that source material from the former East Germany, which could not be seen for decades by researchers in the west, is now available and Helmholtz’s career is receiving much attention.

Helmholtz’s intellect was so well respected that at his autopsy the structure of his brain was studied in a search for unusual development [20]. There has been a long tradition of seeking the origin of genius by examining the brains of famous scientists. Unfortunately gross and microscopic studies of the cerebral cortex of people such as Helmholtz, Osler and Einstein have provided no information [21].

Honors to the Innovator

As early as 1858 the Heidelberg Ophthalmological Society honored Helmholtz at its annual banquet with a silver cup inscribed "To the creator of a new science, to the benefactor of mankind, in thankful remembrance of the invention of the ophthalmoscope" [22]. Von Graefe himself made the presentation. Helmholtz was particularly grateful for this recognition, as he revealed to his wife, since it was "a decoration from the experts" [1] (p. 106). The general public knew of his accomplishments but he was most touched when his colleagues recognized his contributions.

Helmholtz's ophthalmoscope is sometimes described as an invention and at other times as a discovery. Actually he used both words. Initially he used the word invention, as in the 1895 letter to his father mentioned earlier. He was modest, uncomfortable with flattery, and came to use the word discovery more than 30 years after the fact, in 1882. In his words the ophthalmoscope was "more a discovery" than an invention [1] (p. 105). He used the same terms in 1886 when the Heidelberg Ophthalmological Society presented him with its first von Graefe medal. Helmholtz's address on receiving this prestigious honor included these comments:

When I review the history of my ophthalmoscopic invention, I have to admit part of it was luck and the other part was only the work of a trained laborer who had learned to use the means and knowledge acquired by his predecessors. I have expressed the same thoughts in an after-dinner speech given at the memorial celebration to Graefe when his statue in Berlin was unveiled: "The ophthalmoscope was more a discovery than an invention," i.e., when a well-trained physicist arrived and recognized all the importance of such an instrument, all optical means and all knowledge had been developed which were necessary in order to design such an instrument [1] (p. 106).

The ophthalmoscope was so important that Helmholtz was often asked to describe how he came to invent it. The last occasion was in 1893, the year before he died, during his only visit to the United States. The German Emperor Wilhelm II prevailed on him to come to America as a scientific emissary to the World's Columbian Exposition, which was held in Chicago, Illinois. Also encouraging him was Professor Herman Knapp, the head of ophthalmology at Columbia University's College of Physicians and Surgeons, New York, NY, and editor of the *Archives of Ophthalmology*. They had been friends for years, dating from Knapp's years as a student at Heidelberg University. Knapp had been inviting Helmholtz to travel to America for 20 years. In a letter to Knapp describing his plans, Helmholtz wrote this fascinating comment: "I am convinced that America represents the future of civilized humanity and that it includes a vast number of interesting men, while in Europe we have only chaos or the supremacy of Russia to look forward to" [23] (p. 411). Helmholtz was treated as a celebrity by scientists and socialites in New York and Chicago. Among others, he met the inventors Thomas Edison and Alexander Graham Bell, the architect Charles McKim, and the banker J. Pierpont Morgan [24, 25].

He spoke at the dedication of Knapp's new clinic at Columbia and described the creation of the ophthalmoscope: "I think that no physiologist doubted, until the end of the last century, that the eyes of cats, dogs, oxen, and other mammals, and birds, developed light of their own which shown forth at night" [25] (p. 771). He described how this was disproved early in the nineteenth century when the eyes of animals that appeared luminous were found to have a reflecting layer, the tapetum, an light could reflect from the tapetum of a dead animal as well as a live one. About 1846 an English ophthalmologist, Cumming, found that any eye could be made luminous in a dark room if a light is shined in and the observer is nearly on line with it.

Helmholtz continued "Such were the facts known by scientific men in 1847, when I began to search for the ophthalmoscope … But nothing had been seen of the interior structure of the seemingly luminous eye, the impression being only that of a diffuse appearance of light covering the whole pupil. In my lectures I had to give an account of these experiments, and to try to give an explanation of the phenomena. I was obliged, therefore, to seek for an explanation myself, and I may say that it was not difficult to find" [25] (p. 771).

Using a blackboard Helmholtz traced the path of rays that create an image in the observer's eye. He emphasized "All that was original with me in the matter was that I went to ask how the optic images could be produced by the light coming back from the illuminated eye. All my predecessors had failed to put this question to themselves. They had stopped in the middle of their way instead of going on to the end. As soon as I had answered that question I saw how an ophthalmoscope could be constructed, and it took me only 2 days to do it and successfully experiment with the new instrument. I say this to impress upon you how necessary and how useful it is to go on to the end when investigating natural phenomena. You must not go half-way and then stand still or go back" [25] (p. 771).

Long after the fact, we can only admire Helmholtz's ability to ask the appropriate question and arrive at the innovative solution.

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9

Albrecht von Graefe: The Beginnings of Scientific Ophthalmology and Education

Steven A. Newman

Introduction

As this monograph is designed to emphasize fundamental changes in the conceptualization or practice of ophthalmology, Frederick Wilhelm Ernst Albrecht von Graefe (Fig. 1), recognized as the giant of nineteenth century ophthalmology, represents a particular problem. Adler, in reviewing von Graefe's life and legacy, stated: "If someone were to ask pertinently what one great thing he did which brought him fame, an answer would be difficult" [1]. Perhaps this is paralleled during the twentieth century by Hans Goldmann who worked into his tenth decade producing a legacy of multiple advances; almost one a decade, including improvements in the applanation tonometer, the three mirror contact lens, and the first practical quantitative bowl perimeter. During the nineteenth century, Albrecht von Graefe (in a much shorter time span (42 years)) introduced an amazing number of singular observations and changes in practice. Perhaps most importantly, I would argue his seminal contribution was to put ophthalmic education on a firm scientific footing.

Von Graefe: The Beginnings

Central to any analysis of this ophthalmologist who has been the subject of more bio-graphical material than any other is a study of von Graefe the man [2, 3] (Fig. 2). Albrecht von Graefe was born (May 28th 1828 at the Haunt of Finches, a house in the Tiergarten of Berlin) into privilege in the middle of the nineteenth century. He was the third of five children (two brothers and two sisters). His father, Carl Ferdinand von Graefe (1787–1840), was a court physician (to Duke Alexius of Anhalt-Bernburg) and surgeon whose abilities had been recognized by royalty, ennobled (initially by Czar Nicholas of Russia and recognized by Prussian royalty by the addition of "von"), served as Surgeon-General in the Prussian army, authored the *Encyclopaedic Dictionary of Medical Sciences*, and was credited with development of modern plastic surgery (combining the Indian and Italian methods of rhinoplasty among other techniques). Although a general surgeon, Albrecht's father likely performed the first cataract operation in Germany with a corneal cut directed upwards (an improvement on the inferior section of Daviel) (Fig. 3).

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Fig. 1 Picture of von Graefe by Julius Hirschberg in The History of Ophthalmology. Faceplate from Graefe A, Saemisch TH (eds). Handbuch der Gesamten Augenheilkund. Berlin, Verlag von Julius Springer 1918. (Julius Hischberg. History of Ophthalmology, Reformation)

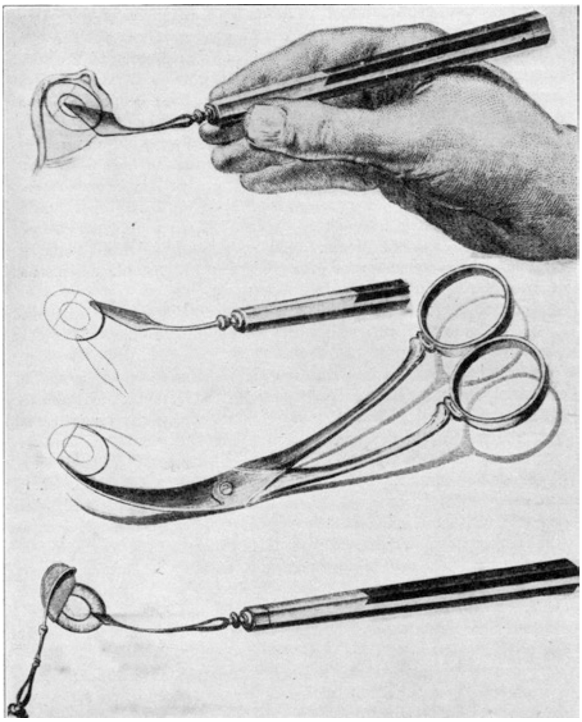
Thanks to his father's prestige and his decidedly upper class upbringing, young Albrecht wanted for little. Yet in spite of this potential to be spoiled, he demonstrated his ability and motivation early. He attended French Gymnasium at age 10, learned to speak French and was taught religion by Molière. He was the youngest student to graduate at age 15 (having lost his father at 12). One year too young to enter the University, he studied mathematics and physics with Professor Goepel, and dabbled with chemistry under the guidance of Professor Rammelsberg [4]. He then enrolled as the youngest pupil at the relatively new University of Berlin. At the university, Albrecht studied under some of the most illustrious names in medicine and surgery at that time. Johann Friedrich Dieffenbach (1792–1847) who performed tenotomy for strabismus starting in 1837 and succeeded Carl Ferdinand von Graefe (Albrecht's father) at the Charité in Berlin, taught him surgery. Graefe was taught internal medicine by Ludwig Traube, who was Jewish and would later become von Graefe's personal physician and attend him up to and including Albrecht's death from tuberculous pleurisy. He was taught pathology by a former student of Johannes Peter Müller (1801–1858), Rudolf Ludwig Carl Virchow (1821–1902) who founded the Archives of Pathology and published 47 papers in 1 year (on his way to more than 2000 publications and the establishment of modern pathology).

Young Albrecht graduated university on August 21, 1847 at the age of 19. His thesis on bromide (*De bromo ejusque praecipius praeparatis*) was written in Latin the year before the revolution of 1848 when theses became acceptable in German. Biographers would emphasize that Graefe never abused his privileged position (pointing out that he would often pay for care for the poor out of his own pocket). About fifteen beds were reserved for such patients as are unable to pay, entirely entertained at Professor von Graefe's own expense [5]. In November 1850 Albrecht von Graefe began his practice of ophthalmology in three small rented rooms with an advertisement in all the newspapers in Berlin: "Dr. Albrecht von Graefe will treat free of charge the eye diseases of the poor" [6]. In spite of his obvious predilection for hard work, it is hard to ignore the huge silver spoon that Albrecht inherited. His financial situation allowed him, prior to opening his practice, to spend 3 years travelling around Europe to view cutting edge medical practice and learn the current status of Ophthalmology.

His first foreign contact in Prague (felt at the time to be the center of scientific medicine) was at the Clinic of Karl Ferdinand von Arlt (1812–1887), who was to have the most lasting influence on young Albrecht. As Graefe himself would say years later, without this exposure he might never have decided to specialize in ophthalmology. "Arlt has introduced me to ophthalmology; he impressed on me the same solid principles which he himself follows when practicing our specialty; he was the first to show me what qualities an eye surgeon should possess. Believe me, without Prague, Paris and Vienna

Fig. 2 von Graefe statue in Berlin highlighting his accomplishments, holding an ophthalmoscope. Figure obtained from http://de.academic.ru/dic.nsf/dewiki/48121

Fig. 3 Illustrations of Daviel's technique circa 1750, linear extraction of a cataract, published in Wood CA (Ed). The American Encyclopedia and Dictionary of Ophthalmology page 1609 originally published by Daviel, Mém. Acad. roy Chir. Paris 1753; 2: 337.



would hardly have been as useful to me; indeed, I believe without Arlt I would perhaps not have returned to Berlin as an ophthalmologist" [7].

His next stop was Paris (during the winter of 1848) where any doubt about his choice of specialty was relieved. "I attended two clinics—Sichel's (1802–1868) and Demarres' (1810–1882)… You cannot imagine what a fiend for work that Sichel is, or the amount of material in his clinic—thirty to forty new and three hundred to four hundred odd patients a day… I watch about two cataract operations there a week" [8]. While in Paris he also spent time with Claude Bernard (1813–1878) working on physiologic problems including the function of the extraocular muscles. "Through his rabbit experiments, Graefe was able to demonstrate all three functions of the superior oblique muscles" [9] (Fig. 4). This work was later to appear in the first issue of the Archiv f. Ophth. [10].

From Paris it was on to Vienna. Once in Vienna it did not take long for the Jägers (father: Christoph Friedrich Jäger (1784–1871) and son: Eduard Jäger Ritter von Jaxtthal (1818–1884)) to perceive that Graefe, who won their hearts from the beginning, was a young man of unusual capacities. They let him make himself at home using their clinical and private patients as he would [11]. Four years later, Eduard was to dedicate a book, "Ueber star und Star-Operation" to von Graefe [11]. This was to be reciprocated by Albrecht who dedicated his Arch. f. Ophthalmol. to Eduard's father Friedrich Jäger.

"During his stay at Vienna, he began a short course on ophthalmology to some of his friends. When these asked me if he would also speak of therapeutics he added the following significant reply, 'That we will study together in Berlin'" [12]. Albrecht found a predilection for lecturing: "For the first time in his life, Graefe now essayed to lecture, displaying at the outset much of the flair, finesse, and yet artlessness, the emotion and skill, that were to make him a world-renowned lecturer and teacher… Like the Syriac lady's irresistible stories, one lecture led to another. He held his listeners in the palm of his hand" [11].

It was also while in Vienna he ran into a university classmate, C. Jean-Renaud, and heard some fascinating news: "It is a coincidence that I meet you, he said, especially since you are going to be an eye physician! You see, the first thing I am going to publish will deal with the eyes! A professor of physiology in Königsberg has written a little paper about something called the eye mirror and I am going to publish it. That's what he calls it. It is a thing to look at the sensitive membrane of the eye and the optic nerve with—for the first time in the eyes of a breathing man, so he says… He is a friend of my father. His name is Hermann Helmholtz" [12].

Although Harvey Cushing (70 years later) was to point out that ophthalmology was the "oldest surgical sub-specialty," the study of ophthalmology in the nineteenth century suffered from a substantial lack of respect. This was brought home to young Albrecht when he visited William Bowman (1816–1892) and George Critchett (1817–1882) in London and was advised by James Wardrop (1782–1869), a Scottish surgeon, ophthalmologist, and founder of the journal *Lancet*, to choose another area of medicine since there were "no Professors" of ophthalmology [13].

Fortunately for our specialty, Graefe chose to ignore the advice to practice another form of medicine. Just how significant this was may be judged by an oration in 1890 by Vincenz Czerny: "Ophthalmology has become a model specialty for all practical fields of modern medicine. It has directly applied theoretical sciences to medical practice and has used critical and conscientious statistics of therapeutic results. It will remain a model for a long time even when the brilliant triumvirate of Graefe, Helmholtz and Donders have long been dead" [14]. It is appropriate that Albrecht was to become the first Professor of Ophthalmology in Berlin (1868). Another event occurred to Albrecht during his visit to Britain which was to have lasting significance; he was introduced to Donders at the Guthrie's clinic. It was actually Jäger who stated, "Here, you two belong together" [15]. Leaving London, young Albrecht journeyed to Scotland to observe the author of the then celebrated textbook of ophthalmology, William McKenzie who proved an amiable host.

Fig. 4 Illustraton from von Graefe A. Beiträge Zur Physiologie und Pathologie dur schiefen Augenmuskeln Archiv für Ophthalmogie 1854;I:44 demonstrating rabbit experiments he had done while in Paris with regard to the function of the superior oblique muscle. This illustrates physiologic work done on rabbits in Paris to understand the function of the extra ocular muscles, and in particular, the superior oblique

bis der Kopf um 40° geneigt worden war, so dass die Kopfnadel nur noch um 50° nach aufwärts sah. Traten auch bei den genannten Drehungen Schwankungen bis auf 5° ein, so waren dieselben doch nicht constant, und mussten auf Beobachtungsfehler bezogen werden. Wurde nun aber der Kopf noch stärker geneigt, so blieb die Hornhautnadel entschieden zurück, so dass, als die Kopfnadel nur noch 10° nach oben sah, die Hornhautnadel noch einen Winkel von 22° mit dem Horizonte machte; es hatte sich also die Hornhautnadel nur um 28° gedreht, während die Kopfnadel sich um 40° gedreht hatte. Wurde der Kopf des Thieres noch mehr geneigt, so zeigte sich das Zurückbleiben der Hornhautnadel immer deutlicher. Eine vollständige Compensation der Kopfdrehung durch Meridianverrückung in der Weise, dass die Hornhautnadel während gewisser Drehungen vollkommen stabil geblieben wäre, trat aber nicht ein, sondern es neigte sich dieselbe für je 10° Veränderung der Kopfnadel noch um 2°, wodurch also der Winkel zwischen beiden Nadeln für jede solche Drehung um 8° wuchs. So ging die Sache fort, bis die Kopfnadel senkrecht nach unten stand, so dass sich während der letzten 10 Drehungen die Hornhautnadel nur um 20° geneigt hatte, mithin 80° zurückgeblieben war, in Summe aber einen Winkel von 92° mit der

Advent of new Technology (the Beginnings of Modern Ophthalmology)

Albrecht also had the luck of ideal timing. As mentioned, during his European sojourn he was to hear of the development of an “eye mirror” by Hermann Helmholtz (1821–1894). This invention was to completely revolutionize ophthalmology taking it from a study of external and anterior segment disease to include diseases of the retina and optic nerve. The extent of this revolution was stated by Helmholtz (1821–1894) in 1868 during his lecture on the advances in the theory of vision: “Ophthalmology has developed during the last twenty years with a speed and a type of scientific aspect which is perhaps unique in the history of medicine. Every humanitarian should be glad about these achievements. They permit us to prevent or eliminate much misery which previously could not be overcome. Any friend of the sciences should be especially proud and joyful. It cannot be denied that this advance was made not by serendipity, but by strict logical thinking and this may lead to further advances" [16]. Graefe recognized the potential of this new instrument immediately and personally wrote to Helmholtz to obtain two (Fig. 5). Although several of Graefe's most important and fundamental observations were dependent on this tool, it has been suggested that the role of the ophthalmoscope may have been over emphasized. "Von Graefe has been regarded by some as one born under a propitious star; the value of his service having been attributed to the fortunate relationship in which they stood to the invention of the ophthalmoscope. Those who so judge run the risk of overlooking his true greatness. The ophthalmoscope has raised the level of ophthalmology; what it has raised to the same level the achievement, the merits of all its representatives" [17].

"For almost 3 years he watched, he questioned, he learned. And, even as a very young man with the first wisps of a beard on his face, he was able to exert on all he met in his travels what one biographer has termed 'his spiritual glamour.' No one who met von Graefe ever forgot him, ever doubted that he was a young man of great talent and promise. But no word of this went back to his native Berlin. As with his father's name, he did not choose to trade on the reputation he had gained in his travels. He was to be completely on his own, even to the extent of financing his clinic" [14].

Early Practice

With his 3 years of wandering (and educating) complete, he established his clinic in Berlin. Within a brief time he was exceedingly busy (230 patients within the first 2 months; 1900 patients in his first year; rapidly rising to over 10,000 patients annually [18], and almost immediately hosted a long line of observers, students and assistants. Graefe was intimately involved in every aspect of patient's care. "He never delegates any of his duties" [19].

Patient appreciation could be effusive. Following successful cataract surgery Don José of Havana had his cataract mounted in gold and inscribed with the words: "Despues de Dios, Albrecht v. Graefe." (Next to God, Albrecht v. Graefe) [20]. "He was a notably handsome and well-grown man. It was said the blind or near-blind patients upon whom he operated, when they had eyes again and could see him, previously known but by his gentle touch, pleasant voice, and the warmth of his humanity, when they could see who it was who had redeemed them from darkness, were as dazzled by his looks as if an angel had stepped down from heaven." [21].

Von Graefe's Observations

If we were to ask his colleagues in the second half of the nineteenth century to pick Graefe's greatest contribution, there is little doubt it would

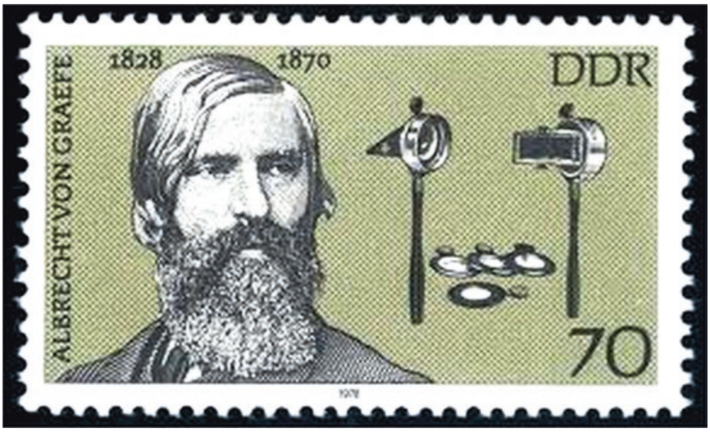


Fig. 5 Stamp issued by the Democratic Republic of Germany (former East Germany) featuring von Graefe and an early ophthalmoscope that he was to widely utilize. Figure obtained from http://www.nausa.uni-oldenburg.de/bohmte/bohmtebilddt.html

be his introduction of iridectomy for the treatment of glaucoma [22]. Graefe was not the first to preform iridectomies (these were done by Georg Beer and others 50 years earlier, usually for optical reasons) but he did recognize that in cases of acute glaucoma (or previous episodes of acute glaucoma), an iridectomy minimized the chance of further acute attacks. "Do not neglect in your patients with acute glaucoma to perform iridectomy at once. The successful results of iridectomy become more rewarding day by day" [23].

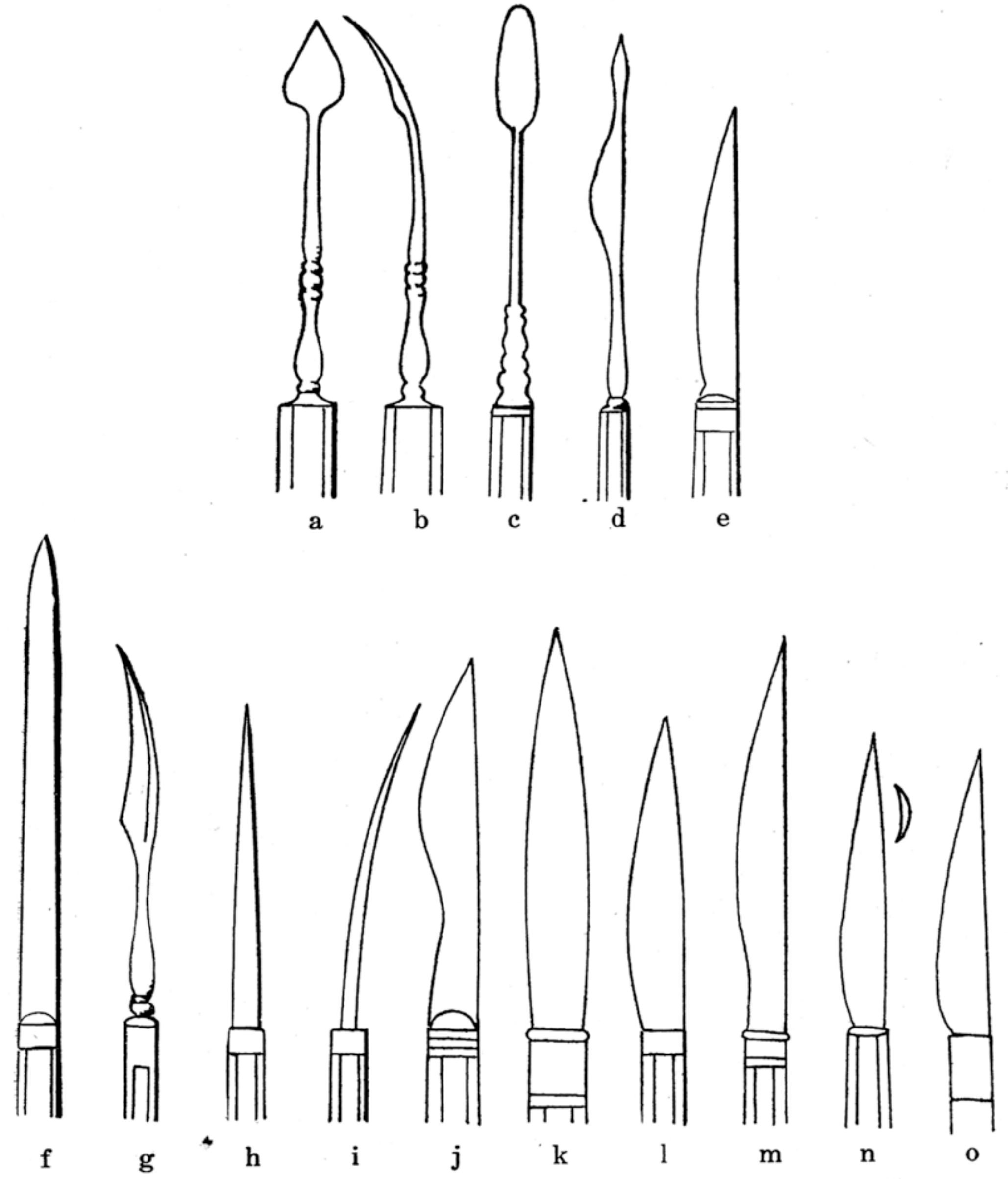
The Beginnings of the 'Cataract Wars' and the Introduction of the Graefe Knife

Also at this time, although controversial and not accepted by all of his colleagues, von Graefe suggested changes in the surgical approaches to cataract extraction. One hundred years after Jacques Daviel (1696–1762) first popularized lens extraction (still competing with lens disinclination), the "best method" for removing cataracts was unclear. By the time of Daviel's announcement to the Academy Royale [24] he had performed 206 cases [25] gradually developing a technique of opening the cornea inferiorly with a sharp-pointed, lens-like knife, and extending the incision with scissors (the incision corresponded to the limbus and involved about one-half of the corneal circumference) (Fig. 3). Pressure upon the lower margin of the wound with the first and second finger-tips placed upon the lower lid delivered the lens [26].

"Daviel is the originator of the bold idea of a cataract extraction. Graefe's undeniable merit was and will always be that he was not satisfied like most of his predecessors and contemporaries to note the purulent infections of the cornea; after long and well-planned experiments, he created a new procedure for extracting the cataract in which the danger of wound infection was reduced to a minimum. His theoretical conceptions may have been erroneous, but his method of extraction has in the last 20 years reduced the incidence of purulent infection from ten to four percent and the incidence of failures in general from twelve to six percent" [27].

Graefe's contributions to cataract surgery included the so-called "Graefe knife," which was a narrow pointed blade that tapered to minimize the egress of aqueous at the time a puncture is made (Fig. 6), allowing the globe to remain formed and not collapse during the creation of the incision. It should be noted that he had not invented this form of knife, which had been in use in various forms for years before his modification. In 1753 Samuel Sharp, endeavoring to improve upon the method of Daviel, made use of the knife in cataract extraction which (Fig. 7) was straight in its flat surface and somewhat convex on its back, it was slightly concaved on its edge, less than an inch long and its heel about one-eighth to one-sixteenth of an inch wide, gradually

Fig. 6 Illustration of the von Graefe knife showing the narrowed tapered blade designed to keep the anterior chamber from collapsing as a double puncture was preformed, utilized for more than 100 years. Illustration from eurotimes.org.



a, b, and c, Daviel; d, Pallucci; e, La Faye; f, Poyfet; g, Sharp; h and I, Tenon; j, Beranger; k, Pomard; l, Richter; m, Pope; n, Casa Amata; o, Demours.

Models of Cataract Knives Prior to 1822. (After Lachmann.)

Fig. 7 List of some cataract knives used prior to 1822 as published in Wood CA (Ed) The American Encyclopedia and Dictionary of Ophthalmology p. 1536

tapering to a fine point [28]. From this time henceforth the single knife, modified in different ways by many operators, soon become a powerful rival of Daviel's knives and scissors, and finally, long before the end of the eighteenth century, it superseded them entirely.

Graefe also made several modifications in the use of his knife, moving the incision closer to the limbus superiorly (Figs. 8, 9, and 10), which undoubtedly had a beneficial effect on problems with corneal melt. Again, he was not unique in emphasizing the advantages of healing a corneoscleral based incision and some of his ideas were developed in conjunction with his student Julius Jacobson (Graefe was always generous in acknowledging contributions [29].) It was Jacobson who postulated: “As far as the shape of the corneal incision is concerned… I believe the healing progresses better in vascularized tissue” [30].

Analysis of Graefe's Surgical Procedures

Graefe’s surgical procedures, as reported by a number of his colleagues, resulted in a reduction in suppurative events following cataract surgery. Of course it is unclear at this point whether this was mainly due to adherence to asepsis (emphasized by his cousin Alfred Graefe (1830–1899) and subsequently popularized by Lister in England) or the positioning of the cataract incision or likely both.

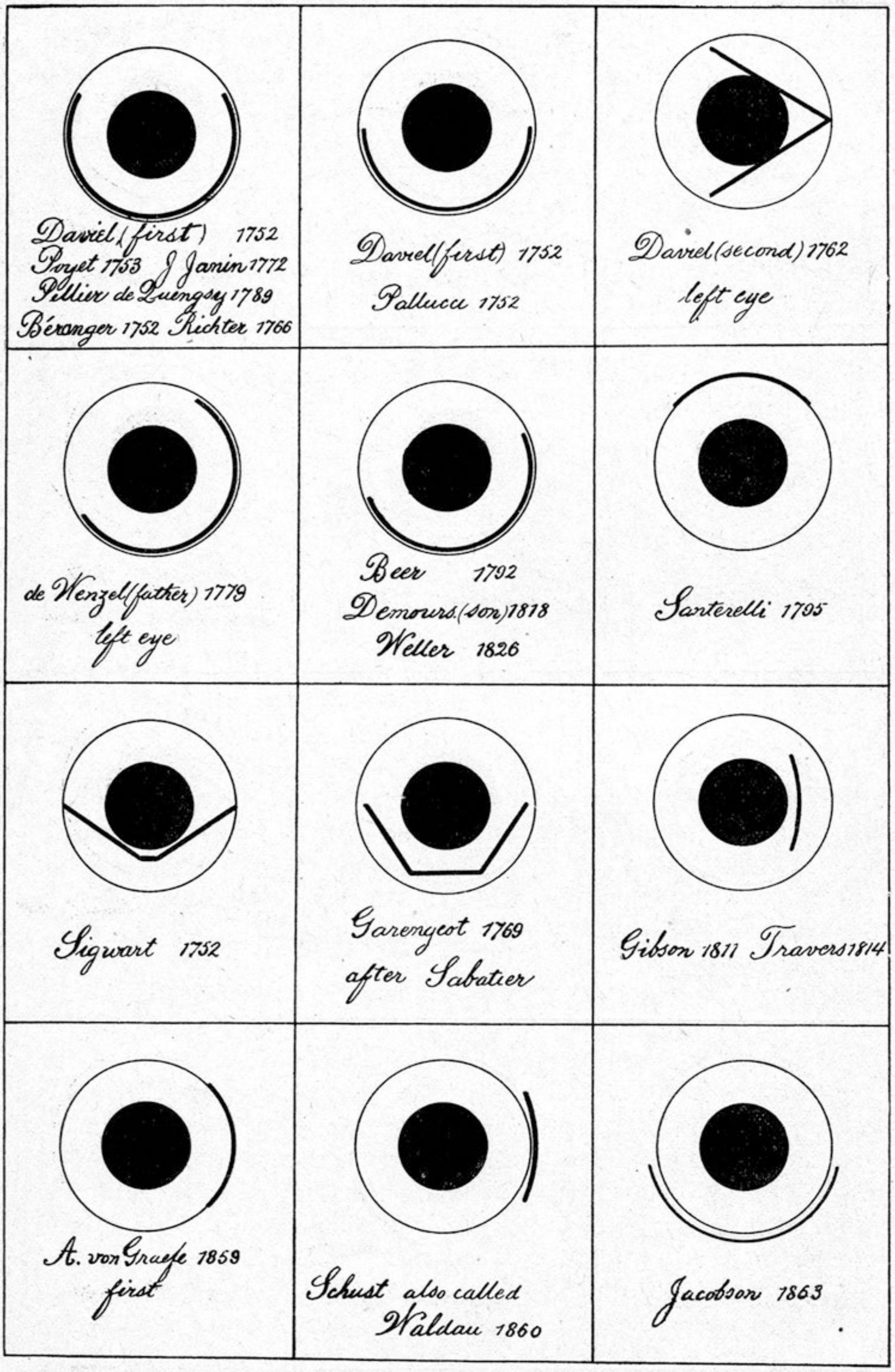
Ideal des peripheren Linearschnittes.
Cornealdurchmesser 12 Mm.
⋮ ⋮ Tangenten zum horizontalen Durchmesser *mn*.
..... Tangente zum verticalen Durchmesser.
a Einstichspunct.
ab Richtungslinie des Messerrückens beim Einstiche.
c Ausstichspunct.
adhec Verlauf der Bindehautwunde.
ac Verlauf der Corneaskleralwunde an der Aussenfläche der Sklera.

Fig. 8 Illustration showing the modification made by von Graefe to place his incision, not in the clear cornea, but rather in the corneal scleral junction between (**a**) and (**c**) from Graefe A, Saemisch T (eds) Handbuck der Gesamten Augenheikunde. Leipzig Verlag van Wilhelm Engelmann III 1874 p. 295

“J. Jacobson of Königsberg made in 1884 a retrospective survey of his 30 years in practice and found a 10% failure rate when using the old classical semicircular corneal incision, a 3–5% failure rate when using von Graefe’s technique; in the years 1883 and 1884 he had not a single case of endophthalmitis among 137 extractions” [31].

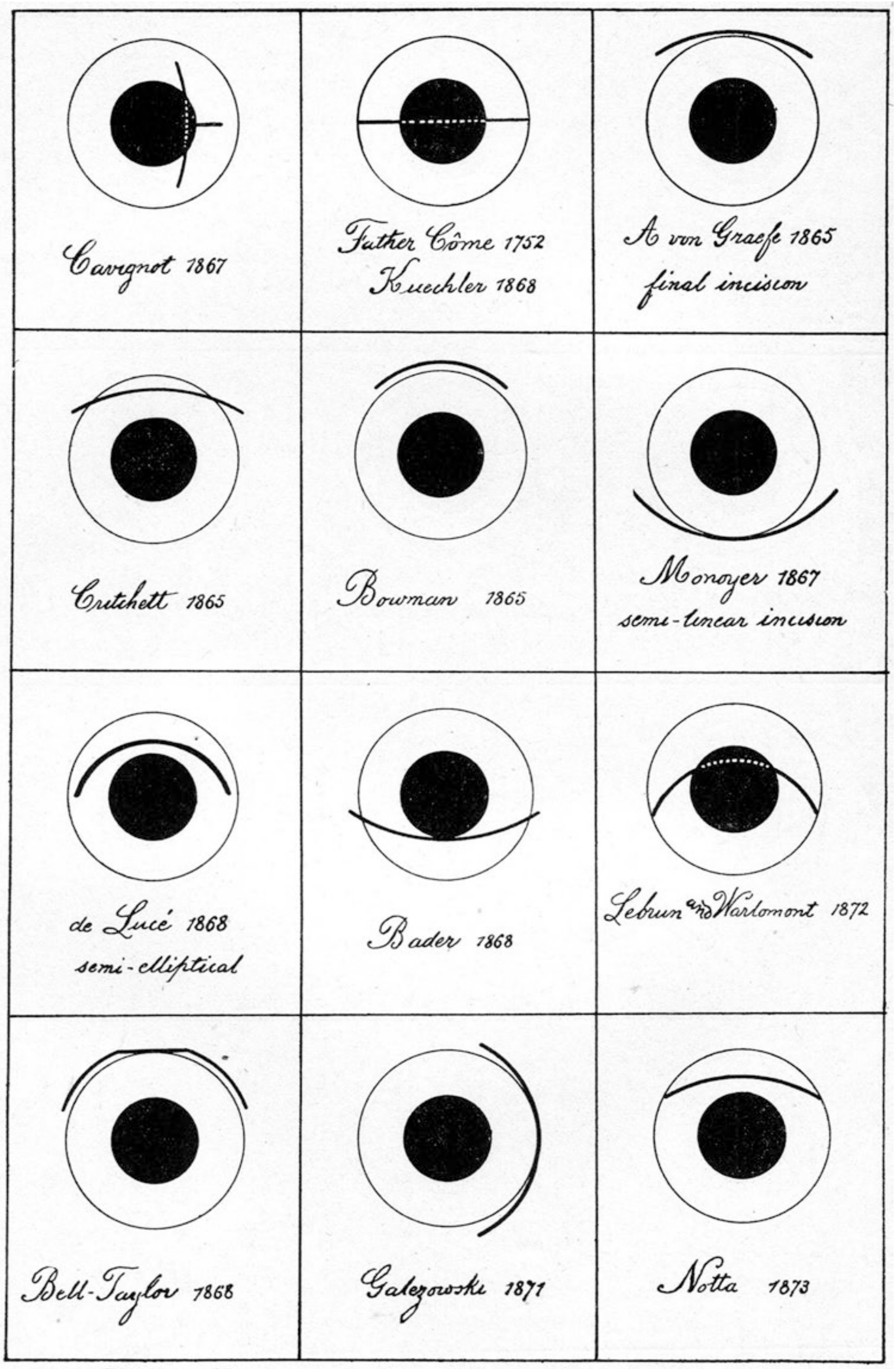
An additional advantage of his knife and incision was a shortening of the operative time which undoubtedly contributed to his decrease in infectious complications. Interestingly there was a significant debate in ophthalmology about the importance of Lister’s aseptic method; the technique being more accepted by the general surgeons than by ophthalmologists. Another change in cataract surgery introduced by Graefe included the performance of an iridectomy which if nothing else provided a better view of the lens during extraction.

In spite of data that supported the introduction of these modifications and their adoption by the majority of surgeons performing cataract surgery (including an aging von Arlt who adopted them in 1866), there was considerable controversy leading to heated arguments about the relative advantages. In particular two of von Graefe’s students, Julius Hirschberg (1843–1925) (“I therefore believe I have shown that the dispute which I began in 1866 by arguing against the Graefe operation and pointing out the advantage that the classical method has been completely justified by the history of the last 14 years” [32] and Carl Ernst Theodor Schweigger (1830–1905)) argued strongly in favor of retaining a corneal incision (reminiscent of some of the technique arguments today). Others were less polite. Joseph Hasner (1819–1892) dealt somewhat bluntly and unfavorably in two monographs (Die neueste Phase der Star-Operation, 1868, and Phakologische Studien, 1868) with Graefe’s linear extraction [33], which brought the debate to an even higher pitch. Most practitioners supported Graefe’s modifications. “In 1885 Arlt drew his final conclusion from his long experience. A modified Graefe extraction gives better results than the corneal



Diagrams Showing the Lines of Incision in the Principal Types of Cataract Extraction to Our Own Times. *(Encyclopédie Francaise d'ophthalmologie.)*

Fig. 9 Illustration from the Encyclopédie Francaise d'Ophthalmologie, published in Wood CA (Ed) The American Encyclopedia and Dictionary of Ophthalmology p. 1617. Illustrating development of various cataract incisions between Daviel and Jacobson (who modified von Graefe's incision in 1863)



Diagrams Showing some of the Lines of Incision in Senile Cataract.

Fig. 10 The further development of cataract incision in the 6 years between 1867 and 1873, including an illustration of Graefe's final excision in upper right taken from Wood CA (Ed) The American Encyclopedia and Dictionary of Ophthalmology p. 1618 incision" [34]. Still, within several years of Graefe's death, there was more than a little backsliding on the changes he had proposed. "Disappointment has spread widely among previous adherents of the Graefe operation. In France, especially in Paris, Louis de Wecker (1832–1906) (who had also written several papers dismissive of the importance of Graefe's contributions regarding iridectomy for glaucoma) in 1875 and Edmund Landolt (1846–1926) in Switzerland in 1878 returned to the corneal flap extraction. In England the surgeons returned gradually to the old extraction method without performing an iridectomy" [32]. The Graefe knife, however, was to continue in use for almost 100 years following his death. As Douglas Koch stated in inducting von Graefe into the ASCRS Ophthalmology Hall of Fame: "It is hard to imagine one whose techniques were adopted by more surgeons and utilized over a broader period of time" [35] (Fig. 11).

Clinical Observations

To those of us with an interest in history, probably the most impressive contribution of von Graefe was his astute clinical acumen. It is amazing that in such a short career he made so many observations (perhaps mirroring the future perspicuity of J. Donald Gass in retina). It is not surprising that Theodor Saemisch called him the "master of clinical observation" [36]. Clearly, his timing was propitious. As mentioned he was one of the earliest to use Helmholtz's ophthalmoscope, and along with Weber, pointed out that changes in the disc position included possible excavation (Fig. 12) (correcting Jäger who in 1854 [37] (Fig. 13) thought the disc elevated [38]).

What is truly most impressive is Graefe's recognition in his 1857 article on glaucoma [39] (Fig. 14) that a combination of increased intraocular pressure (prior to the development of instruments to measure pressure; although he had designed an impression-tonometer (impractical before topical anesthesia)), arcuate visual field defects (before Jannik Petersen Bjerrum (1851–1920) and Henning Rønne (1878–1947)), and increased cupping, were signs of glaucoma [39]. He singularly discounted (and is criticized by modern reviewers) what we would now call open angle glaucoma, to emphasize on what he had recognized, but not realized, was angle closure glaucoma. It is remarkable that less than a decade after the invention of the ophthalmoscope he was able to put these three observations together and define glaucoma in terms we would appreciate today. It is not surprising that this article translated into English is the first paper highlighted in

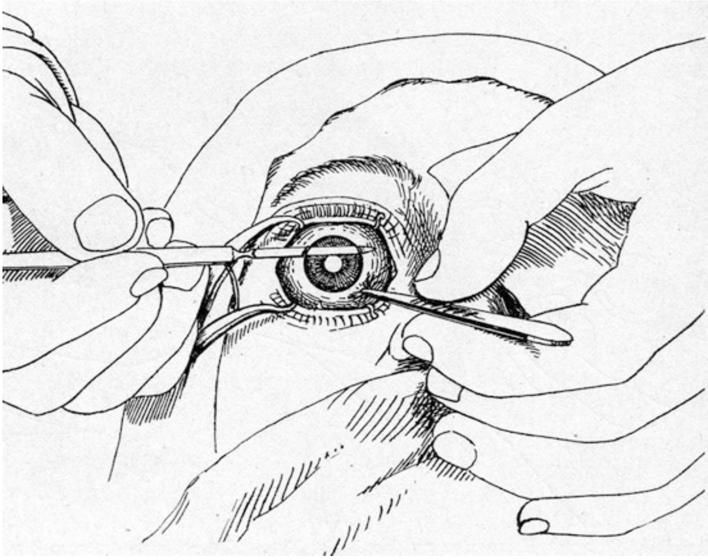


Fig. 11 Illustration of the technique of Graefe incision, holding the globe in position and double puncturing the eye superiorly from Wood CA (Ed) The American Encyclopedia and Dictionary of Ophthalmology. p. 1638

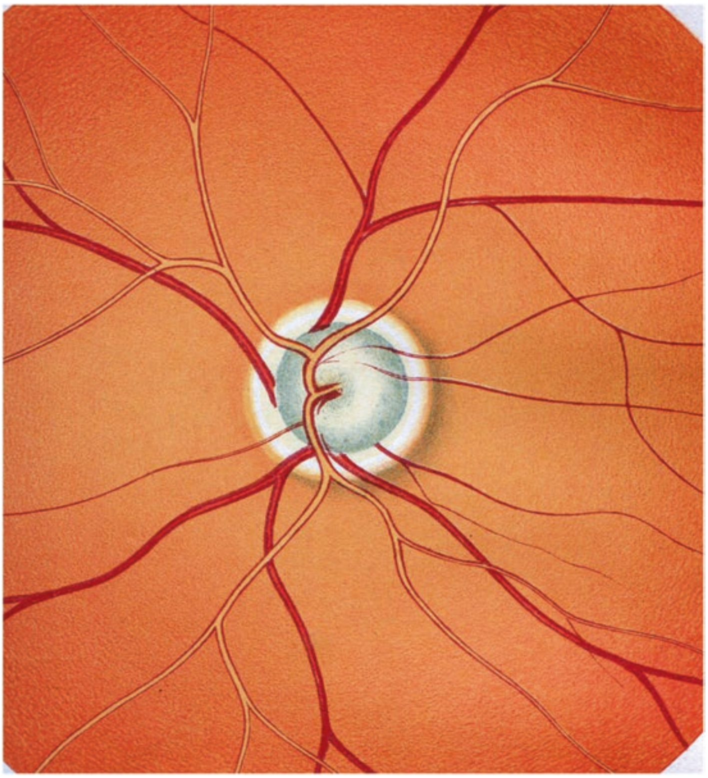


Fig. 12 Drawing from von Graefe illustrating glaucomatous cupped out disc published in Archv für Ophthalmologie 1855; I: 481 color plate Taf III

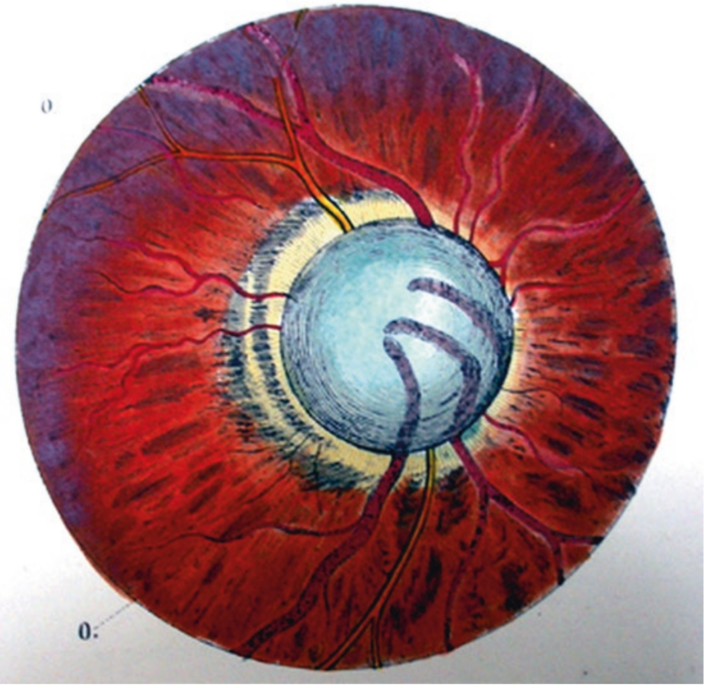
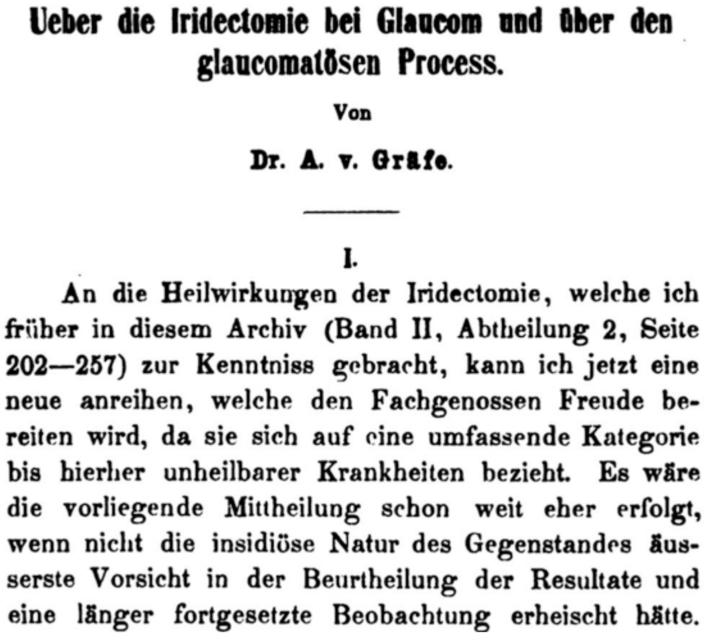


Fig. 13 Illustration from Eduard Jäger (1854) illustrating misconception of an elevated disc published before Graefe's 1855 illustration



Ueber die Iridectomie bei Glaucom und über den glaucomatösen Process.

Von

Dr. A. v. Gräfe.

I.

An die Heilwirkungen der Iridectomie, welche ich früher in diesem Archiv (Band II, Abtheilung 2, Seite 202—257) zur Kenntniss gebracht, kann ich jetzt eine neue anreihen, welche den Fachgenossen Freude bereiten wird, da sie sich auf eine umfassende Kategorie bis hierher unheilbarer Krankheiten bezieht. Es wäre die vorliegende Mittheilung schon weit eher erfolgt, wenn nicht die insidiöse Natur des Gegenstandes äusserste Vorsicht in der Beurtheilung der Resultate und eine länger fortgesetzte Beobachtung erheischt hätte.

Fig. 14 Faceplate of seminal article written by von Graefe outlining three classical features of glaucoma including arcuate visual field defect, increased cupping, and elevated intraocular pressure published in Archv für Ophthalmologie 1857; III(2): 456

Robert Ritch's monograph on the Classic Papers in Glaucoma [40]. With due respect to Richard Banister (1570–1625) [41], and notation that McKenzie had described "firmness" in eyeballs with glaucoma [42], it is truly von Graefe who first combined the salient characteristics of glaucoma that we still recognize [43].

Graefe made important observations beyond glaucoma. He early recognized the connection between optic disc swelling and intracranial disease [43]. He was also one of the earlier observers of a central retinal artery occlusion [44]. "Ophthalmic examination showed marked narrowing of the vessels" (Fig. 15). The patient had "absolute blindness in the right eye" and an amaurotic pupil unresponsive to light in the right eye but contracted sympathetically when the left pupil was exposed to light or to accommodations (anticipating Marcus Gunn by almost 50 years) [45]. In a talk on exophthalmic goiter in March 1864, at the Berlin Medical Society he described lid lag on down gaze (von Graefe's sign) [46]. He emphasized that the finding was not caused by exophthalmos but was "dependent on a disturbance in the innervation of muscles of the eyelid" [47]. He was also one of the first to recognize keratoconus [48]. He described and removed cysticercosis from the eye [49], recognizing resulting visual field defects [50], and later summarizing his experience in 1866 [51].

Graefe was also quick to recognize potential complications of ophthalmic surgery. Two of his patients died of secondary meningitis following enucleation for purulent endophthalmitis. His review of the then current literature revealed ten cases of meningitis following enucleation, seven of them lethal. Graefe proposed evisceration instead of enucleation to avoid this relatively rare lethal complication [52].

Graefe was involved in the investigation of the affects of Calabar bean extract on normal eyes, often utilizing his students and assistants including August Colsmann (who trained with von Graefe in 1868) as subjects (obviously before IRB's) [53]. Von Graefe was also instrumental in introducing the use of silver nitrate in neonates [54].

Having personally seen the results of Dieffenbach's tenotomy which turned esotropes into exotropes Graefe demonstrated an interest in improving strabismus surgery. "It was he who revised and improved the strabismus operation, which had fallen into disuse" [55]. His interest in strabismus lead him to suggest "recording of diplopia would be important in diagnosing

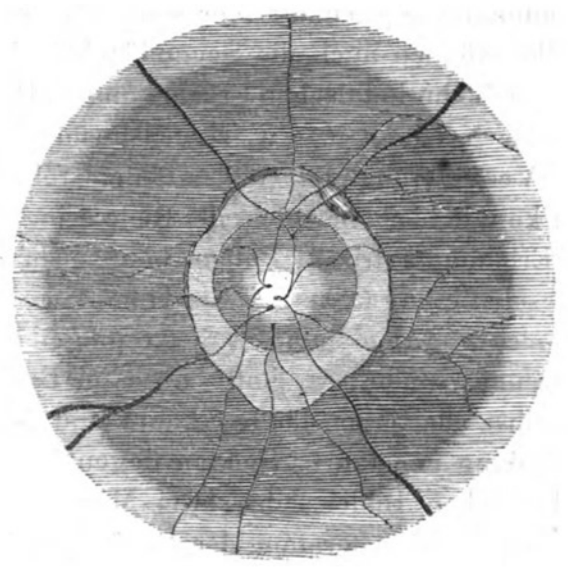


Fig. 15 Illustration, published by von Graefe, of severe arteriolar narrowing after central retinal artery occlusion published by Graefe A v, Archv für Ophthalmologie 1859;V(1):136–57

paralytic squint. Following the suggestion of Böhm (1845), he used colour glasses, preferably violet, to enable the differentiation of the right and left eye images: 'A large board, divided into many numbered squares, is placed as far as possible from the patient'" [56]. This technique preceded W.R. Hess by 55 years.

Not all of his observations or interpretations were correct. While he was one of the first to describe a retinal detachment related to renal failure, he couldn't explain how the noted "retinal detachment" could resolve (failing to understand the difference between a rhegmatogenous detachment and an exudative one). A. v. Graefe published the first (1855) report on the ophthalmic findings (anemic amaurosis): "I recall vividly a woman who suffered soon after delivery from Bright's disease. There were extensive white exudative plaques on the retina, also an advanced retinal detachment. I was surprised when the patient returned a few months later and the retina had completely re-attached" [57]. "Even the faults of Graefe—and which mortal is free of these?—derived from his positive attributes. His slight neglect of form, of order and of schedules was due to his desire to concentrate on the substance; his restlessness did not allow him to spend a single day without seeing patients was a consequence of his enthusiastic desire to heal" [58].

Albrecht von Graefe the Educator

To me the most important and lasting contribution of Albrecht von Graefe was that of an educator. In many ways, his clinic (Fig. 16), which was open to visitors not only from Europe but also from the United States (including Aaron Friedenwald (Harry Friedenwald's father and Jonas Friedenwald's grandfather), Hasket Derby (of Boston), Egon von Ullman (eventually settling in Portland), Richard Derby (of New York)) served as an incubator for ophthalmic practice, science, and education. His American visitors were only a small part of continuous stream of visitors coming through his clinic. It was thus not surprising that Graefe is often credited with forming the first "school of ophthalmology," although realistically that honor should be applied to the Vienna school (1773) founded by Joseph Barth, J.A. Schmidt, and G. J. Beer [59]. In establishing his routine Graefe adopted the best of the techniques that he had observed around Europe or heard subsequently. He maintained an extremely close contact with his contemporaries and seniors including Donders, Arlt (both of whom would join him as editors of the Archiv für Ophthalmologie), Bowman and others.

His students and assistants (mostly "voluntary;" often present for months if not years) played multiple roles, including helping with surgery and

Fig. 16 Illustration of von Graefe presiding over his clinic

teaching. Carl Schweigger (1830–1905), a trained microscopist who had studied anatomy and pathology with Heinrich Müller, assisted with Graefe's microscopic studies (6 years as von Graefe's assistant). "Assistants played other roles in the various courses von Graefe organized on the use of the ophthalmoscope (including C. Schweigger who taught ophthalmoscopy). "During the '50s and early '60s of the nineteenth century, a teacher of ophthalmoscopy did not yet have the support of a useful textbook and certainly there was none that he could recommend to his students. Assistants also helped to teach surgery. "Dr. Waldau teaches the ophthalmic operations in a course of 12 lessons, giving, we believe, four courses in each of the two academic divisions of the year" [60] (Table 1).

By all accounts Albrecht was an engaging lecturer. "Graefe was a master enthusing his audience, readers of his journal, and the participants in

Table 1 Notice appeared in Goeschen's deutscher Klink, 1855, No 45 [61]

The instruction course in the eye clinic of Dr. von Graefe begins on November 12; for the current semester the following lectures have been announced	
1	Anatomy and histology of the eye, Dr. Liebreich, public
2	Comparative anatomy and embryology of the eye, Dr. August Müller, public
3	Dioptris of the eye, Dr. Zehender, public
4	The eye diseases and their treatment, Dr. Av Graefe, public, Monday, tueday, Thursday and Friday, 9–10 in the morning
5	Clinic of eye patients, Dr. Av Graefe, private, Monday, Wednesday, Saturday, 10–12
6	Introductory clinic of eye disease, Dr. Eduard Michaelis
7	Practice of microscopic examination of the eye, Dr. Liebreich
8	Ophthalmoscopic practices, Dr. Liebreich.
9	Surgical practices, Dr. A.v. Graefe

meetings of his society towards ophthalmology, in particular numerous visiting fellows of whom many spread his teachings as professors and directors of clinics. Numerous ophthalmologists, far exceeding the confines of central Europe, are proud to be able to trace their ophthalmological pedigree back to Albrecht von Graefe through their ophthalmological fathers, grandfathers, and great-grandfathers" [62] (Fig. 17).

"E. v. Bergmann, who was at Graefe's seminary in 1865: '...there gush forth thoughts which would cause the brain of an ordinary mortal to exhaust itself or even burst asunder, rather than produce such masterly concepts'" [63]. "One was spell-bound in his clinic, as if in a magic place. The multitude of new facts, viewpoints never heard before, the fascinating presentations and glowing enthusiasm acted like a revelation" [5].

Von Graefe's educational reach (at age 26), was extended by his 1854 founding of the Archiv für Ophthalmologie (Fig. 18), the longest continuously published periodical in ophthalmology (now the Graefe's Archives for Clinical and Experimental Ophthalmology (Graefes Archiv für Klinische und Experimentelle Ophthalmologie)). There were other journals of ophthalmology that preceded it including the Ophthalmologische Bibliotek (founded by Himly and Schmidt but lasting only 6 years), Annales d'oculistique (originated in 1838; edited by Florent Cunier (1812–1853); [64] and interestingly later edited in Belgium) and the Archives d'ophtalmologie (which was suspended in 1855), but none with as long a reach. As editor-in-chief, (alone for 1 year, then joined by Arlt and Donders) von Graefe personally reviewed all of the articles submitted; writing eighty percent of the articles in the first edition [63]. "The first volume contained three of his important articles—one on the action of the oblique muscles of the eye, [10] another on diplopia [65] (making a clear distinction between paralytic and comitant strabismus); rediscovering Johannes Müller previous introduction of the concept of comitance [66, 67] and a third on diphtheritic conjunctivitis [68]. With these, at the age of 26 years, he became one of the best-known ophthalmologists in the world" [47].

Graefe was instrumental in founding that the Heidelberg Ophthalmological Society, the oldest ophthalmological society ("In 1857 Albrecht von Graefe met…with some of his followers, among whom were Horner, von Zehender, and Weber, in order to discuss the most recent advances in ophthalmology. In the next year there appeared also by von Graefe's invitation Arlt, Müller, and myself" [69]. In 1863, it first formed itself into a "society;" "the articles of association were written by Graefe and accepted on 5 September" [70].)

"By the age of 39, von Graefe was internationally a unique figure and presided and dominated over the entire Third International Congress of Ophthalmology held in Paris in 1867. He read four papers including the classical description for choroid tubercles, but his most notable contribution was his exposition of his 'modified linear extraction' as a new technique for the operation of cataracts" [71].

Graefe's desired to summarize the advances in ophthalmology included his own contributions (not the least of which was the publication of the afore mentioned article on glaucoma). Graefe was also one of the first in his role as an educator to recognize the importance of extrafoveal function. He introduced perimetry done on a tangent screen, which set the stage for the understanding of the importance of non-macular function [72]

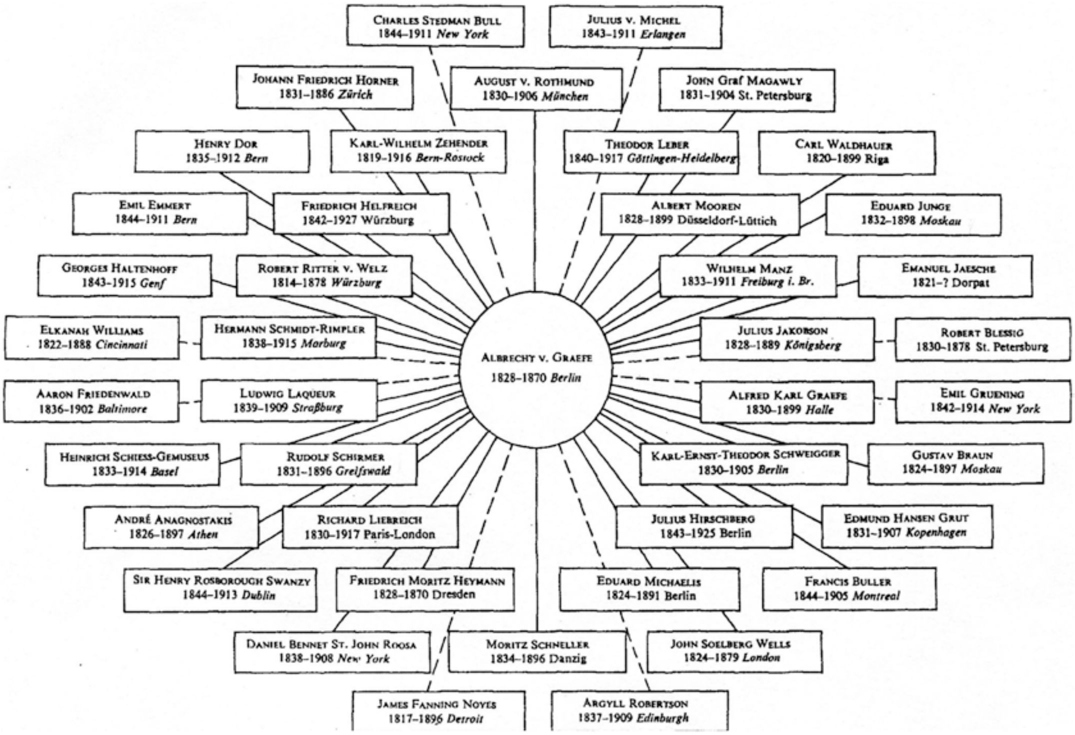
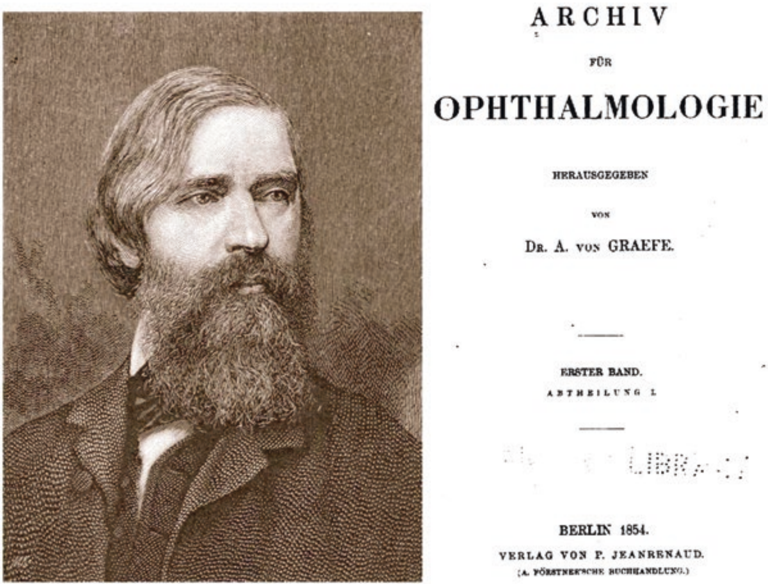


Fig. 17 Illustration of the influence of von Graefe on his assistants and volunteers published by Remky H. in Graefe Arch. Clin. Experimental Ophthalmol. 1995; 233: 547 (used with permission)

Fig. 18 Another portrait of von Graefe, and the faceplate of his first volume of the Archiv für Ophthalmogie, published in Berlin in 1854


ARCHIV

FÜR

OPHTHALMOLOGIE

HERAUSGEGEBEN

VON

DR. A. VON GRAEFE.

ERSTER BAND.

ABTHEILUNG I.

BERLIN 1854.

VERLAG VON P. JEANRENAUD.

(A. FÖRSTNER'SCHE BUCHHANDLUNG.)

and later for the development of the arc perimeter, by Aubert and Förester (a colleague influenced by, but never a student of Graefe), and the quantitative studies to come from Bjerrum and Rønne in Denmark. In many ways Albrecht's interest in education easily outlived him, not just through his extensive writing, but through the teachings of his students, many of whom were to become important educators in their own right.

Unfortunately, Albrecht was never to write a textbook; although some of his review articles (particularly his monograph on amblyopia and amaurosis) could be viewed that way. Contemporary biographers have attributed this lapse to his extraordinarily brief life and his unbelievable clinical load in spite of developing medical problems (pulmonary tuberculosis with pleurisy that was to kill him). Hirschberg specifically stated: "We have to remember that Albrecht von Graefe was continuously endeavoring to expand the horizon of our specialty; he did not have time to write a textbook before he died so tragically at the age of 43" [73]. Many of his students and collaborators more than filled in. What had been lost to tuberculosis far too early in 1870 was recognized not only by Graefe's students and adherents, but also by those that had challenged him. This was probably best expressed by his most vociferous critic in the great cataract debate, Hasner (who was to follow Arlt as Professor in Prague). Hasner called Graefe one of the most meritorious representatives of our science and says about the achievements of Graefe as far as glaucoma is concerned: "This is a great achievement and will suffice to assure him the gratitude of posterity and his worth a life in the service of science" [74]. Even in the succeeding century Albrecht was recognized as "one of the greatest ophthalmologists of the century ... known as the master of ophthalmic surgery. ... the most esteemed ophthalmologist of his period and founder of a great school, to which physicians flocked from all parts of the world, tireless in his activities and a man of high intelligence and profound culture" [75]. Going further, Shasted suggested that he was "One of the greatest ophthalmologists of all time…" [76].

For those of us interested in ophthalmology today, it is useful to remember the contributions of this meteoric (but all too brief) career in the middle of the nineteenth century. "He was the ophthalmologist secondary to none of his epoch and the traces of his earthly existence will never be erased" [77]. On the centenary of Albrecht's birth the British Medical Journal stated: "Of von Graefe it may truly be said that he touched nothing that he did not adorn" [78]. Snyder stated that "No figure in ophthalmology has ever reached the stature of von Graefe" [79].

I will give the final word to Sir Stewart Duke-Elder who in his System of Ophthalmology did for the British what Graefe and Samisch had done for the Germans. In the introduction to the Clinical Evaluation in Ophthalmology Duke-Elder stated: "It would seem to follow almost as a natural corollary that the birth of ophthalmology as a separate science dates from the discovery of the means of examining the inner eye. Since the introduction of the ophthalmoscope in the middle of last century, a constant succession of new and more refined methods of diagnosis has been invented, elaborated, and perfected by innumerable workers as brilliant and as devoted as are to be met with in any other branch of knowledge. Out of these, as an introduction to this chapter, we have chosen for special mention the pre-eminent figure of Albrecht von Graefe (1828–1870), the first German Professor of Ophthalmology, not because he had the prolific inventive genius of a von Helmholtz or an infinite capacity for elaborating perfection of instrumental detail as had Gullstrand, but because, more than any other, he had the genius to apply methods of examination to their utmost clinical use, to reason from his observations more profoundly and to greater purpose than any other clinician before him, and from his reasoning to lay the foundations of a scientific and practical clinical ophthalmology. In the subject-matter of the present chapter alone, he was the first to apply to their full extent the principles of focal illumination in the clinical examination of the outer eye, he was the pioneer in the examination of the inner eye with the ophthalmoscope and in describing and interpreting the new world which was opened up, he was among the earliest exponents of the use of transillumination for detection of tumours, he was among the first to interest himself in and to apply the results of measuring the tension of the eyeball by instrumental tonometry, and he was the first to take clinical records of the pathological visual field. Apart from these activities, there is hardly an aspect of clinical ophthalmology upon which he has not left the mark of his influence; these are too numerous even to refer to, but the most spectacular and dramatic of them ought to be noted in passing—the discovery of the relief of raised tension in glaucoma by the operation of iridectomy" [80].

Acknowledgments I would love to dedicate this chapter to Fredrick Blodi, a remarkable individual whose tireless efforts made Hirschberg's monumental work on the History of Ophthalmology available for those of us whose classical education did not include German.

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10

Karl Koller: The Introduction of Local Anesthesia

Ronald S. Fishman

> *A discovery that bursts on the scene and seems to come out of nowhere has not actually done so. There is always a back-story, sometimes simple, sometimes complicated, sometimes surprising, always interesting.*

The *Allgemeines Krankenhaus*

There is a small museum at the famous *Allgemeines Krankenhaus*—the teaching hospital of the University of Vienna and the general hospital for the city. On the wall next to the staircase leading up to the museum are portraits of some of the luminaries who had worked at the hospital in the nineteenth Century and had made Vienna famous at the time as a font of innovation in medical knowledge and practice.

These include Georg Joseph Beer (1763–1821) first director of the University Eye Clinic; Carl von Rokitansky (1804–1878) one of the founders of modern pathology as a discipline; Joseph Škoda (1805–1881) pioneer in correlation of physical diagnosis with pathological anatomy; Ignaz Philip Semmelweis (1818–1865) the tragic hero of the puerperal sepsis story; Theodor Billroth (1829–1894) founder of modern abdominal surgery; Theodor Hermann Meynert (1833–1892) pioneer In neuroanatomy and neuropathology [1].

And there at the top of the stairs, looking oddly young among this group of gray heads, is Karl Koller (1857–1944), nattily dressed, with a mustache nicely waxed to the tips in the best style of the day (Fig. 1). The great accomplishment that places him there was his introduction to the medical profession—in such a way as to make its utility immediately apparent, immediately adopted and widely applied—was the local anesthetic property of cocaine. He is now the only ophthalmologist to routinely appear in histories of surgery or anesthesiology as the discoverer of local anesthesia.

Coca

The leaves of the coca plant had been used for centuries by inhabitants of the high plains of the Andes where the plant grew naturally. Chewing the leaves gave natives the ability to work long hours in the mines and fields on a minimum of food or rest, often preferring the leaves over food.

Its continued use was encouraged by the conquistadores who defeated the Incan Empire in the sixteenth Century as well as the Spanish overlords of later centuries. That the mouth and tongue were rendered numb by this chewing of the coca leaves was a minor nuisance, not a serious drawback [2].

Surgeons in the ancient Inca Empire had been well aware of this numbing effect. The surgeon would chew the coca leaves and spread his saliva on the scalp in preparing the patient for trepanning or trephining the skull for whatever conditions they found this drastic procedure to be indicated.

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Fig. 1 Karl Koller (1857–1944) as a young man in Vienna. From http://museumofvision.org/dynamic/files/uploaded_files_filename_153.pdf (public domain). Accessed on April 6, 2017

Skulls from archeological digs show many of these skull defects healed at the edges over time, so at least some of the patients survived.

Knowledge of this use of cocaine to enhance labor under hardship conditions percolated over to Europe through several sources in the first half of the nineteenth Century, particularly in the popular writings of the great German naturalist Alexander von Humboldt and the historian of Spain in the New World, William H. Prescott. An Italian physician, Paolo Mantegazza, had practiced in South America in the 1850s and published in 1859 an article extolling coca for its effect on resisting fatigue and speeding up thought processes, remarking in passing that chewing the leaves rendered the tongue and mouth numb [3].

The German chemist Friedrich Gaedcke had already isolated in 1855 an active principle from the coca leaves, naming it *erythroxyline* (after the coca plant *Erythroxylum coca*). Soon other chemists developed other extraction techniques, particularly Albert Nieman who gave his particularly potent alkaloid the name *cocaine* in 1860, and thus transforming the relatively innocuous coca leaves into a dangerous drug. Tasting a chemical was a common part of its identification then and Nieman recognized cocaine's numbing effect. The product was a white powder that varied in purity. Eventually it was realized that the active principle in the coca leaves was unstable and the leaves often lost potency if they either dried out or were soaked during transport overseas to European laboratories. The dissolved cocaine was also unstable when heated. Without an immediate large market for the compound, its commercial prospects were uncertain.

The chemist who first realized a fortune could be made with cocaine was a Frenchman—Angelo Mariani [4]. In 1863 he read Mantegazza and started to sell Mariani wine, made from Bordeux wine mixed with coca leaves, the alcohol acting as a solvent for the alkaloid. Eventually to keep up with competitors it was a 7% cocaine solution. Advertisements promised that Mariani wine led to health, strength, energy. The Pope was known to keep a hip flask filled with Mariani Wine. One advertising poster (Fig. 2) showed a scantily clad showgirl gaily pouring the wine, declaring "Popular French Tonic Wine—Fortifies and refreshes Body and Brain—Restores Health and Vitality" (The showgirl makes one suspect that the brain was not really the organ the message was most interested in—and "vitality" was really a code word for something else).

Montegazza was not the only medical man to note the local anesthetic property of cocaine, but no one recognized it for its potential in surgery before Koller did his work. The unreliability in the potency of extracts may have discouraged early experimenters, and cocaine's unique stimulating effect when taken systemically probably overshadowed the anesthetic element. Still, the pharmacologist von Anrep, experimenting with cocaine in 1879, was aware of its anesthetic effect on his own tongue and even applied it to the eye so as to note the pupil dilatation it caused without taking any special note of the corneal and conjunctival insensitivity [5–9]. Even Koller's own medical school textbook on drugs had recognized the effect and blandly thought it might deserve to be looked into further.

Fig. 2 Advertising poster for Mariani wine. Lithograph by Jules Chéret, 1894. From http://museumofvision.org/dynamic/files/uploaded_files_filename_153.pdf (public domain). Accessed on April 6, 2017

The "Discovery"

This is where matters stood when Koller graduated from medical school. By 1882, he had spent over two years in the laboratory, doing original work in embryology on the origin of the mesoderm in the chicken embryo. His work was recognized as outstanding in the small world of embryologists at the time and was incorporated into a major textbook. He had impressed the famous embryologist Karl von Kollicker and could well have made his career as an embryologist, but turned from this to ophthalmology. Koller was an intern at the *Allgemeine Krankenhaus* when he spoke with Carl von Arlt, the director of the ophthalmology department. Koller hoped to eventually obtain one of the two highly prized assistantships in ophthalmology, a position with a better stipend and the opportunity to develop the surgical experience one could not obtain no matter how long one attended ophthalmology clinics as an intern. Such assistantships were essentially apprenticeships under prominent professors and not the multi-layered residencies we know today. Koller wanted a research project where he could prove his worth to Arlt and qualify for the appointment.

Arlt told Koller that there was an urgent need for a local anesthetic in eye surgery. General anesthesia at the time was of little use. The inhalation technique for ether or chloroform at the time required a mask over mouth and nose and left little room for the eye surgeon. Placing the patient in deep anesthesia and removing the mask to allow the surgeon room made the surgeon rush to finish before the anesthetic wore off, and could lead to catastrophic retching or coughing during surgery or shortly afterwards. Thus the reality was that eye surgery was usually done without any anesthesia, at a time when general anesthesia had already been available to other surgeons for over three decades. Some cataract surgeons before operating had their cataract patients undergo training sessions until they showed they could stand pain without moving.

Taking Arldt's suggestion to heart, Koller, already quite familiar with laboratory procedure, promptly did a series of experiments trying to induce a local anesthesia of the eye by topical applications of solutions of the narcotic morphine, the sedatives chloral, bromide, and other drugs. But these drugs had no demonstrable anesthetic effect, not surprising since we now know they act solely on the brain, not peripherally.

Working at the hospital already was a friend from medical school days who was working in neuroanatomy and neurology—Sigmund Freud (Fig. 3). Freud was also ambitious and knew the best way to fame and fortune in medicine was to come up with an effective new way to treat illness. He was particularly interested in depression and various neurological conditions. In 1884, Freud searched the literature on cocaine, including Mantegazza's report, and was particularly impressed by articles from America describing the substitution of cocaine for morphine in an attempt to treat morphine addiction. Freud wrote a review entitled "On Cocaine" in which his euphoric description of cocaine's effect on himself resulted from his obtaining a quantity of the expensive powder and using the drug while writing the paper. He hoped it would be particularly useful in treating neurasthenia, indigestion, and morphine withdrawal. The anesthetic properties might be useful in treating the pain of local skin infections, as an analgesic. There was no mention of any use in surgery.

Fig. 3 Sigmund Freud (1856–1939) in 1884. From https://www.google.com/search?q=images+sigmund+freud&tbm=isch&tbo=u&source=univ&sa=X&ved=0ahUKEwjCpZeB84_TAhXGMSYKHbJLChoQ7AkILg&biw=1362&bih=1041#imgrc=jDE8ZxcvhLwixM: (public domain). Accessed on April 6, 2017

One day at the end of August or early September of 1884, about to leave Vienna on vacation in order to meet the fiancée he had not seen for a year, he met with Koller at the hospital and discussed the experiments they had done together in measuring the effect of cocaine on muscle strength and endurance, and what further work they could do. Koller took some of the powder and put it in his pocketbook. Then Freud left, not to return for a month.

Koller later described what happened next. He let a colleague test a pinch of powder on his tongue. "How that numbs the tongue" he said. "Yes" said Koller "that has been noticed by everyone who has eaten it."

> And in that moment, it flashed upon me I was carrying in my pocket the local anesthetic for which I searched some years earlier… I went straight to the laboratory, asked the assistant for a guinea pig for the experiment, made a solution of the powder which I carried in my pocketbook and instilled this into the eye of the animal." [9]

The resident at the laboratory later recalled they first used a frog, then a rabbit and dog. Then they tried it on each other's eyes. Koller went to some lengths to detect how deeply the cornea was affected.

> "The insensitivity is complete. It lasts for about ten minutes. During this time the cornea can be scratched with a needle at will, scraped in all directions, perforated or cauterized with siver nitrate until it becomes completely white, and it can even be cut without any reaction from the animal. Pain occurs only if the aqueous humor flows out or if the iris is being touched [10]."

Koller was lucky here that Freud had obtained a particularly pure sample of cocaine, one that had not been degraded either before or after the chemists had worked on it. If the anesthetic effect had been incomplete or unreliable, we would not be hearing the barely suppressed excitement he felt during those hours in the laboratory.

Koller quickly wrote up a report. He knew that the important German Ophthalmological Society meeting was to be held in Heidelberg in mid-September—the ideal forum in which to demonstrate this property of cocaine. However, being an impecunious intern and not having ready funds to pay for his own trip to Heidelberg, he managed to get a more senior colleague—Josef Brettauer—to read the report at the Heidelberg meeting on September 15. After Brettauer had done this, he had with some showmanship demonstrated cocaine's action on a dog's eye in front of the audience and created a sensation.

The Acceptance of Local Anesthesia

Arldt was in the audience and must have been gratified. Another member of the audience was Herman Knapp, who promptly on returning to America reported the news in the journal he founded and edited—the new *Archives of Ophthalmology* [11]. He then heroically experimented on himself (on all his own available mucous membranes, including his urethra as well as the eye) and reassured readers that cocaine was marvelously effective as an anesthetic, and not only for the eye. By 1885 he had combined his own report with others in a comprehensive description of cocaine's utility in many forms of surgery. Soon Knapp was the first to use a retrobulbar injection, in an enucleation. It worked nicely, but for some reason was not regularly used in cataract surgery for 30 years. The facial nerve block for akinesia in cataract extraction also had to wait till Van Lint's use of it in 1914 [12].

Another American ophthalmologist at Heidelberg, H.D.Noyes, [13] reported the news to the New York Medical Journal, a weekly newsletter whose subsequent issues in the next few months carried a cascade of positive reports by surgeons who duplicated Koller's successes. Koller himself presented a longer account of cocaine four weeks later on October 17 to the Vienna Royal Imperial Society of Physicians in which he also described the analgesic action he had observed in patients with corneal and conjunctival disease. But its most remarkable usefulness was for surgery. Making sure that Freud would share some of the credit, the paper was published in December with the statement "Cocaine has been prominently brought to the notice of Viennese physicians by the thorough compilation and interesting therapeutic paper of my hospital colleague Dr. Sigmund Freud" [14]. Freud indeed had been surprised by the sudden turn of events when he returned from seeing his fiancée, but he was supportive, and we shall see later how important this was.

Koller also promptly suggested to his friend, Jellinek, an ENT assistant, that he make experiments with cocaine in his own sphere of activity, and Jellinek reported the results at the same October 17 meeting [9]. Topical application to the eye was promptly expanded for use in surgery of the mouth, nose, throat and teeth as well as hypodermic infiltration of small regions of the limbs. Tourniquet techniques were described in trying to prolong cocaine's action. Its tendency to constrict blood vessels was noted as augmenting its effective duration, although the danger inherent in repeated applications to the same area of mucous membrane, particularly the nose, took much longer to be widely appreciated.

Why was Koller so successful in bringing local anesthesia into surgery? Unlike the men who had previously mentioned the anesthetic quality of cocaine and speculated on its use in a rather off-hand way, Koller actually did a planned series of experiments and eventually had extended the work to clinical situations, ameliorating the pain of corneal ulcers and other eye disease. Then, most importantly, he got the ear of a group that could best appreciate this innovation.

Why did use of the local anesthetic spread so quickly? True, there was a well-recognized need for it, obvious to any surgeon, but that had not been enough for Humphrey Davy in 1799 to take his knowledge of how nitrous oxide, the so-called "laughing gas", could induce insensibility to pain and bring it to the operating table, although he had been a surgeon's assistant and must have been well aware of the crying need for it. Ether and chloroform were also known for some time before being widely accepted in the operating room. Once they got there, the need for new instrumentation was recognized, as well as the experience to measure and safely administer these inhalant gases, which on occasion could be deadly.

This did not seem to apply at first to the topical administration of a cocaine solution. It was a simple and quick addition to surgical routine. It was not a disruptive technological innovation in the same way that aseptic surgery was. This required years to take hold because it required so much reorganization in hospital routine and surgical habits, and infection was not an invariable result of surgery, so that it took longer to overcome surgeons' obdurate conservatism. The rapid spread of local anesthesia stands as an exception to Ernst Mach's witticism that science advances funeral by funeral, until a new generation accepts the innovation.

The advent of general anesthesia in the 1840s was more than a humanitarian nicety. It allowed surgeons to refine their techniques with careful hemostasis, dissection, and suturing, avoiding unnecessary tissue damage and encouraging them to introduce a whole range of hitherto impossible procedures. The advent of local anesthesia gave the same benefits to eye surgery.

It is true that the modern physician is struck by how casual was the attitude of physicians in those days who, hearing of this white powder, made up their own solutions and blithely started using it on patients in various ways, doubtless without spending much time explaining how untested it was.

As usual with any new therapy, eye surgeons soon encountered complications. The vasoconstrictive action of cocaine occasionally led to sloughing of the conjunctival flap in cataract extractions. Rebound vasodilation made any bleeding worse, sometimes leading to a vicious circle when repeated doses of the drug were applied to control hemorrhage. Eventually various congeners of cocaine with fewer side effects were introduced, especially Novocaine in 1905. As a result, by 1921, Novocaine was by far the most commonly used agent for local anesthesia "ten times safer than cocaine" since it was not habit forming [15], although cocaine continued to be used for cataract surgery well into the twentieth Century [5].

Koller himself soon recognized that relying solely on topical application of cocaine to the corneal and conjunctival surfaces was unreliable—the effect was too variable in depth and duration, and well-nigh useless in strabismus surgery or enucleations. He began relying on subconjunctival and perimuscular injections of sterilized solutions, and here he was fortunate that he could rely on the new standards imposed by asepsis [16].

Epidural and spinal anesthesia required several years to be widely used but use of regional nerve block anesthesia was almost immediate. William Halsted, the founding chief of surgery at the Johns Hopkins Hospital, was able to claim success, within a year, in over 1000 cases of local and nerve block regional anesthesia, although the paper usually cited in proof of this [17] is incomplete and generally so incoherent as to indicate that Halsted had already become addicted to cocaine, a condition his doctors tried to rid him of by using morphine, so that he suffered from a double addiction for the rest of his life [18–22].

The Cocaine Epidemic

In fact Koller and Freud had inadvertently opened a Pandora's Box of cocaine addiction, a virtual epidemic among medical personnel who self-experimented with this new addition to their armamentarium. Within a year the

New York Medical Journal backtracked on its prior unconditional advocacy of cocaine to point out that several physicians to its knowledge had become insane from overuse of the drug. Even worse, because its absorption from mucous membranes into the systemic circulation was not recognized for some time, inadvertent overdosage of it by repeated local applications had also caused the death of several general surgical patients [20].

In the midst of this burgeoning controversy came the paradoxical case of Dr. William A. Hammond (1828–1900). As Surgeon General of the Union army for two years during the Civil War, he had founded the Army Medical Museum. Afterwards, specializing in neurology, he wrote the first American textbook of neurology and helped found the American Neurological Association. This was a man with considerable prestige in American medicine who could be expected to provide a sound arbitration of the situation. Instead he failed spectacularly. Having previously published a book on the effects of tobacco and alcohol with observations made by experiments on himself, he decided to do the same with cocaine.

In November, 1886, he described to a meeting of the New York Neurological Society the effects of injecting himself on different nights with increasing doses of cocaine. When he came to the point of injecting himself with four grains of cocaine, he quickly developed a severe tachycardia alternating with bradycardia. Then he was overwhelmed with an irresistible urge to write, frantically writing page after page that he thought at the time were clear and logical with a beautiful diction he had never been capable of before, only to find the next morning the writing to be strange and worthless, almost incoherent. Failing to be discouraged from his project by these symptoms he finally one night injected 12 grains of cocaine, a near-fatal dose. Within a few minutes the cardiac arrhythmia returned and he felt his “mind passing beyond his control”, feeling elated and believing nothing could harm him. He then lost his memory of the experience but the next morning found books and overturned chairs scattered on the floor of his library [20].

This manic behavior resembles nothing so much as the story of *The Strange Case of Dr. Jekyll and Mr. Hyde*, written in 1884, (published in1886) and makes one wonder about whether cocaine inspired Robert Louis Stevenson to write the story in the first place. Although Hammond recognized that his “experiment” had almost killed him, he denied that cocaine was addictive and remained a proponent of it in talks to medical societies. This in spite of the fact that in treating his own chronic rhinitis he had obviously abused cocaine himself [20].

Other voices however were being heard, counseling against the wholesale, untrammeled exploitation of the drug into tonics and nostrums of all sorts, jncluding a spray for hay fever and a solution to be applied to the gums of teething infants. The leading authority in the US on the adverse effects of indiscriminate use of cocaine, particularly the mental ones, was J.B. Mattison, medical director of a rehabilitation institution for addicts in Brooklyn. By the mid-1890s he was able to describe many instances of mania, paranoid delusions, and other harrowing features of cocaine misuse [20].

One of the victims of cocaine was Freud himself, and he does not cover himself with glory when it comes to this affair. Experts in treating addiction strenuously reproached him for the reckless enthusiasm with which he had advocated the use of cocaine to wean addicts off of morphine. This was particularly reprehensible when his experience was with only one disastrous effort by means of cocaine to wean an admirable and promising medical colleague, Ernst Fleischl von Marxow, off his morphine addiction due to chronic pain from an amputated thumb. This made him a double addict and led to the man’s tragic premature death in 1891. Still, Freud continued to prescribe cocaine to his own patients for various ills and continued to use it intermittently himself for some years into the mid-1890s, when he began using a cocaine nasal spray for alleviation of his own migraine headaches and seriously abused the drug for at least two years. A plausible case has been made that some of the ideas that became part of the foundation of psychoanalysis were inspired by cocaine [20, 22]. Freud did remain addicted to cigars for the rest of his life, a vice that, as it had Ulysses S. Grant, eventually killed him [23].

The Immediate Aftermath

Koller himself escaped cocaine addiction. But all did not go well for him. On January 4, 1885, a few months after the cocaine work, Koller was in charge of the admitting room and was presented with a man whose injured finger had been so tightly bandaged previously that the tip was cyanotic. The surgical intern, a Friedrich Zinner, claimed the patient for the surgical service, but this did not stop Koller from removing the tight bandage right then and there. This perceived infringement on his prerogatives so annoyed Zinner that he loudly called Koller an "impudent Jew". (Freud heard it was "Jewish swine".) Koller, proud and touchy at best, was not the sort to turn the other cheek and hit the man in the head [9].

The two men were both medical lieutenants in the army reserve, familiar with the military honor ethos and otherwise disinclined to dismiss the insult with hot words or a shrug. The later police report remarked that "There was no attempt at mediation, inasmuch as a settlement of the insult was automatically precluded by the nature of the insult" [24]. A duel was arranged. Duels were ostensibly illegal, but still popular between Austro-Hungarian aristocrats, particularly military officers, though not among doctors. Koller had never dueled, was unfamiliar with swords, but took a practice lesson. At the duel, *spadones,* thin sharpened foils, were used, not in the swashbuckling sword fights that go on for some time with thrusts and counterthrusts familiar to us from the cinema, but in three separate and quick rounds. On the third thrust, Koller gashed his opponent in the arm and face and escaped harm himself. His opponent was led away to be bandaged. Koller received letters of congratulations from colleagues, including Freud. The two duelists had to appear before the district attorney in February, when Zinner presented in mitigation that he feared losing his army rank if he had not made the challenge. Koller refused to answer any questions and remained silent. Neither was punished. The story was written up in the local newspaper and Koller, having enjoyed fame, now tasted notoriety [9, 24] (Fig. 4).

All this might be too extravagant to bring into Koller's story If this were only fiction. It could still have been just a minor episode if Koller, expecting the offer of a prized assistantship after the Heidelberg meeting and not receiving it, had not finally realized that he had no chance of obtaining it. He had fulfilled Arldt's challenge and yet it had not been enough. The disappointed Koller became depressed. When Freud's father came to his son at the hospital one day in April, complaining of recent poor vision in one eye, Freud was ready to dismiss it as a minor problem, but Koller diagnosed glaucoma and administered the cocaine anesthetic at the operation the next day [25]. The surgery was a success but it did not change Koller's outlook. He left Vienna to try his luck elsewhere. His prospects were explicitly spelled out for him by Freud, who wrote him in July 1885 with hospital gossip about vehement anti-Semitic comments made by an ophthalmologist there about appointing Jews.

> "This was naturally said without any reference to you…but you will retain sufficient reasons to form an unfavorable judgment of your own prospects. That you should come home now does not seem very sensible to me. You get into bad situations too easily in Vienna and you have not anything to come back for. Stay away as long as you can. Even if you don't accomplish much there, it is still more than you would do here. And when you are ready, go confidently to America. You will be pleased with this advice. [9]"

In August, 1885, having no qualms about giving unsolicited advice, an endeavor usually bound to fail, Freud again wrote to Koller:

> "Dear Friend: What could you possibly wish to do during these months other than to recuperate like everyone else in beautiful country, good air, and to ride, to climb mountains, and to do anything that will help you to get well?
>
> By the middle of September you could really go to the International Meeting of Natural Scientists in Strassburg. In the first place you are sufficiently human to enjoy the attention you will attract, and secondly there may be a market in which someone would buy you. If you cannot find

Fig. 4 German students in a sabre duel around 1900. Painting by Georg Mühlberg. From https://en.wikipedia.org/wiki/Georg_M%C3%BChlberg (public domain). Accessed on April 6, 2017

> a post quickly you may have to return to Berlin. I don't know of any better place if you don't want to go to America straight away. You know very well that as long as you have not transformed yourself thoroughly you dare not hope to get on better than before in Vienna. They will forgive you your bluntness but not your irritability. [9]"

This was good advice. Koller did attend the meeting and was "bought" there by none other than the famous Frans Cornelis Donders. Koller went to Utrecht, Holland, and studied with Donders and his son-in-law Herman Snellen for two valuable years. There was likely no better ophthalmological training anywhere else in the world.

Freud himself, the authentic genius, wanting a career in research but having no independent income and wanting to get married, had already decided to leave laboratory work for medical practice. He served at the hospital for three years as the equivalent of a resident in internal medicine, neurology and psychiatry. He then applied for a position on the staff and was appointed as a *Privatdozent* in neuropathology. This was a valuable recognition by the medical school that he could give lectures and collect whatever fees he could from willing students, a common feature of medical education in those days. Freud then won a highly prized traveling fellowship that allowed him to go off to spend 5 months attending Jean-Martin Charcot's neurology clinic in Paris. He then opened an office for the private practice of neurology and psychiatry. Despite all his later fame, he never advanced to a secure university professorship. His office after 1891 was in a townhouse only four blocks away from the hospital, (the famous *19 Berggasse)* where he and his large family lived and he practiced till 1938, when they escaped the Gestapo to get to London where Freud died the next year.

At one point Koller wanted to send Freud a gift to mark Freud's new practice. Remembering that Freud had spent years of laboratory work in neuroanatomy and written several articles on it, suggested a microtome. Freud responded

> "…thank you therefore very much for the microtome you mean to send me. If you want to give me something I need urgently, let it be a perimeter, since as a clinician I depend more than anything else on the study of hysteria and one cannot publish anything nowadays without a perimeter [9]."

Freud did get the perimeter and thanked Koller on January 1, 1887.

> "Dear Friend: After a long wait to see whether your beautiful but silent present would be followed by a letter, I am using New Year's Day to thank you very much and to tell you how much pleasure the perimeter (just the thing I wanted) gave me… Soon you will get a trifle from me, a lecture I gave to the Medical Society. I thank you for your last paper which I naturally did not understand when I tried to read it. However, I am happy to think what clinical schooling and association with men of good will must have made of you [9]."

These chatty letters clearly show the friendship between the two at the time. Koller went to England for several months, incidentally meeting the American ophthalmologist Lucien Howe at an Oxford congress, a meeting Howe was to recall with effect later. Hesitating at first, Koller finally bit the bullet and emigrated to New York in 1888.

Fig. 5 Koller in middle age in practice in New York City. From https://en.wikipedia.org/wiki/Karl_Koller_(ophthalmologist) (public domain). Accessed on April 6, 2017

Koller in America

Koller found in New York City a receptive profession, developed a thriving practice, became a staff member of the Mt. Sinai Hospital and later the first head of ophthalmology at the Montefiore Hospital. He married and had a son and a daughter. He signed his name as "Carl" instead of "Karl" and became a U.S. citizen in 1902. He practiced for over 50 years, becoming prosperous enough to enjoy fly-fishing in the Rocky Mountains and traveling widely in the United States, evidently never returning to Vienna. Asked to cooperate in a *New Yorker* Profile, he declined. His articulate daughter—Hortense Koller Becker—after his death found the many letters from Freud that her father had carefully saved and wrote an account of his time in Vienna—the best account of Koller yet published [9] (Fig. 5).

Koller in later years was sensitive about being introduced to cocaine by Freud and appearing as an opportunist and stealing the idea from him. This tended to be implied by overenthusiastic and careless admirers of Freud. Their friendship had foundered, but not due directly to this controversy [26]. Koller did disdain psychoanalysis and did object that Freud's mention in his 1925 autobiography "that he had told [Koller] also about cocaine" was ambiguous, and Freud had not been quick enough to contradict his careless admirers. But Freud had been quite clear in his autobiography about giving Koller credit: "Koller is therefore rightly regarded as the discoverer of local anesthesia by cocaine, which has become so important in minor surgery" [27]. Koller also remembered the honorable way Freud had acted back in 1884 when another doctor at the hospital tried to claim the credit. Freud had the man write a retraction and then explicitly got the truth on record in print in January 1885 [28, 29]. Still, when he was almost 80, and even after he had started receiving belated awards recognizing his accomplishment, Koller still bitterly felt Freud to be " a grand writer, but a thoroughly dishonest and unscrupulous person", a sad end to an old friendship [30].

Freud was ambivalent in remembering the affair, sometimes conciliatory, sometimes dismissive. At the time of the original reports, he clearly supported Koller. In writing to his fiancée, he was elated that something so substantial had resulted from his own preoccupation with cocaine [25]. Later, after his hopes for cocaine as a panacea were dashed, he would have been less than human if he had not been upset with himself, chagrined and dismayed about not recognizing the one medical benefit of cocaine that would stand the test of time. But he was well aware that Koller's discovery was an instance of Pasteur's idea that chance favors the prepared mind. Freud admitted that his own interest had been too diffuse, whereas Koller was concerned mainly with eye problems. "This is the only way to make important discoveries, to have one's ideas exclusively focused on one central interest" [25]. Then tongue-in-cheek: "It was the fault of my fiancée that I was not already famous at that early age… But I bore my fiancée no grudge…" [27]. Back in 1884 there had been no animosity between them. Freud playfully inscribed a reprint of his cocaine review to Koller as "Coca Koller" (the formula for Coca Cola initially included cocaine). From this vantage point it appears clear that even if Freud had been around all that September, he had no inkling of its potential in surgery. Koller would have still been the one to have the crucial insight, the one to do the organized experiments, the one to report them to a group that could appreciate them.

Koller was never awarded the Nobel Prize, joining Jules Gonin and Gerd Meyer-Schwickerath as ophthalmologists who earned it but were passed over. He did receive the first Howe Medal of the American Ophthalmological Society—an award some say that Howe, remembering the demonstration in Heidelberg and that meeting in Oxford, created with Koller in mind (Fig. 6).

After his death in 1944, a patient who was treated by him when she was a child remembered that his brusque ways terrified her at the time. A colleague at the Mt. Sinai Hospital in New York remembered that Koller could be a martinet with the residents [31]. No doubt Koller sometimes found the casual attitudes of Americans at odds with the *Mittel-Europa* culture he was trained in, and had to leave behind.

On the other hand, colleagues remembered that he was quite respected professionally, and although he could be irascible, he could also be humorous, even whimsical. "… a stimulating personality, always speculating and wondering about the unknown and the unsolved problems… [we] sensed in him a real person—true, reliable and fearless…" [32]. He would have added to the glory of the *Allgemeines Krankenhaus* if Arldt had fostered his career in Vienna, but its loss was New York's gain.

Fig. 6 Koller as an older ophthalmologist, during the time he received many belated awards. From https://www.general-anaesthesia.com/images/karl-koller.html (public domain). Accessed on April 6, 2017

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Allvar Gullstrand: Dioptrics of the Eye and the Slit Lamp

11

Richard Keeler

Introduction

The Swedish ophthalmologist Allvar Gullstrand (1862–1930), the inventor of the slit lamp, should perhaps be as well known among ophthalmologists as Hermann von Helmholtz (1821–1894) but this is not so. Helmholtz had the advantage of inventing the ophthalmoscope, which instantly and dramatically revolutionized ophthalmic practice. The slit lamp, invented by Gullstrand in the first decade of the twentieth century, was slower to gain acceptance and was thus less recognized. But it is used today to examine all parts of the eye including the retina, and has withstood the test of time as a critical component of clinical care.

Gullstrand did not set out to devise a slit lamp, but his studies on the dioptrics demanded new lenses and instruments. One such invention was his slit lamp for which he is best known, but there were others whose impact was also significant in the evolution of ophthalmology such as aspheric and best form ophthalmic lenses and reflex-free fundus examination that led to improved ophthalmoscopes and a fundus camera.

Early Years to Lecturer in Ophthalmology 1891

At a very early age while at school at Landskrona in Sweden where he was born in 1862, Allvar Gullstrand (the name Allvar in English means "serious" or "earnest") (Fig. 1) demonstrated an exceptional inclination for mathematics. His teacher at the grammar school in Jönköping recognising this talent had taught him so effectively outside the curriculum that by the time he left for university he had a good knowledge of differential and integral calculus [1]. This was an early indication of a career that was to have such a profound influence and produce such lasting benefit to the development of modern ophthalmology.

The young Gullstrand's decision to study medicine at university instead of other more technical subjects, was almost certainly influenced by his father, Dr. Pehr Alfred Gullstrand, who was an accomplished and highly respected physician and the town's Principal Municipal Medical Officer. In 1885 Gullstrand went with his young wife, Signe Breitholtz, to Vienna for 10 months to further his studies in medicine learning about ophthalmoscopy, otoscopy and laryngoscopy.

In 1888 Gullstrand qualified as a doctor. His next quandary was to decide which medical speciality to choose. With his knowledge of mathematics it was obvious that ophthalmology would suit his talents admirably and he moved to

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Fig. 1 Gullstrand as a young man. (Portrait of Allvar Gullstrand from the Hagströmer Medico-historical Library, Karolinska Institutet. Reproduced with permission)

Stockholm where he entered the ophthalmological clinic of the Seraphim Hospital under Johan Widmark (1850–1909) the first Professor of Ophthalmology at the Karolinska Institutet. After his training as an assistant he started practicing as an ophthalmologist in Stockholm. He also worked in one of the outpatient ophthalmic clinics and took a position as assistant at the Board of Health.

It was during his period of medical studies that he became interested in astigmatism.

Gullstrand started to question the concept of the astigmatic pencil as a conoid with two focal lines at right angles. He concluded the result of his research with a new theory which formed the basis of his doctorate thesis *Bidrag till astigmatismens teori* (Contribution to the theory of astigmatism) [2] which he published in 1890. This work on astigmatism was the start of Gullstrand's dedication to the study of the physiology of the eye and its optics. The material he had accumulated led him on to undertake the most detailed work by anyone on the dioptrics of the eye and to challenge the calculations of both Helmholtz and Marius Tscherning (1854–1939).

In 1891 Gullstrand was appointed Lecturer in Ophthalmology at the Karolinska Institutet in Stockholm and embarked on a period of intensive work, both clinical and in research. In his new job Gullstrand was obliged to undertake clinical work, including the practice of refraction. He had in any case determined to continue his research work on refractive aberrations.

During these years of research Gullstrand turned his attention to refraction of the eye using the current knowledge and laws as his guideline, but soon found that existing information on the refracting surfaces of the eye was not sufficiently reliable or detailed for his requirements. His research began with the study of the contours of the anterior corneal surface and for this he used a photographic technique. He mounted a camera at the centre of a keratoscope (after Placido's disc) and took photographs at 25 cms from the eye. The keratoscope was specially constructed so that the concentric rings would give images of half a millimetre at the working distance.

At this time photographic film was yet to make an appearance and glass plates were used in cameras to record images. As an example of Gullstrand's meticulous attention to detail he coated the plate with a mixture of soot and benzol with the same refractive index as the glass, in order to avoid double images [1]. He then measured the distances between the individual rings with a microscope and developed suitable algorithms to reconstruct the corneal shape. This was the first successful *quantitative* evaluation of the shape of the cornea (this original photographic work with the keratoscope was later taken up by Marc Amsler in 1930 with his photokeratoscope).

At the end of four exhausting years it was clear to Gullstrand that the time he was giving to several areas of public service in ophthalmology together with his private practice, was not allowing sufficient time for his scientific work but in 1894 a piece of good fortune came his way. A Chair of Ophthalmology in Uppsala was created specially for him, (at the age of just 32) allowing him the extra time to fully concentrate on his scientific work.

The new Professor, His Research and His Inventions

With his appointment as Professor of Ophthalmology, Allvar Gullstrand moved his home to Uppsala in 1895. Once there, he had first to organise rooms and equipment for patients to be examined and operations performed. The teaching of students which was also an integral part of the new appointment was spread over two terms lasting 3 months each.

Having set up the department Gullstrand was able to resume his scientific work. He continued his investigation into aberrations and how they affected the optical system of the human eye, his work culminating in 1900, with a major publication on the subject "*Allgemeine Theorie der monochromatischen Aberrationen…*" (General theory of monochromatic aberrations and their immediate significance for ophthalmology) [3]. In this paper he emphasised the importance of aspherical lenses to improve optical imaging.

In the following year he made a first visit to the Zeiss optical company in Jena which was to prove of great importance. This was the start of a close collaboration with this company and it was from this initial visit that the great inventions with which he is associated followed. Gullstrand's contact on this visit in August 1901 was Siegfried Czapski (1861–1907) (Fig. 2) who had been a member of the executive board since 1889 and had published several papers on the results of Ernst Abbé's "Theory of Optical Instruments" [4]. Gullstrand was inspired by this compilation and had sent Czapski his paper on monochromatic aberrations which he acknowledged and which resulted in the invitation to Gullstrand to visit Jena.

The person who took on the design and calculation of the optics for Gullstrand's ideas was Moritz von Rohr (1868–1940) (Fig. 3).

One of the most fruitful results of Gullstrand's collaboration with von Rohr was the design of a new point-focal or best form glass "Punktal" spectacle lens significantly reducing distortions when looking through the periphery. Gullstrand also computed a doublet for aphakic patients, the Katral cataract lens, which was launched by Zeiss in 1910. The artist Claude Monet bought a pair of these lenses

Fig. 2 Siegfried Czapski c.1905. Source. ZEISS Archives

Fig. 3 Moritz von Rohr c.1900. Source. ZEISS Archives

Fig. 4 Gullstrand-Zeiss operating loupe. (Royal College of Ophthalmologists' Collection)

in 1923, following his cataract operation, helping him in his drive to continue painting.

Another successful outcome of the Gullstrand-von Rohr collaboration at this stage was the manufacture of the Gullstrand adjustable spectacle magnifier (Fig. 4) used for microsurgery, including ophthalmic surgery, by many surgeons throughout the world.

In 1906, Robert Tigerstedt (1853–1923), the Finnish medical scientist and physiologist, was in the process of compiling his Handbuch der physiologischen Methodik, [5] and invited Gullstrand to write a section on the methods of examination of the eye. In a long paper Gullstrand explains in one section that the best way of examining the optical media and refracting surfaces was with oblique slit focal illumination in conjunction with a pair of telescopes for examination.

To create an exact schematic eye, which had become his over-riding ambition, Gullstrand needed to measure, very precisely, the refractive powers of the successive transparent layers of the ocular media, the anterior and posterior surfaces of the cornea and lens, and those of the media of the eye. From these measurements he would be able to calculate the constants of the eye and produce his schematic eye. At this point, however, something of great significance took place, for while Gullstrand was investigating a way of measuring the anterior and posterior curvature and thickness of the cornea, the concept of the slit lamp was born.

The Slit Lamp

In order to measure the thickness of the cornea it was necessary to observe the reflex image of the posterior surface and then use the same method as had been used to measure the thickness of the lens using Purkinje's catoptric images. Helmholtz had tried in vain to see the posterior reflex of the cornea using an oblique spot illumination but this light source was too weak and diffuse. Gullstrand found the solution in the Nernst lamp. This lamp provided him with a source of light which combined with optics produced a line of intense light on the cornea. The lamp did not use a glowing filament. Instead, it used a ceramic rod of zirconium oxide—yttrium oxide that was heated by a separate heater filament to incandescence. The significance of the construction of the light element of this lamp and its recognition by Gullstrand cannot be overstated. Instead of a filament producing diffuse light, the Nernst lamp had a linear "glower" 20 mm long and 5 mm wide enabling a far greater concentration of light, in the form of a slit, to be imaged on the eye.

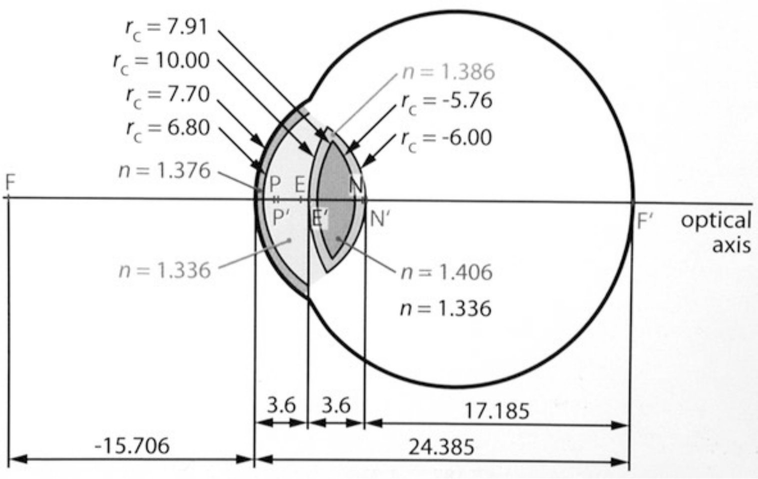

Fig. 5 Exact Gullstrand Schematic Eye. (Michael Kaschke, Karl-Heinz Donnerhacke, Michael Stefan Rill. Optical Devices in Ophthalmology and Optometry. 34, 2014. Copyright Wiley-VCH Verlag GmbH & Co KGaA. Reproduced with permission)

In use the lamp unit was inserted at one end of a darkened tube with its glowing rod imaged by an aplanatic condensing lens on a diaphragm with a slit opening at the other end. The light emerging from the illuminated slit aperture was focussed by a 14D aspheric lens producing a slit-shaped image on the anterior part of the eye.

The use of this light source, projected at an angle to the line of examination enabled Gullstrand to measure very accurately the interface of the anterior and posterior surfaces of the cornea and subsequently calculate its constants. This was one of the steps that led him to complete what became known as the Gullstrand Schematic Eye (Fig. 5). The modern presentation in Fig. 5 (2:1 scale), incorporating all of Gullstrand's data, shows the scheme of the Exact Gullstrand Eye (for relaxed vision with the radii of curvature and lengths given in millimetres). This "eye" has since been used by ophthalmic researchers in countless ophthalmic and optical calculations.

In order to put theory into practice Gullstrand, with the assistance of the engineering department of Uppsala University, built a trial model known as the Nernst Slit Lamp designed by Professor Gullstrand (Fig. 6) which was shown for the first time at the Heidelberg Ophthalmological Society meeting in the summer of 1911.

When Gullstrand embarked on his research into the structure of the cornea he had little idea how important the instrument he had invented was to become, nor the profound effect it would have on the world of ophthalmology. There is no record of Gullstrand himself publishing anything about the clinical use of his slit lamp. The first mention of this new method of examination was some years later in 1914 by Heinrich Erggelet (1883–1969) in his paper "Befunde bei fokaler Beleuchtung mit der Gullstandschen Nernst-Spaltlampe" (Findings in focal lighting with the Gullstrand Nernst slit lamp) [6].

Gullstrand examined the illuminated structures of the eye with a pair of short focus binoculars of x4 magnification (Fig. 7). Although the slit lamp was mounted on a stand and was therefore quite stable, both the aspheric condensing lens and binoculars were hand-held. The patient sat on a chair next to the table with the slit lamp mounted on it, but initially there was no chin-rest. By Gullstrand's own admission this method of examination of the anterior part of the eye required great manual skill. As a result, the Nernst Slit Lamp found little clinical acceptance. This slit lamp illumination was also used as a hand-held light source for ophthalmoscopy, both direct and indirect, retinoscopy, and stigmatoscopy. Clinical acceptance by ophthalmologists of this new form of examining the structures of the eye was slow, most of them seeming to be quite content to use a hand-held light source with a low power monocular loupe.

In hindsight it is surprising that Gullstrand was satisfied with the comparatively low magnification of the x4 binocular telescopes for his slit

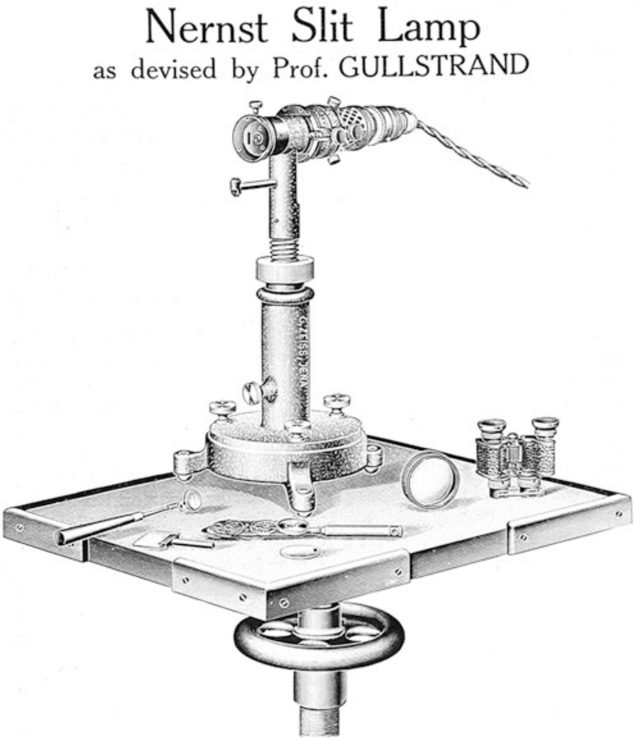

Fig. 6 Gullstrand Nernst Slit Lamp

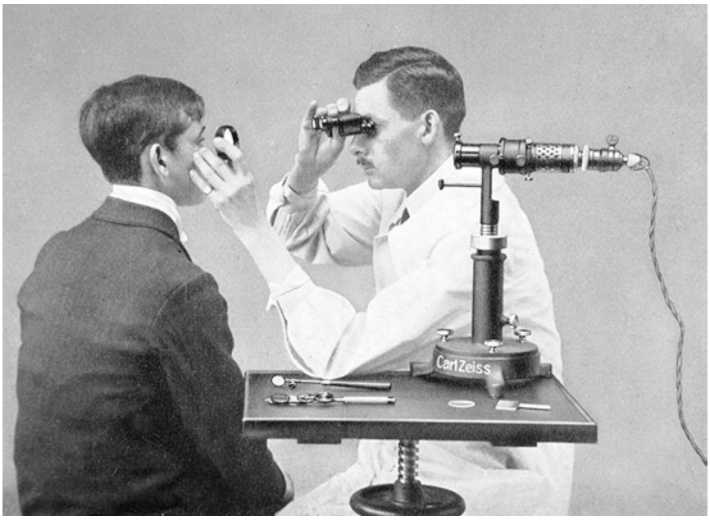

Fig. 7 Gullstrand Nernst Slit Lamp with x4 telescopes for viewing

lamp examination but this combination of slit illumination and binocular loupe continued to be used for a further 4 years. Gullstrand knew of the binocular corneal microscope of Czapksi (Fig. 8) as early as 1898 a year after it was introduced. But it was for someone else to suggest that a greater magnification in the form of a stand microscope could be beneficial when examining the eye with slit, oblique illumination.

This person was the German ophthalmologist, Leonard Koeppe (Fig. 9) in 1915 who suggested to Zeiss that the slit lamp of Gullstrand should be com-

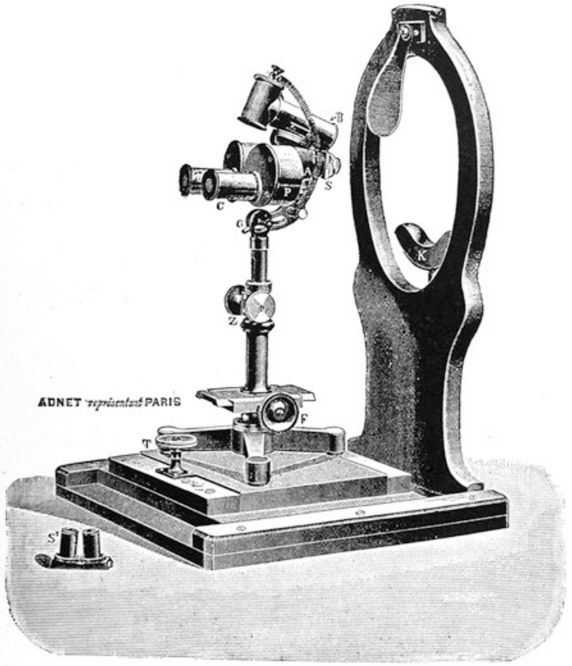

Fig. 8 Czapski Corneal Microscope

Fig. 9 Leonard Koeppe (courtesy JP Wayenborgh, Hirschberg's History of Ophthalmology)

bined with the binocular microscope of Siegfried Czapski. The following year Otto Henker (1874–1926) (Fig. 10), scientific head of the department of Medical Optical Instruments at Zeiss Jena, presented the new combined slit lamp instrument. The microscope was mounted on a base and placed on a glass-topped table for smooth positioning. The Nernst lamp unit was mounted on an articulated double arm making it easy to swing the lamp around the microscope from one eye to the other. A condensing lens was positioned at the end of the arm holding the lamp.

This combined instrument was the first commercial product of a long line of models and was called the Nernst Slit Lamp after Koeppe (Fig. 11).

After the First World War the Nernst lamp became unavailable due to the scarcity of platinum used in the resistance coil, and was superseded by the more robust and brighter Nitra lamp. Over the next few years Koeppe, Erggelet and Vogt who had embraced oblique slit lamp illumination with enthusiasm worked with Henker to produce new designs and additions to the Gullstrand Slit Lamp.

Reflex-Free Fundus Examination and Photography

Mention has already been made of Gullstrand's contribution to Robert Tigerstedt's Text Book explaining his work with the Nernst slit lamp. His contribution included another important section, this time on the examination of the fundus by reflex-free ophthalmoscopy.

Fig. 10 Otto Henker. Source. ZEISS Archives

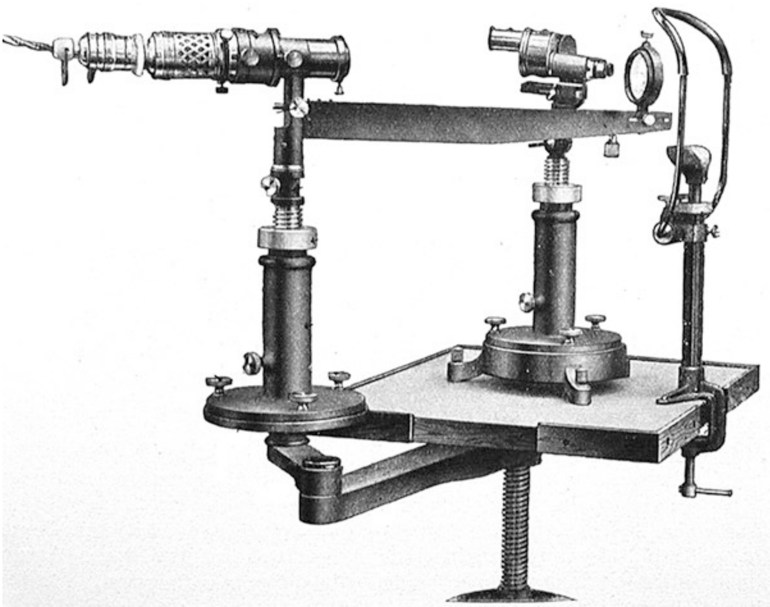

Fig. 11 Gullstrand Nernst Slit Lamp after Koeppe

In attempting to eliminate or reduce reflexes when examining the fundus, others before Gullstrand had made instruments with varying degrees of success, but there had been no detailed theory on the subject. Although Gullstrand is widely credited with inventing the reflex-free ophthalmoscope, Walter Thorner (1874–1948) had designed such an instrument based on similar principles a decade or so earlier, but it was not as commercially successful as Gullstrand's and therefore did not have such an impact on the world of ophthalmology.

A trial model of a table-mounted ophthalmoscope was made in the university workshop and was shown by Gullstrand at the Heidelberg meeting in 1910. Zeiss took up the manufacture of this instrument and Gullstrand was presented with the first of six prototypes for evaluation in January 1911. Later that year the Gullstrand Large Ophthalmoscope (Fig. 12) was demonstrated at the Heidelberg meeting by Wolfgang Stock (1874–1956).

Gullstrand's principle was that, in order to eliminate the corneal and other reflexes, the light

Fig. 12 Gullstrand Large Ophthalmoscope (Royal College of Ophthalmologists' Collection)

path illuminating the fundus should not overlap the visual path. For his theory to work in practice a small, narrow, short slit of illumination of 1.5 mm was projected at an angle in the margin of the patient's pupil, the fundus being observed monocularly or binocularly through the central 2.4 mm of the dilated pupil.

Other Gullstrand models using this optical principle followed including hand-held mono and binocular (Fig. 13) ophthalmoscopes in 1912/3 and the Large Simplified Ophthalmoscope in 1919 (Fig. 14).

The most important instrument to evolve using Gullstrand's reflex-free optics was, however, a fundus camera. The Swedish ophthalmologist Johan Wilhelm Nordenson (1883–1965), who followed Gullstrand at Uppsala University, was the inventor. This was the first clinical fundus camera and was destined to revolutionise ophthalmic practice for many years to come. It was launched by Zeiss in 1925 (Fig. 15).

Annus Mirabilis 1911

The culmination of Gullstrand's work up to 1911 and another turning point in his career, was the award of the Nobel Prize for Medicine or Physiology in October of that year.

The year was also a significant one not only for ophthalmology but in the history of science. In March an invitation-only meeting was held in Belgium called the Solvay Conference. It was the first gathering of the world's outstanding scientists organised by the Belgian industrialist Ernest Solvay at the suggestion of Walther Nernst. Their subject was Radiation and the Quanta. Among the twenty four delegates were Madame Sklodowska Curie, Albert Einstein (at 24 the youngest member) and Walther Nernst. All three were to feature in Gullstand's life in one way or another.

Madame Curie (1867–1934) received her second Nobel Prize, at the same ceremony as

Fig. 13 Gullstrand Reflex-Free Binocular hand-held Ophthalmoscope (Royal College of Ophthalmologists' Collection)

Gullstrand, this time in a different science, Chemistry, for her discovery of radium and polonium. Einstein (1879–1955) was to be denied a Nobel Prize for Physics until 1922 despite being nominated ten times between 1910 and 1922 for several papers including his one on the Theory of Relativity.

Gullstrand served on the Nobel Physics committee of the Swedish Academy of Sciences from 1911 to 1929 and was Chairman from 1922 to 1929. He was a strong personality with considerable influence on the committee. He argued against giving the prize to Einstein for his Theory of Relativity which he did not fully understand. Gullstrand was not the only member of the committee against awarding a Nobel Prize to Einstein. However, in 1922 Einstein was awarded the Physics prize for 1921, which had been reserved in that year, not for his Theory of Relativity but for his discovery of the law of the Photoelectric Effect [7].

It was the last named delegate at the Solvay Conference, Walther Nernst (1864–1941), inventor of the Nernst lamp that provided Gullstrand with the essential component for his invention of the slit lamp and ophthalmoscopes. Gullstrand's Nobel Prize was not, however, for the invention of the slit lamp, as many people today assume because it came in the same year, but "for his works concerning the Dioptrics of the Eye". It is interesting to note that Walther Nernst himself was also a Nobel Laureate being awarded the chemistry prize in 1920, in recognition of his work on Thermo-chemistry.

Gullstrand is the only ophthalmologist, practising over a significant period, to have received a Nobel Prize (Fritz Pregl (1869–1930) and Walter Hess (1881–1973) both of whom received Nobel Prizes during their careers in ophthalmology were honoured for work in other disciplines) [8]. In addition, Gullstrand is the only individual to have been awarded and turned

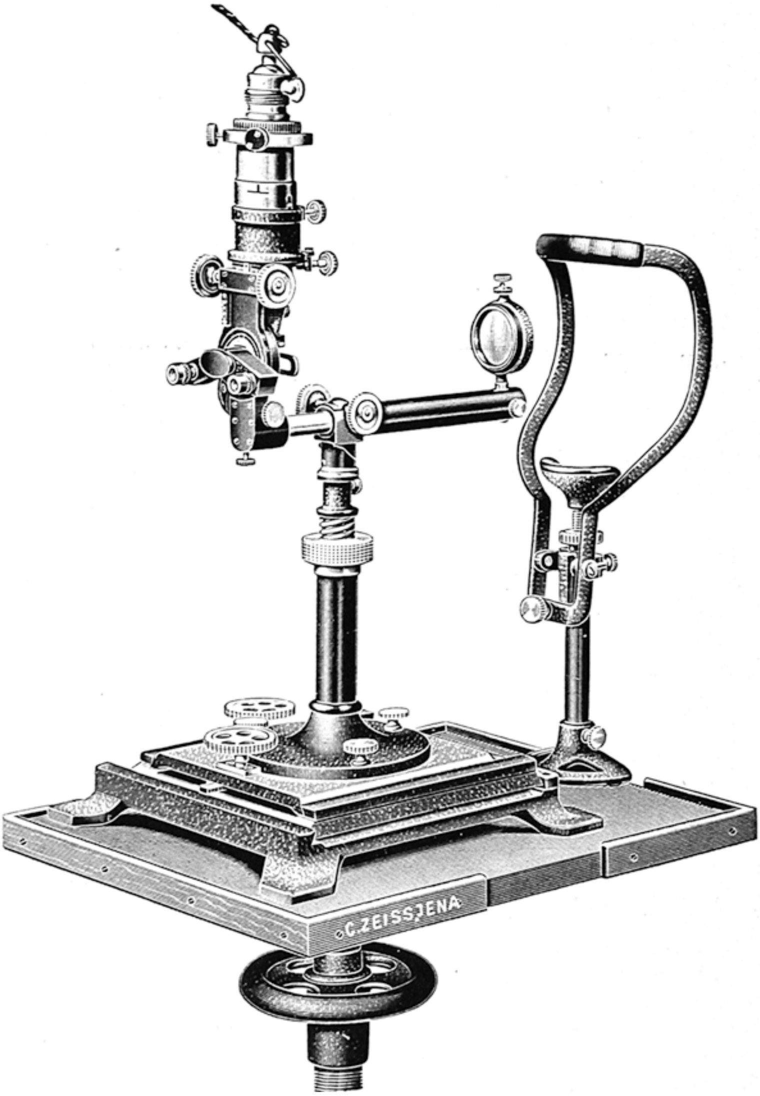

Fig. 14 Gullstrand Large Simple Reflex-Free Ophthalmoscope

down a Nobel Prize (in Physics). He was first nominated in 1910 for the prize in Physics but in 1911 he was nominated not only for the prize in Physics but also in Physiology or Medicine, accepting the latter. In his Nobel Lecture he took as his title “How I found the mechanism of intra-capsular accommodation”. This lecture summarised much of his knowledge up to this point in his research into the dioptrics of the eye [9]. Apart from the enormous prestige of being awarded the Nobel Prize, Gullstrand’s Annus Mirabilis of 1911 saw the introduction of two of the most important instruments in the history of ophthalmology his Slit Lamp and Reflex-free Ophthalmoscope (Fig. 16).

Professor of Physical and Physiological Optics and Retirement

In 1914 the Academic Senate of the University of Uppsala created a new post for their brilliant Nobel Prize winner and inventor. He was given a

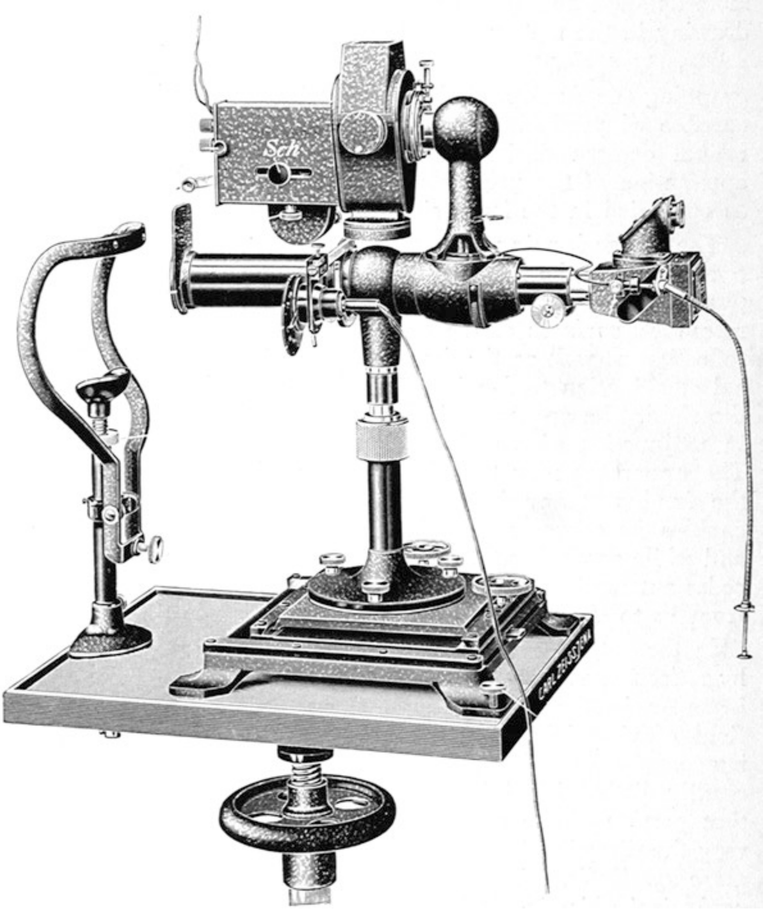

Fig. 15 Nordenson's Fundus Camera

personal Chair as Professor of Physical and Physiological Optics which meant giving up medicine to devote his whole time to research.

In his new position Gullstrand undertook two major investigations. The first was into the polishing of aspheric lens surfaces, a subject which had preoccupied him since early in his career. The second was into geometric optics of the eye using highly complex calculations of the fourth and fifth orders of optical law.

One of the more remarkable things about Gullstrand was that he was largely self taught. He preferred to use the old laborious system of differential geometry, with which he was very familiar, ignoring the much faster and more up-to-date method of vector calculus. His labour extending over 15 years on the calculation of light rays in the eye, was truly heroic, if not a little misguided (Fig. 17).

Fig. 16 Allvar Gullstrand holding monocular eye piece of his Large Ophthalmoscope. Portrait by Emil Osterman (courtesy of Swedish Medical Society)

Fig. 17 Gullstrand's Calculator (courtesy of Uppsala Medical History Museum)

In 1927 Allvar Gullstrand retired as Chair of Ophthalmology at Uppsala University, a position to which he had been appointed in 1894, and became Emeritus Professor. He died 3 years later. During his life he had been showered with many awards but the one that must have given him the most satisfaction was the vote given by the membership of the "Deutsche Ophthalmologische Gesellschaft" for him to receive the Graefe Medal, on his 65th birthday in 1927. The award, given every 10 years, goes to a contemporary of whatever nationality who may be designated as having done the most for the progress of ophthalmology. In his acceptance speech in 1928 at the award ceremony Gullstrand highlighted the importance of the so-called ancillary sciences in ophthalmology. Although he was an ophthalmologist, he was awarded the Graefe Medal for his scientific contributions in the field of the ancillary sciences (optics). He described this as follows "*My compelling urge for scientific work and the limited conditions in Uppsala with only one assistant robbed me the time and opportunity for clinical publications. On the other hand my scientific work was hard to understand by a "normal" ophthalmologist. Therefore my scientific work first became known through the new diagnostic methods and devices on which it is based.*"

Character and the Nobel Prize

When he received his Nobel Prize in 1911 Gullstrand was halfway through his career as an ophthalmologist and optical researcher but his most important work was already behind him.

It is interesting to speculate to what extent Gullstrand's worldwide fame was due to his Nobel Prize. Did he deserve it? Certainly Gullstrand provided the Swedish Nobel Committee with the opportunity to award this prestigious prize to one of its own countrymen which until then had not occurred. His work on the Dioptrics of the Eye was without doubt meritorious but its contribution to ophthalmology was beyond the comprehension of most ophthalmologists. The deliberations on awarding a Nobel Prize have always been kept secret and this may be just as well especially when examining the story of Einstein's failure to win the Nobel Prize in Physics for his Theory of Relativity. Gullstrand was at the very centre of this resistance and much has been written about this.

Gullstrand's character can best be described as a mixture of brilliance, arrogance, dogged determination and stubbornness each of which had manifested itself on a number of occasions in his career. He had demonstrated brilliance, bordering on genius, with his insight into the discoveries of how the eye functioned as an optical organ and the subsequent invention of the slit lamp and other instruments. But he was not kind to those with whom he disagreed or found deficient. He pushed Marius Tscherning aside when, wrongly, claiming priority that the centre of the eye was the point of rotation for optical calculations. He was insensitive and highly critical of Tscherning's work in the 3rd edition of volume one of Helmholtz's Text-Book which he edited. One colleague who had worked with him commented that he was a mean-spirited and difficult man.

Another example of his arrogance occurred when the vacancy for the position of Professor of Ophthalmology in Stockholm occurred on the death of Johan Widmark in 1909. Gullstrand was invited to succeed him but declined perceiving that this would diminish his time for research. He contacted Professor Johan Albin Dalén (1866–1940) who had been at the University of Lund for 2 years suggesting that he applied for the post. Dalén was unwilling to consider this as, like Gullstrand, he saw it as a curtailing of his own research. When he pointed this out to Gullstrand he received the reply "Certainly, but that's a smaller loss." Dalén accepted the Stockholm position. With delicious irony Dalén accepted the Nobel Prize in Physics on behalf of his blinded brother Gustaf in 1912.

Throughout his career he tended to be dogmatic in his approach, most notably demonstrated in his long defence that there was no yellow pigment in the macula, a controversy of Homeric dimensions lasting 25 years [10]. Gullstrand had dissected post-mortem eyes and found that no yellow colour pigment existed in the macula and concluded therefore there could not be any in the living eye. He demonstrated his laboratory preparations at the German Ophthalmological Society in 1902. This set off fierce public arguments, firstly with Fredrick Dimmer (1855–1926) and then Alfred Vogt (1879–1943), who later in 1917 stated that Dimmer had been right after all in this dispute maintaining the existence of yellow colouring in the macula both in vivo and post mortem. Leonard Koeppe (1884–1969) in 1919 joined the controversy stating categorically that following research with the slit lamp and special filters a yellow colour existed in the macula contradicting Gullstrand's assertions.

Gullstrand maintained his position, doggedly, for the rest of his working life even suggesting that the word lutea be removed from the anatomical description macula lutea.

But perhaps his doggedness and stubbornness can best be demonstrated in his unwillingness to adopt more modern methods of optical calculations available at that time which cost him many years of extra effort.

Conclusion

Although Allvar Gullstrand was a good teacher and worked tirelessly on his research, however, this left little time for clinical ophthalmology.

In spite of this, on his death in 1930 at the age of 68, he left behind a legacy of huge achievement in ophthalmology. His schematic eye evolved from his relentless research into how the human eye functions as an optical system. This schematic eye is as relevant today as it was when he presented it over a 100 years ago. One of the by-products of all this research was the establishment of the reflex-free principle in the design of ophthalmoscopes, leading to the first fundus camera. But his greatest legacy has been the slit lamp biomicroscope, an irreplaceable instrument used daily by ophthalmic practitioners throughout the world.

Acknowledgments I wish to acknowledge the great assistance I have received in the preparation of this chapter from Dr. Karl-Heinz Donnerhacke, past employee of Carl Zeiss, and now adjunct professor for ophthalmic technology at the Ernst Abbé University of Applied Sciences in Jena.

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12

Marie Curie: Radiation as a Medium That Can Cure

Jasmine H. Francis

Introduction

Marie Curie (1867–1934) made her discovery of radiation during the scientific revolution that occurred at the end of the nineteenth century [1, 2]. Roentgen discovered X-rays in 1895, with one of the first X-rays in history being an image of his wife's hand (Fig. 1). This was followed only 3 months later by Becquerel's discovery of uranium rays. Becquerel placed a phosphorescent salt (composed of uranium and potassium sulfate) on a photographic plate and following stimulation by sunlight, the developed plate revealed the black silhouette of the salt. However, quite unexpectedly, he would obtain a similar result during a period of cloudy weather in Paris and by leaving the experimental setup in a closed desk drawer. These latter conditions excluded the theory of stimulation of phosphorescence. Instead Becquerel attributed the effect to radiation emitted by the uranium present in the salt, leading to his term, "uranic rays". Further work on these rays was largely abandoned until a few scientists revisited the topic at the end of 1897, including Marie Curie who chose it as the topic of her thesis.

Early Years

Marie Curie was born her Polish name, Marya Salomee Sklodowska (nicknamed Manya), on November 7 1867 in Warsaw, Poland. She was the last of five children and had three sisters and a brother (Fig. 2). Her mother was headmistress of a highly regarded girl's private school and her father was a professor of physics and mathematics. Marie demonstrated her strong intellect at a young age, and is said to have read fluently at the age of only four and had a remarkable memory. According to one childhood story, Marie liked a poem that was read to her by a friend of the family. She requested a copy of the poem, and the acquaintance joked by saying he would read it to her again so that she could "recite it by heart" [1]. Thirty minutes later she produced a perfect written transcription. At 15, she was awarded a gold medal of merit for her outstanding work in secondary school.

In order to save enough money to support her further academic pursuits, Marie spent 6 years as a governess in the Polish province with the Zorawski family. During this time, Marie sent half her salary to her eldest sister, Bronya, who was obtaining a medical degree at the Sorbonne, Paris. Once Bronya had graduated from the Faculty of Medicine (as one of only three women out of a thousand students), she returned the support to her sister. Bronya encouraged Marie to

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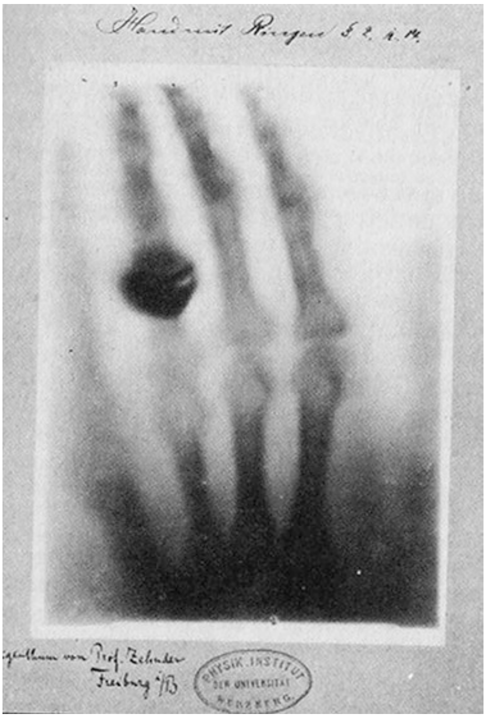


Fig. 1 The hand X-ray of Konrad Roentgen's wife [8]

Fig. 2 Marie (*left*) with her sister, Helena (*right*) around 1887

travel to study at the Sorbonne, offering a few hundred rubles and a place to live with her and her physician husband, Casimir Dluski. In 1891, Marie enrolled at the Sorbonne. She signed the registration papers, not with her Polish name Manya, but with the French equivalent, Marie. Among the almost 2000 students enrolled in the School of Sciences, Marie was only one of twenty-three women. However, Marie has made no remark on this gender disparity and instead was delighted at the opportunity of being taught by Paul Appell and Gabriel Lippman.

At the Dluski apartment, the physician couple would hold office hours to see patients (reserving two evenings a week to see patients free of charge), and in the evenings would entertain a cadre of physicians, artists, socialists, scientists and musicians. Marie was distracted from her studies, and Bronya's insistence to eat regular meals irritated her and she soon looked for a new place to live. With the help of Bronya, Marie moved and lived in a top-floor, unheated servant's garret on three francs a day. As her daughter writes, this was "a microscopic income which had to provide for everything: rent, food, clothing, books, university fees" [3]. Despite these monetary and physical constraints, Marie graduated from the Sorbonne with two degrees, ranking first in physics and second in mathematics.

One of her professors, Gabriel Lippman, arranged for the Society of the Encouragement of National Industry to support Marie with 600 francs to study and chart the magnetic properties of various steels. After setting up her unwieldy equipment in Lippman's laboratory, it became obvious that more space was required for her to progress efficiently with her work. Bronya's friend heard of Marie's quandary and suggested that she meet a less-known scientist called Pierre Curie who was a growing expert in the field of magnetism, and who had reportedly invented a collection of delicate instruments that would be useful to Marie's research. The first introduction evoked profound emotion in both Pierre and Marie and became the start of a relationship that would lead to collaboration, marriage, children and immense love and respect.

The couple married on July 26, 1895 during a garden reception in Pierre's parents house (Fig. 3). They purchased bicycles as a wedding present to themselves and used them to tour the countryside of France for the rest of the summer.

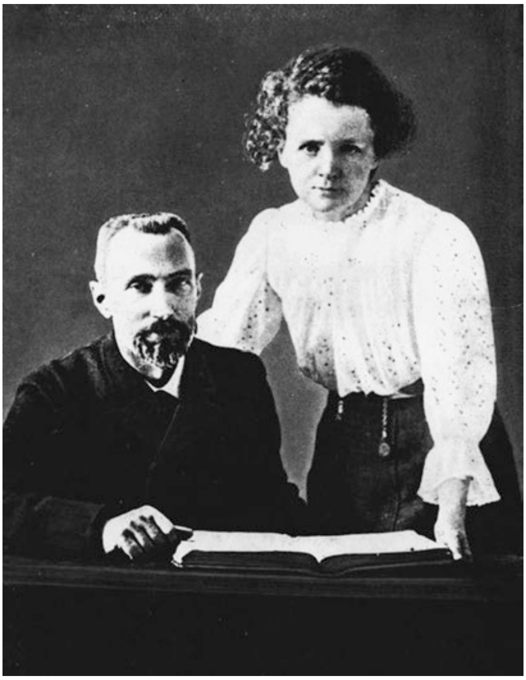


Fig. 3 Marie and Pierre in 1904 [9]

Upon returning to Paris, they rented a three bedroom apartment in Marie's old neighborhood, which was modest, but overlooked a lush garden. The Curies' afforded themselves the luxury of displaying fresh flowers in every room of their three-room apartment. Marie was meticulous, even with her household duties and kept an expense book in which the most trivial of expenditures was mindfully recorded. In September 1897, Pierre's father, physician Eugene Curie, delivered their first daughter, Irene. Their second daughter, Eve, was born on December 4th 1904.

Radium

Marie started her investigation of uranium radiation under the supervision of its discoverer, Becquerel. To aid in her work, Marie first developed an accurate method for measuring radiation. With the valuable tuition of her husband, Marie mastered the delicate technique of piezoelectricity and selected this as the means to measure radiation [1]. At the age of 18 and in collaboration with his brother, Jacques, Pierre had discovered piezoelectricity, which formed the basis for the piezoelectrometer. This method was reportedly a superior means of measurement, but was tiresome and required ample patience and a steady hand: both of which Marie possessed. Marie was reportedly the only person alive who had the skill for this technique and with this she precisely measured the electrical activity generated by rays emanating from various minerals picked at random.

Among the compounds that Marie tested was pitchblende, a high-density black ore mined in St. Joachimsthal (along the border of Germany and then Czechoslovakia). Pitchblende was known to be rich in uranium, which was historically extracted and used for creating the luminous glaze of Bohemian glass and pottery. However, to Marie's surprise, she found pitchblende to be four times as active as uranium. She concluded that pitchblende must contain another element to account for its heightened activity.

Marie would often work for long hours, propelled by her voracious curiosity. She carefully separated the various elements of pitchblende and used Pierre's sensitive equipment to measure each product's activity. In July 1898, she announced the discovery of a new radioactive element, which she named polonium for her beloved country. During the course of this published work, Marie made a number of important observations. She proposed the word "radioactivity" to describe the spontaneous emission of radiation, asserting that it could be measured (thus opening the door to discover new elements) and describing it as "an atomic property".

Following the discovery of polonium, Marie and Pierre spent a 2-month summer vacation in the countryside of France revisiting the activities of their honeymoon, which included riding bikes and picnicking. In only a short time since publishing their findings on polonium, in December 1898, they discovered radium with the collaboration of G. Bemont. On a December morning, Marie extracted a substance that measured 900 times more radioactivity than pure uranium. Fearful that it may be unstable, she quickly ran upstairs and rushed into Demarçay's laboratory. He analyzed the substance and recovered a unique spectral line, confirming a new and isolated element. In the Curies' notebook, they declared this element as "Radium", a name derived from the Latin radius, meaning "ray [1]". She correctly placed it as 88 on Mendeleev's chart.

In the ensuing years, they undertook the laborious task of isolating pure radium from Pitchblende residues. The stock was donated to them on the provision they pay for the freight cost to Paris, which they managed to out of their scanty savings. They set up their workspace in a dis-used shed with a glass roof that let in rain and conditions in which it was stifling in the summer and frigid in the winter (Fig. 4). Furthermore, there was no ventilation to exhume the poisonous gases released from their work. The purification process took 45 months. Marie describes the process as "killing work, shifting the jars, pouring their content from one jar into another, and then stirring the boiling fluid in a smelting basin over a fire with an iron rod nearly my own height. I had to stir for hours on end, and I went home at night aching all over" [3]. Marie believed the proportion of radium would be at the utmost, 1% of the ore. But after years of incessant work, realized that it was more along the lines of one part in one million. In 1902, they announced their feat of isolating 0.1 g of pure radium chloride from almost three tons of pitchblende! [4] Almost 4 years of work was distilled into a tiny amount of powder that filled the volume of one-fiftieth of a teaspoon.

As they approached isolation of the pure element, the couple noted an increasing spontaneous luminosity emanating from their extracted material. They marveled at its sight and reportedly found it irresistible to sneak back to their workshop at night and admire this glowing substance.

Marie defended her doctoral thesis in June 1903 and became the first woman in France to achieve this academic level (Fig. 5). Among the gathered scientists was her sister Bronya, who hastily took her to a dressmaker. Marie chose a black colored dress since it would hide the stains of the laboratory. In the same year, four scientists came together to nominate Pierre Curie and Henri Becquerel for the 1903 Nobel Prize in Physics. The letter recounted an inaccurate description of the discovery of radium and polonium, and made no mention of Marie or of her work. Pierre refused to consider the nomination unless the committee also included Marie Curie. The committee relinquished and submitted a new letter of

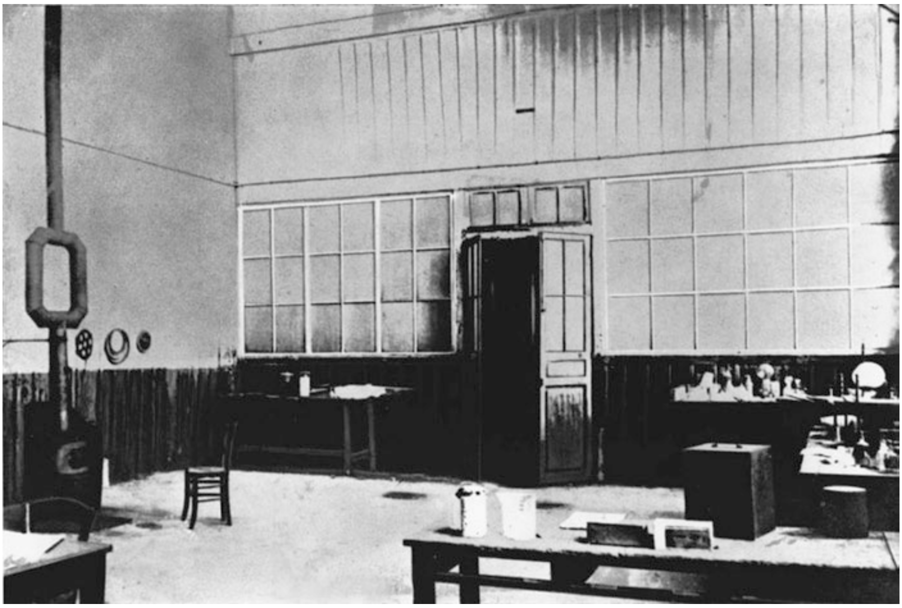
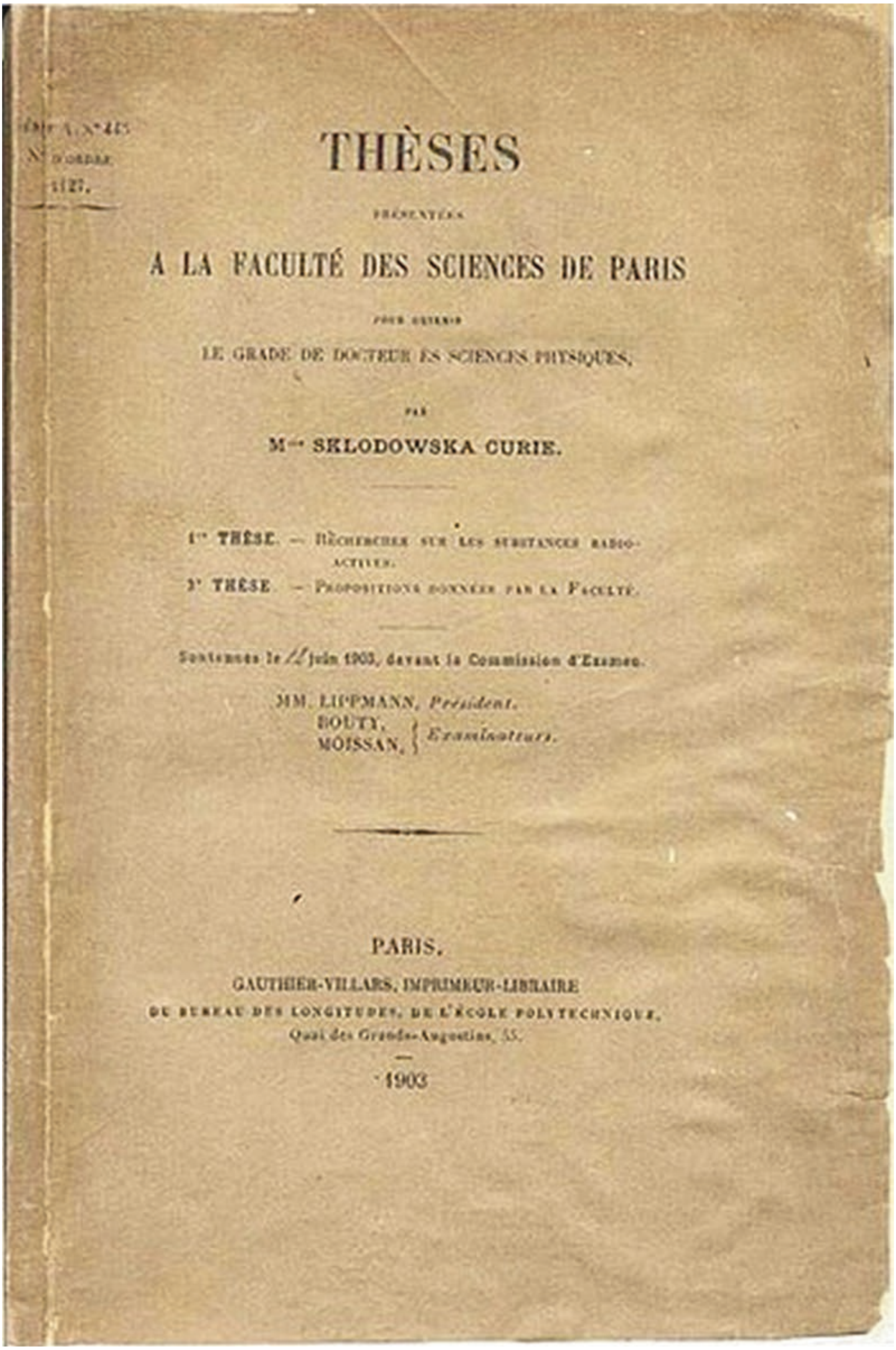


Fig. 4 The laboratory where Polonium and Radium were discovered on Rue L'homond [9]



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THÈSES

PRÉSENTÉES

A LA FACULTÉ DES SCIENCES DE PARIS

POUR OBTENIR

LE GRADE DE DOCTEUR ÈS SCIENCES PHYSIQUES,

PAR

Mme SKLODOWSKA CURIE.

1re THÈSE. — Recherches sur les substances radio-actives.
2e THÈSE. — Propositions données par la Faculté.

Soutenues le [illegible] juin 1903, devant la Commission d'Examen.

MM. LIPPMANN, *Président.*
BOUTY, MOISSAN, *Examinateurs.*

PARIS.
GAUTHIER-VILLARS, IMPRIMEUR-LIBRAIRE
DU BUREAU DES LONGITUDES, DE L'ÉCOLE POLYTECHNIQUE,
Quai des Grands-Augustins, 55.

1903

Fig. 5 Marie's 1903 doctoral thesis cover: *Recherches sur les substances radioactives* (Research on Radioactive Substances). Photo: Public domain, via Wikimedia Commons nomination, which included all three scientists. At that time, Nobel recipients were each awarded 70,000 francs. While Bequerel received his 70,000 francs, Pierre and Marie were given the same amount to share, as though they were only one person.

In November 1903, they received a formal letter stating they had won the Nobel prize and inviting them to receive the prize in Sweden in the presence of the King. The couple accepted the prize but were the first recipients to decline the overseas trip to the awards ceremony due to their declining health. Both had been feeling unwell, weak, and fatigued, presumably from radiation exposure, and did not feel fit to endure the travel to Sweden. Bequerel appeared alone to accept the prize and attend a ceremony, which reportedly over-exaggerated his own involvement in the scientific work and undermined the contributions of Marie and Pierre.

Other Achievements

Subsequent accomplishments included Marie being named a full professor and chair, becoming the first woman to achieve this position in the history of the Sorbonne. As a continued tribute to the Curies' discovery of radioactivity, in 1910, the "curie" was adopted as a unit of measurement of radioactivity, defined as "the quantity of emanation in equilibrium with 1g of radium". In 1911, Marie was notified by telegram that she was the sole recipient for a second Nobel prize: this time in chemistry and for "producing sufficiently pure samples of polonium and radium to establish their atomic weight… and for her feat of producing radium as pure metal" [1]. Marie is one of only five recipients to be awarded two Noble prizes. In 1912, the University of Paris and the Pasteur Institute signed an agreement for the creation of the Radium Institute (Fig. 6).

Fig. 6 Marie in her laboratory at the Radium Institute, April 1921. Source: Nationaal Archief of the Netherlands

Marie is quoted as calling her eldest daughter, Irene, "my companion and friend" [1]. Irene similarly pursued studies at the Sorbonne and received honors in physics, chemistry and mathematics. The mother and daughter team collaborated on work. Later Irene married Frederic Joliot and the two were awarded a Nobel Prize for their work on artificial radioactivity.

Ups and Downs

Marie's life was mixed with triumphant successes and very low periods of melancholy. There were a number of events that occurred throughout her life that were unexpected and in many ways tragic. These left Marie, understandably, in a dark lull of depression that would often take months for her to emerge from. Maria's youth was shadowed by the successive deaths of her eldest sister from Typhus when Marie was 9 years old, and then 2 years later by her mother from Tuberculosis. Between the births of her two daughters, Irene and then Eve in December 1904, Marie suffered a miscarriage when 5 months pregnant and on a bicycle trip.

Perhaps the most damaging event occurred on April 18th 1906. On the day that they returned from a joyous Easter holiday trip, Pierre, who walked with a limp, (likely due to deterioration of his leg bones from his prior radiation exposure) left for meetings. He was killed when a horse drawn wagon knocked him down and rolled over him. At the age of 49, his was dead.

Other Pursuits (X-Rays)

During the 4 years of the war, Marie focused her efforts on organizing radiology and radiotherapy services for military hospitals. Impelled by the sight of French soldiers returning with deforming limb injuries, Marie repurposed retired X-ray equipment from doctor's offices and laboratories. With support, she established approximately 200 radiological mobile units (vans) and implemented a radiology course at the Radium Institute for training nurses as radiology technicians. These X-Ray ambulances were called “Little Curies”. Each unit was composed of an x-ray tube on a movable arm that would be wheeled to the area of interest, heavy curtains to block out light, photographic plates, a screen, a folding table for the patient and ampules of radon (the gaseous decay emission of radium). A small generator was included, which could be attached to a car battery should electricity be inaccessible.

Despite women not being permitted to work at the battlefront, Marie continued with her efforts. One account describes her as bundled up in an alpaca coat with a Red Cross armband driving along at 20 miles per h [1]. Accompanied by her eldest daughter, Irene, she herself examined the wounded at the battlefront while also educating the technicians on how to operate the radiographic apparatus. It is estimated that, as a result of their activities, more than 150 radiologists were trained at her courses and more than 200 X-ray laboratories were organized for military hospitals… and a staggering more than one million solders were helped by radiography [5].

Applications in Medicine

Marie wrote a letter to her father, Wladyslaw Sklodowski, triumphantly describing her discoveries. His response was of a man that was seemingly never satisfied: he wrote, “You are now in possession of pure radium salts. If we consider the amount of work done in obtaining this, it would certainly be the most expensive of chemical elements. What a pity it is that this work has only theoretical interest” [1]. He died 6 days later and never lived to realize how wrong he was.

Some have pointed out that Marie was more interested in the applications of science rather than its fundamentals [6]. Her granddaughter explains that Marie was striving for new possibilities for the application of radium in experimental physics, other fields of research and in particular in medicine [2]. Marie was quick to recognize the potential use of radium to treat and cure cancer. In 1923 she wrote, “the radiumtherapy and the radium production…were more and more important, for the treatment of several diseases, and particularly of cancer” [7]. This was significant for the field of oncology, which in the early 1900s relied solely upon radical and often defacing surgery as treatment (chemotherapy was not introduced until the 1940s). Instead, Marie and Pierre believed radiation could destroy the cells that caused disease by a method alternate to surgical excision. Almost half a century later, Marie's youngest daughter elaborates on the context of radiotherapy when she points out, “many cases of cancer are now being cured by radium, X rays, or surgery. But the battle is still very far from won: medical science of 1950 does not yet know *what cancer is*. [3]”.

Despite this enthusiasm for exploration, medical discovery was difficult and delayed due to the scarcity and high price of pure radium (in 1904, a gram of radium cost the equivalent of approximately 110,700 U.S. dollars today). The scarcity was further exacerbated by the Austrian embargo on the export of radium between 1904–1906. The embargo was an attempt to control supplies and increase prices, which prohibited scientists outside Vienna from purchasing radium at a reasonable price.

The Curies refused to apply for a patent for radium, despite its high demand, evidence that it would be amply monetized and the strong likelihood that it would bring them great personal financial rewards. The both believed in the importance of their scientific project and its applications and that, “it would be contrary to scientific spirit” [1] to profit from patenting radium.

While the medical uses of radium were limited by cost and shortage, and were not widely implemented until the 1930s, scientists continued to explore medical uses for radium and there are examples many applications that were pursued in the interim. In 1901, Becquerel learned he had a skin burn after carrying a tiny tube of radium in his waist pocket. Pierre Curie deliberately exposed his arm to a tube of radium. The exposure lasted 10 h and the burn took 52 days to heal and “left deeply mortified tissues” [3]. This lead to the new treatment coined, “Curie-therapy”, in which radium was used in the treatment of lupus and some cancers. Before this in 1899, the Swede Tage Sjoergren reported the first case of skin cancer treated by application of X-rays– this was on the heels of successful treatment of throat and breast cancer with X-rays [8]. In 1904, the first report of successful treatment of basal cell carcinoma was described in two patients in St. Petersburg using radium as the source [8].

Initially, radium was first used in brachytherapy, and as the Greek term “brachy” meaning “near” implies, the radioactive source was placed directly on the surface of the tumor. Subsequent delivery methods included intracavitary and interstitial placement, as was done for cancers of the prostate, breast, brain and esophagus [8]. In 1904, Alexander Graham Bell suggested developing delivery methods to treat internal pathology. In the same year, Parisian doctors started implementing the use of a glass capsule filled with radium salts created by Henri-Alexandre Danlos, and a hollow tube with a cup at one end that was coated with radium-impregnated varnish and used to treat dermatological manifestations of lupus. This was a valuable discovery since these radium applications proved to be successful where X-ray’s were not an option. Then in 1906, New York-based surgeon Robert Abbe generated celluloid capsules filled with radon. A decade later, at Memorial Hospital in New York, Dr. Gioacchino Faillo added a gold shield to radon seeds, making them more tolerable to work with. The story goes that one basement worker, who was charged with disposing of the used gold shield, collected the unused precious metal to make a ring for his fiancé. It is reported that she eventually had her ring finger amputated due to radiation damage [1].

Meanwhile, Marie made a number of strides in the effort to better understand medical applications of radium. In connection with her ties at de Lisle factory, Marie processed radium and manufactured products for the purposes of medical treatments. In 1909, Dean of University of Paris and Director of the Pasteur Institute jointly founded “Institut du Radium” in response to the extraordinary success of radiumtherapy for curing cancer and the need to give Marie Curie a laboratory to further develop applications of radioactivity. At the institute, Marie collaborated with Claudius Regaud who was responsible for biological and medical applications and together in 1921 they created the first clinic dedicated to radiumtherapy. Marie devoted her research to the study of radioactive substances and their medical applications [5].

During a visit to the United States in 1921, Marie received a gift of 1 g of radium, which was worth $100,000. The money was raised by public subscriptions from American women and donated for the purpose of medical treatment in Paris [9]. During a second visit to the United States in 1929, she was given another gram of radium, which was dedicated to medical applications in Poland. In 1932 she brought this radium to the Warsaw Radium institute and during her speech to inaugurate this newly built establishment she asserted that “therapy should be permanently backed up by scientific research without which no progress is possible” [6].

Under Marie’s guidance, about 483 scientific papers were published, 34 doctorates were awarded to her students and 8319 patients were treated with radium in the medical unit [5] (Fig. 7).

Applications for the Eye

Foster Moore first published on the use of radon seeds for the treatment of a “melanotic sarcoma” (uveal melanoma) in a 65 year old man [10]. At the time, enucleation was the standard treatment,

Fig. 7 Marie with four of her students. (Photo taken between 1910 and 1915) Source: Library of Congress

but was avoided in this patient since the fellow eye was blind. In February 1929, a radon seed was prepared by Professor Hopwood. It was 1 mCi of strength and shielded by 0.5 mm of platinum [10]. Moore describes, "the seed was taken in a pair of finely ribbed forceps and inserted straight into the growth along what was judged to be the track of the knife". Given the dose of radiation to the sclera, there was a fear of "sloughing" of the sclera, but Moore noted that it did not occur in this case, or in any subsequent case treated with a higher dose. The seed was removed 14 days later, upon which Foster noted tracking of "collections of pigmented cells" from the incision, although no "extraocular growth" on follow-up [10].

Due to tumor growth, a second radon seed was inserted, this one being 5 mCi with 0.5 mm platinum shield for 10 days, after which it was noted that the growth was shrinking [10]. It continued to shrink and was measured as a quarter of its size 1 year later. The vision was 6/60 at baseline and had decreased to 3/60 on follow up presumably due to a radiation-induced lenticular opacity. Given the reduction in size of the tumor and the limited side effects, the treatment was considered a success and subsequent cases were undertaken [10].

Moore's single case provides numerous facets of knowledge that would inform the future use of brachytherapy for intraocular tumors. This includes: brachytherapy can suspend the growth of uveal melanomas and cause them to shrink, tumor shrinkage occurs over the course of years and may not result in complete tumor regression, the sclera can withstand a high (obscene) base dose of radiation, local side effects include cataracts and vision may decline following treatment.

Furthermore, in his conclusion, he writes, “it seems unlikely that actively growing cells will be thrown off from a tumor which has begun to regress”. Moore was 70 years before his time in hypothesizing: “the eye no longer remains as a menace to the subject, and he is in fact as much protected against dissemination … as if he had had the eye removed” [10]. Moore had predicted what would be proven by the 20-year National Institutes of Health sponsored multi-institutional Collaborative Ocular Melanoma Study, which demonstrated equivalent metastatic rates and survival for patients with uveal melanoma treated by brachytherapy or enucleation.

Nine months later, in November 1929, the same team treated their first retinoblastoma case [11]. It was in a 1-year-old boy with bilateral retinoblastoma following enucleation of the left eye and refusal by the family to remove the fellow eye. A 3 mCi radon seed was implanted into the tumor for 10 days, followed by a second 5.3 mCi radon seed 8 months later. The tumor appeared to regress without signs of recurrence by 10 months follow up.

These cases paved the way for future brachytherapy as treatment for uveal melanoma, retinoblastoma and other intraocular tumors. Along with changes in the isotope, the placement of the seed also evolved over time, largely due to the pioneering work of H. B. Stallard: instead of penetration through the wall of the eye, the seeds were sutured to the sclera, then affixed with the aid of either a metal band or dental wax stent and subsequently placed into plaque applicators (spherical shell) which were likewise sutured to the surface of the eye in an area corresponding to the location of the intraocular tumor [12, 13]. In the United States, approximately 2500 patients will be diagnosed with uveal melanoma per year; and approximately 75% of these patients will receive radiation as definitive treatment of their intraocular tumor. The pioneering work of Marie Curie has contributed to improving the lives of many of the patients we treat.

Late Years

Marie had endured the decades-long exposure to radiation, and by the end of her life, the toil became evident. She had developed cataracts and despite two painful surgeries, she did not regain much useful sight. As she was dying, her youngest and compassionate daughter Eve came to care for her. On July 1934, at the age of 67, Marie died. The cause of death was given as “aplastic pernicious anemia”, presumably from the decades of radiation accumulation in the bone marrow. How tragically ironic that Marie, the discoverer of radium, while having garnered great success from its discovery, would eventually die from years of exposure to it.

Other family members also displayed medical signs of radiation exposure: Pierre walked with a limp in his lower extremity, presumably from radiation damage. Irene Curie died from leukemia, which was probably attributable to radium exposure along with the wartime effort on the Little Curies and further aggravated by the explosion of a polonium capsule in her laboratory. Irene’s husband, Frederic Joliot died from the effects of polonium and radium and was quoted as naming their radiation-induced death, “our occupational disease” [1]. While the Curies’ instituted protective measures in their laboratory, they often ignored them. They were known to use bare, unprotected hands during their experiments and even transfer radioactive substances between vessels by sucking up the material with a pipette [1].

Conclusion

Marie Curie’s relentless and meticulous scientific explorations were essential in laying the foundations of our radioactivity knowledge. And one would presume that even more satisfying for Marie was the realization of her work for medical applications. Even to this day, the majority of subspecialties in oncology use some form of radiation (either XRT or brachytherapy, or other modern applications) in their treatment armamentarium. The summary of her accomplishments are best described in her own words, “it may be easily understood how deeply I appreciated the privilege of realizing that our discovery had become a benefit to mankind, not only through its great scientific importance, but also by its power of efficient actions against human suffering and terrible disease. This was indeed a splendid reward for our years of hard toil” [7].

In 1995, the coffins of Pierre and Marie were placed in the Pantheon, making Marie was the first woman to be laid there in recognition of her own achievements.

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13

Jules Gonin: Proving the Cause and Cure of Retinal Detachment

Michael F. Marmor and Balder P. Gloor

Jules Gonin (1870–1935) is justly famous as the man who made retinal detachment a treatable disease (Fig. 1). His struggles to convince a reluctant group of colleagues of the true pathophysiology and surgical approach have been chronicled in two recent reports by Gloor and Marmor [1], and Albert et al. [2], and this chapter can add little to those accounts of what took place. The emphasis here will be on the insight that made it possible to manage holes, and the complex of scientific and personal qualities that are needed to advance medical practice in the real world. Helmholtz devised an ophthalmoscope, and first demonstrated its clinical applicability. It is likely that Purkinje and possibly Babbage before him had also made working instruments, but they failed to communicate the information, and the discovery could not impact ophthalmology until it became known and practical. Gonin did not originate the concept that retinal holes are a cause of detachment, nor did he originate the idea of cautery to seal retina. Yet he had the insight to recognize the concept of holes as a cause rather than a result of detachment. He made the critical observation that to treat holes it was necessary first to localize them. And then one could explore means of sealing them. He had the drive and resources to persevere with clinical trials in an era of limited technology for retinal examination and surgery, until the cumulative weight of his successes proved the point.

Gonin was born in Lausanne, and raised in a family of intellect and culture [3]. After graduating from gymnasium, where he excelled in foreign languages, he entered the College of Sciences at the University of Lausanne and began medical studies. He earned distinction for a research study on the metamorphosis of butterflies [4], and they remained a lifelong passion for him. He was still a student when he came to the attention of Marc Dufour, the professor of ophthalmology, and Dufour asked him to temporarily replace his assistant, who had fallen ill. Thus began a long friendship. After graduation in 1894 he studied at the Institute of Pathology in Lausanne, and traveled about Europe visiting eye clinics and extending his knowledge of pathology. He returned to Lausanne in 1896 to begin ophthalmology training under Prof. Dufour, and in 1898 became Dufour's private assistant. It was not surprising that Dufour asked him in 1902 to assist with a chapter for the French Encyclopedia of Ophthalmology. In preparation, Gonin examined a series of 70 enucleated globes with retinal detachment, among which three had

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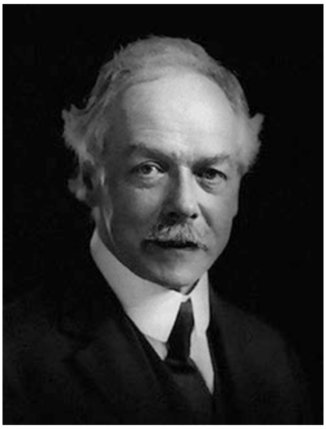

Fig. 1 Gonin in the 1920s

spontaneous or idiopathic detachments [5]. He noted that these all showed retinal holes with tears adherent to the vitreous [3, 5]. This is the beginning of our story.

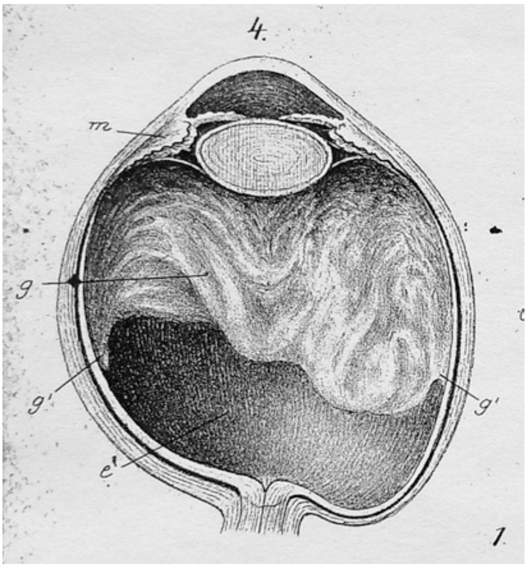

Fig. 2 One of Iwanoff's illustrations of different forms of vitreous detachment [10]

The Insight

There were many theories about the formation of detachments towards 1900, but most specialists including von Arlt [6] and von Graefe [7] thought the fluid came from choroidal effusion, and the way to cure was by making holes in the retina to facilitate drainage from the subretinal space. Von Graefe (1858) had observed holes, but thought that they developed after detachment and ameliorated the course of the disease [8]. This belief led many giants of that era, including Sichel, Arlt, von Graefe and Bowman to make multiple surgical perforations of the retina in an effort to cure detachment [1] The results were disastrous, needless to say—but these were the most trusted minds in ophthalmology and it would be many decades before alternate hypotheses were taken seriously.

Muller [9] observed in 1858 that retinal detachment can be preceded by vitreous detachment, and Iwanoff [10] argued in 1869 from histopathologic studies that this occurred regularly with shrinkage of the vitreous pulling retina away from the RPE (Fig. 2). De Wecker in 1870 made the connection, and wrote in 1873 "the vitreous is displaced forward, … causes tears and in this moment fluid … detaches the retina." (cited in Dollfuss [11]). But de Wecker still thought subretinal fluid would also drain out of the subretinal space through holes, and he followed surgical approaches of the day that punctured both retina and choroid. Leber independently reported on a series of his detachment cases, and found tears in half of them at the beginning of detachment [12]. And he published a histopathologic case with a tear and vitreous traction. Nordenson from Leber's department found tears in 39% of a large series of detachments (1887) [13].They concluded that traction causes tears, which allow liquid vitreous to penetrate and detach the retina. But resistance to these ideas remained strong. And Leber viewed the primary cause of detachment as the vitreous traction rather than the hole, so that his surgical effects aimed at the relief of traction rather than sealing the defect [12].

Gonin had begun his research with Dufour assuming the conventional knowledge about detachment was correct. However, the pathologic cases with tears soon convinced him that Leber was in fact correct and the hole was a part of the pathology. He and Dufour examined their clinical cases more carefully, and found that 60% had one or more tears (and they guessed the percentage was actually higher because of ophthalmoscopic difficulties in many of the cases) [14] (Fig. 3). This led them to consider that it might be the hole, rather than vitreous traction, which was the critical element in forming a detachment (Fig. 4) [16]. And if this was true, the logical conclusion (which Leber had not considered) was to treat the retinal tear. In the 4th volume of the French Encyclopedia of Ophthalmology, which appeared in 1906, Dufour and Gonin wrote "in order to effectively fight a pathological process, we must know its nature and anatomic conditions. Only the study of pathogenesis of spontaneous detachment, based on facts and not on hypotheses, will make it possible to find the treatment of this disease" [15]. Unfortunately, at that time (1906) there were no good ways to prove a hypothesis, and they faced a great deal of opposition since standard therapy was still the creation of multiple retinal (and often choroidal) perforations. Dufour's untimely death in 1910 left Gonin alone to pursue these new ideas.

Translation Into Practice

We know less about Gonin's work for the next decade, as his hospital (the Asyle des Aveugle) lost its affiliation with the University and with

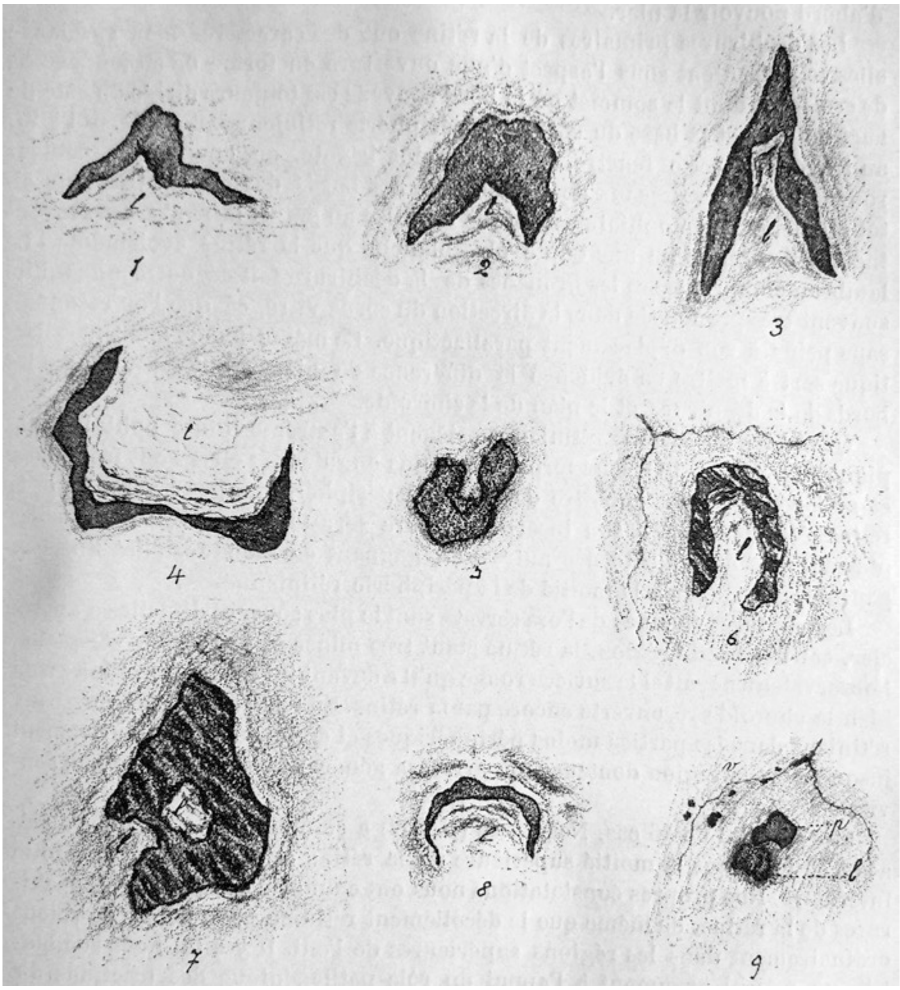

Fig. 3 Different types of peripheral retinal tears found by Dufour and Gonin in recent detachment [15]

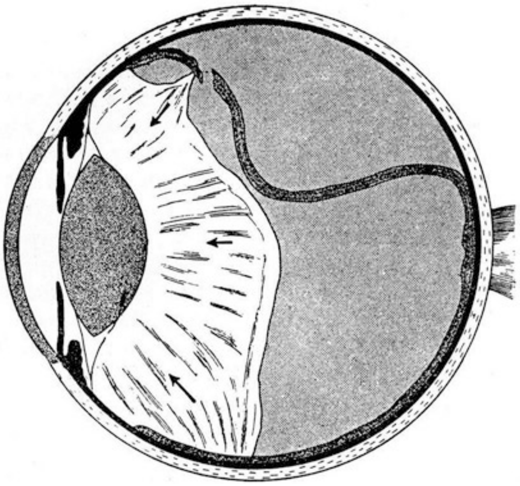

Fig. 4 Gonin's explanation of the pathogenesis of retinal detachment from a peripheral tear. Tears typically begin at a point of attachment to the vitreous which rips peripherally towards the ora, and produces a hole [16]

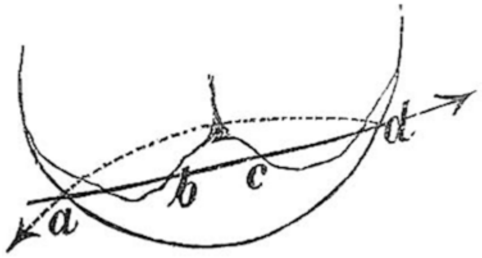

Fig. 5 Deutschmann's surgical treatment of retinal detachment [17]. He perforated the retina at least four times with a Graefe knife, and also cut vitreous strands

that the management of most of the detachments. Nonetheless, he continued to search for tears when he could, and to think about how holes might be attacked surgically. He felt passionately about his vision of the pathogenesis of detachment, which seemed so clear and obvious. But giants of the time, such as Sourdille and Deutschmann, were vigorously opposed to Gonin's ideas about the role of holes, even if their cure rate was at best a few percent (Fig. 5) [17].

A few pathologic cases from the laboratory were not going to convince these clinicians, and Gonin recognized that the only answer was to achieve success in the operating room—but for that he needed tools. Ophthalmoscopes of the day were still primitive, lasers had not been invented, and surgical cauteries were little more than heated wires. Gonin had the further insight to recognize that finding and localizing holes in the clinic would be just as important as finding technology to close them. Figure 6 shows drawings from his chapter with Dufour in 1906 [15]. Many of the surgeons who decried his theories observed holes in only a small percentage of their patients with detachment [17]. A hole had to be found if it was ever to be sealed. He would say "The instrument needed to cure retinal detachment is the ophthalmoscope" [18], and if his examinations were lengthy it was because he was always searching for a possible second hole. He remarked once at a lecture in Glasgow, for the benefit of his Scottish audience, "No golfer would be content after playing only one hole" [18].

Gonin insisted, that to find the holes in the periphery one had to use indirect ophthalmoscopy. He devised a careful system of marking the location of holes upon the sclera with calipers. And he began to explore methods of cautery, settling upon the Paquelin instrument whose tip was a fine wire [1]. He operated on some severe, essentially hopeless, cases by 1913, and in 1916 began to try some cases with good visual acuity [1]. He was cautious and honest: when he contemplated his first operation he warned the patient that the procedure was experimental, although the sole hope of cure [18]. Fortunately it was a success. During the decade after Dufour's death, Gonin's reputation grew largely from his work in other aspects of ophthalmology (he served as president of the Swiss Ophthalmological Society) and he published little on the management of detachments. But he began to report new results in 1919, and in 1920 he returned to the University in Lausanne as Professor of Ophthalmology, following the footsteps of his mentor.

With practice, both Gonin's diagnostic and surgical results improved. His success in finding tears was 60% in 1904–1905, [1, 19] but 91% in a series beginning in 1921 [1, 20]. Visitors to his clinic found holes in 83% [21] whereas surgeons who denied a role for tears such as Galezowski, Horstmann, Elschnig and Deutschmann were only finding holes in 13–46% [1]. Gonin devised a complex but rationale surgical procedure (Fig. 7).

Fig. 6 Illustrations from Gonin's article with Dufour showing the detail of his ophthalmoscopic exams and his ability to identify holes [15]. *Left* Spontaneous shallow detachment with far peripheral breaks superiorly (Planche IX, Fig. 15). *Right* Detachment with a secondary macular hole (Planche IX, Fig. 16)

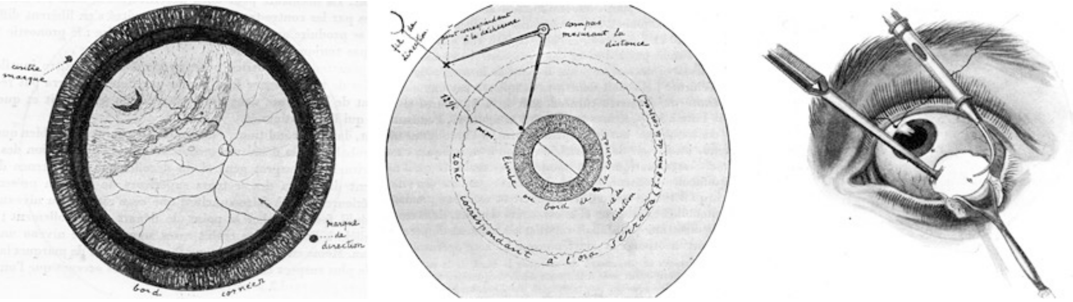

Fig. 7 Gonin's procedure to repair detachments [22]. *Left* The hole was localized and limbal ink marks made on its meridian. Middle: The distance of the hole from the ora was determined, and calipers used to mark the hole location. *Right* A Paquelin cautery was inserted deeply through a Graefe knife incision to cauterize the hole and drain fluid

After finding a hole, the patient would be put at bedrest, positioned so that the hole was at the lowest point in the eye and the retina would settle. When this occurred, Gonin would localize the hole and estimate the meridian and the distance from the limbus to mark the site in India ink.

In the operating room, a Graefe knife incision allowed the tip of a heated Paquelin cautery through the incision for several millimeters to cauterize the hole and also drain fluid locally. Then the patient was put at bed rest for a week, positioned again with the hole at the lowest point [22]. The procedure was difficult for the average surgeon, particularly the accurate localization of the hole, and surgeons had to tolerate a disturbing blast of steam that emerged from the incision during cautery. Gonin became very skilled at this, but was the first to emphasize that the key to success was not his specific procedure but closing the hole [18] (Fig. 8 [23]). He always welcomed better techniques and instruments as they came along, such as the Weve diathermy in 1932 [24].

By 1923 Gonin [25] was reporting a success rate of 30–40%, much better than any reliable

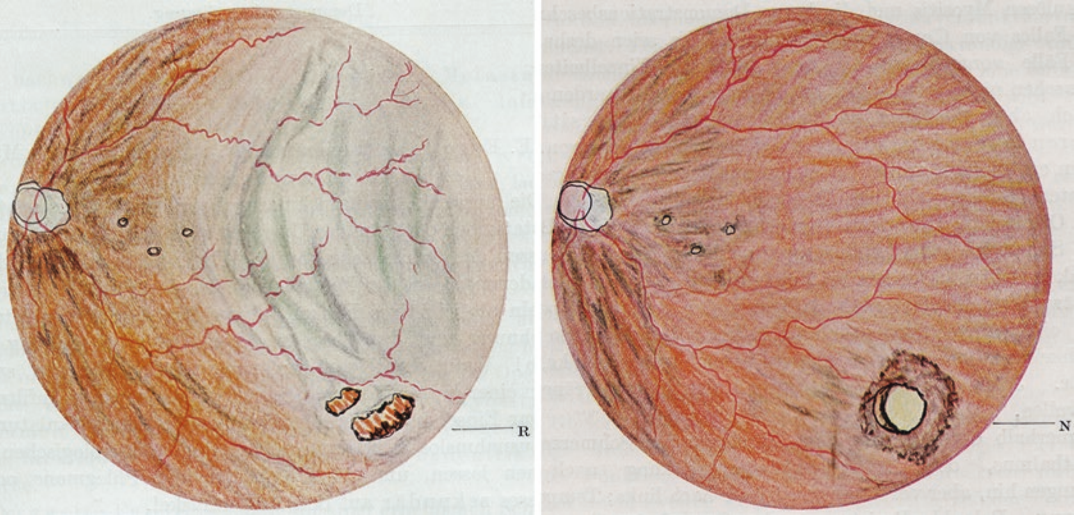

Fig. 8 Gonin's first published illustration of a healed detachment, caused by two holes in a myopic eye (1929) [23]

Fig. 9 Gonin operating with visitors in 1927

series from those who denied a role for the hole. His most vocal opponent was Professor Gabriel Sourdille, whose response to Gonin's report was "You have not convinced anyone" [26]. Sourdille made deliberate holes in sclera and retina, and then instilled a weak mercuric cyanide solution around the sclerotomies; and he repeated this procedure every few weeks for months. He reported an initial small series in 1923 with 50% success [26], but this did not hold up with more patients [27]. Gonin not only was curing many detachments, but he was gaining disciples. Visitors who observed and began to use his procedures included Amsler, Arruga, Siegrist and Vogt (Fig. 9) [1, 18].

Gonin spoke widely across Europe in the next decade, and the tide turned at the Amsterdam Congress in 1929 when multiple reports confirmed success rates above 50% for uncomplicated detachments [28]. Sourdille still resisted, commenting on a report by Amsler that the "search for tears was a long and painful procedure for the patient … [and the doctor] had to loosen his collar as for gymnastics… Is it really necessary to dedicate so many hours … unless it is really and absolutely indispensible?" [27]. But more and more surgeons were convinced by the results. And Gonin was recognized in Switzerland with a high scientific honor, the Benoit prize.

Acceptance

Gonin presented a series of over 200 detachments with a success rate of 53% overall, and 67% for those no older than 3 weeks· [28]. Weve presented similar results in 1932, citing 85% for recent cases using his diathermy instrument [29]. Sourdille continued to grouse that the tear was only an epiphenomenon, but his son sent 2 months with Gonin and introduced the procedure to Paris in 1930 effectively ending the feud—although the father would not acknowledge Gonin's rationale till after he had died [1]. Gonin worked tirelessly in these last years, seeing patients, training visitors, and championing the rational treatment of detachments. His beloved wife Helene died in 1932, and he was despondent, but went on working and decided that it was time to summarize his understanding and results on retinal detachment, and the battle to achieve a therapy, in a book (Fig. 10) [22]. His modesty and desire for accuracy led him to hold up publication until after the International Congress in Madrid in 1933 where Arruga, Ovio and Vogt would make presentations and at which there would be constructive discussion (Fig. 11) [30]. Gonin received a standing ovation at that meeting. His definitive book, *Le Décollement de la Rétine* finally appeared in 1934, and closed the chapter of controversy [22].

He was nominated for the Nobel Prize in 1934, and strongly supported by ophthalmic referees except for one member of the committee who was concerned about claims that had arisen about priority [18, 31] because Vogt, who had been a great supporter of Gonin, wrote that Galezowski had coagulated holes in 1902 [32, 33]. But Vogt had noted only short fragments of Galezowski's writings, and distorted the fact that Galezowski denied the role of traction and tears, and made multiple holes in both retina and choroid in his attempts at surgery. He did introduce cautery into some of these wounds, but without any localization [34]. By the next year, when this claim of priority was proven false and Gonin would have been proposed, his death prevented the award. Gonin reacted to the negative Nobel vote with characteristic style, saying "After all, this saves me from the nuisance of the tailor, the tail coat, the boredom of the ceremony, the Scandinavian December cold" [18].

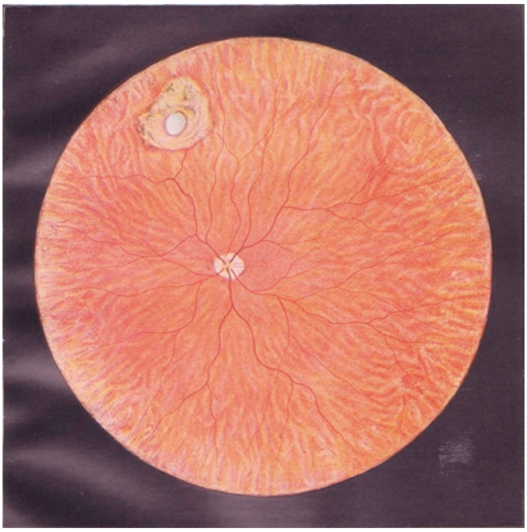

Fig. 10 Healed detachment illustrated in Gonin's book [22] (Tables XXI and XXII)

Gonin had been subject to migraine attacks all his life, but they passed [35]. May 23, 1935 he awoke with an attack that was much more severe and persistent than usual. He managed to keep working and on May 28 to give a final lecture to his students, but a few days later he lost consciousness and died from brain hemorrhage on June 10. He left most of his modest estate to those he could not cure, the blind of the Asile des Aveugles.

The Man

Gonin was a public figure, running a large clinic and speaking widely about his work. He was described universally as remarkably modest and

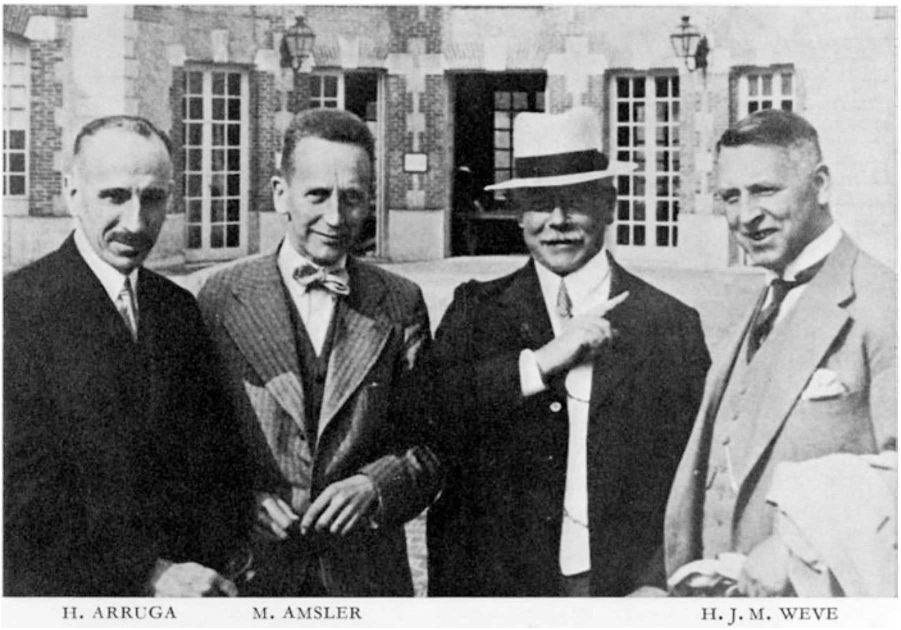

Fig. 11 Gonin with some of his followers in 1934: From the left, H. Arruga, M. Amsler, Gonin and H. J. M. Weve

reluctant to accept praise, despite his unquestioned drive to prove rational therapy for detachments, and of course a parade of awards toward the end of his life. He was fiercely honest, and intolerant against falsehood or deception [18]. François said that when posed an embarrassing question, he would not demur or stand on ceremony: "he never hesitated to respond simply: I don't know." His medical fees were low, and patients would leave his clinic surprised at the modest bill [18]. His management style was "hand's off." He would see all the new patients in the department once a week, but that done his associates had complete freedom to run their practice and treat patients as they wished.

For all his modesty, his patience with pride or folly was very limited. Arruga relates a number of revealing stories from his associates. When a patient burst into his office at the end of along day in the operating room, demanding that Gonin and no one else remove his cataract, Gonin replied "And, by the way, do you want me to cut your hair too in the meantime?" To a medical observer who said he just could not understand how a red-hot cautery could cure a detachment, Gonin said there were probably many things about which he could not get the drift. And he was annoyed with a colleague Remy who continually spouted off about the benefits of his diploscope. At the 1909 International Congress in Naples, Gonin made an exact replica and had guides bury in the ruins at Pompei. When the delegates visited the next day, they watched with amazement at the exhumation of a diploscope from the First Century! [18].

He was a great outdoorsman, and loved to hike and climb over the glaciers in the mountains. On one trek in the Pyrenees, his quick thinking may have saved his life [3, 18]. A flock of sheep cornered him on the brink of a precipice, but he had the idea to bark like a dog … and the sheep retreated. His love of butterflies was lifelong. He had many pictures in his house, and put a butterfly on the ceiling of his clinic room for patients to fix upon during examination. Arruga relates that as he became increasingly famous, and visitors flooded his clinic to watch his techniques, he referred them increasingly to his assistant Noelle Chome-Bercioux. When she ushered one such visitor from Boston towards the exit, he informed her that the reason for his long voyagec was simply to meet a certain

Doctor Gonin, expert in butterflies. When Gonin was notified, he abandoned everything else, and the two men disappeared into the countryside armed with butterfly nets [18].

He had great respect for women. Switzerland was more enlightened than many countries by the turn of the century, and welcomed women in medicine. Proportional representation was a hot issue then, and Gonin was a strong supporter [3]. He advocated the vote for women, as well as weighted votes (two for parents, people with high school certificates and noncommissioned officers; three for parents of large families, officers or university graduates). His wife Helene assisted in keeping his patient records, and handled much of his correspondence (Fig. 12).

His daughter Gabrielle assisted in the preparation of his great book towards 1934, and in sorting through his patient records after his death. And his primary assistant, who worked with him until his death, was Noelle Chome-Bercioux. Gonin had some 38,000 private patients by the end of his career, organized by number rather than name, and he would write clinic notes on any available piece of paper. Thus, finding the record if a patient forgot the number was a challenge (and Gonin would get upset). Noelle once remarked [3], "Professor, I cannot afford to be as disorganized as you are." But she was devoted, managed his visitors, and filled in to lecture for him at conferences such as the critical 1929 meeting in Amsterdam. At the 1933 conference in Madrid, Gonin introduced his daughter Gabrielle as his "logical daughter" and his long-time assistant and co-worker Noelle Chome-Bercioux as his "ophthalmological daughter."

The Legacy

Gonin's role and legacy in ophthalmology is unchallenged. He recognized the logic of retinal tears and holes as the primary and critical event in the development of primary detachments, and had the perseverance to seek therapy (in the face of professional opposition) that could seal the holes (recognizing that the first step of localizing was as critical as the surgical approach). Did his personality account for his achievements? That would be difficult to accept, for as much as he was brilliant, honest, driven confident, perhaps even lucky in some respects, these are all traits of many scientists and physicians. Gonin had the fortune and the insight to meld critical qualities at a critical time, and the necessary confidence and perseverance to prove his point to a reluctant medical establishment. So much in the advancement of medicine goes beyond the discovery to

Fig. 12 Gonin with his wife Helene on his sixtieth birthday in 1930

translation and awareness. The better mousetrap will never work until it can be tried out, advertised and sold. Gonin did not “invent” the theory that holes cause detachment—but he recognized its validity and was willing to work to achieve its acceptance. He did not develop the best therapy—but he was the first to cure detachments effectively. He understood that finding holes was the first step, even if his approach in the operating room was only one of many that might achieve the goal. This drive where needed, and this essential modesty about his approach, are perhaps less common traits in the medical establishment.

Gonin also worked in an era without some of the modern controls and constraints. He did not have to contend with an institutional review board (although as noted, he was honest and thoughtful in explain new procedures to his patients). He had no special need for funding, being a clinician. He did not have an animal model, and he did not need a PhD. When a visitor once asked him where his laboratory was, Gonin replied, pointing at his forehead, “That’s my lab” [3].

It is intriguing that the name “rhegmatogenous,” that we apply nowadays to the type detachment that Gonin analyzed and treated, was not used in his day. Gonin separated idiopathic from traumatic detachments, and at various times used other terms like spontaneous or simple. The term rhegmatogenous was first used by Schepens and Marden in 1961 on the basis of Gonin’s theories on the pathogenesis of detachment [36, 37]. They wrote “It is universally recognized that retinal breaks play an essential role in the causation of idiopathic retinal detachment; therefore, the term *rhegmatogenous* has been coined to denote a detachment resulting from a retinal break.” The word comes from the Greek for “breach” and reflects acceptance of the role of a breach in causing the disease.

It is not necessary to catalog here the enormous progress in management of detachments over the decades after Gonin’s death. Diagnosis has been improved by binocular indirect ophthalmoscopy, wide field photography and increasing sophistication of cellular imaging. Surgical technology has vast new options ranging from buckles, to air and silicon, and of course to the ability now to operate safely within the eye itself upon vitreous and retina. Diathermy has been shelved with the advent of lasers. Who can say what the next great step forward in the management of detachments will be. Whatever it is, however, and whether a prevention or therapy, it is likely still to be focused on the retinal hole as the proximal cause of separation. That is Gonin’s legacy. His posthumous honors are many, such as the Gonin Society in his name, and the prestigious Gonin Medal awarded every 4 years by the International Council of Ophthalmology for the highest achievements in ophthalmology. We can still follow Gonin’s path between clinic and home in modern Lausanne, along Avenue Jules-Gonin [3, 36] (Fig. 13).

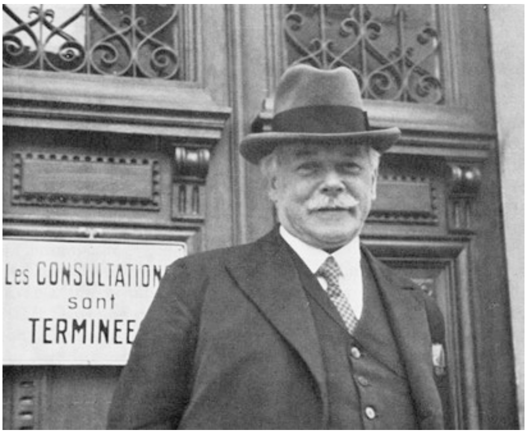

Fig. 13 Gonin leaving the clinic, late in his life

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Harold Ridley: The Development of a Plastic Implantable Lens

14

Curtis E. Margo

> *"Moments of great cultural significance are often appreciated only in retrospect."*
>
> Tony Judt [1] p. 390

> *"Until the Bayh-Dole Act of 1980, academicians considered the worlds of the university and industry incompatible."*
>
> Gordon K. Klintworth [2] p. 58

Introduction

On November 29, 1949, Harold Ridley (1906–2001) implanted the first intraocular lens (IOL) in a 45-year-old woman with unilateral cataract at St. Thomas' Hospital, London [3]. Few events in the annals of medicine or surgery have so unequivocally marked a departure with the past as that day in surgery. Replacing a cloudy cataract with a clear molded lenticel of light-weight plastic signaled a new era in ophthalmology, although at the time its impact on eye care would have been hard to predict.

Treatment of cataract through couching or extraction had existed for thousands of years, but it left patients dependent on thick spectacle correction, which inflicted its own annoying hardships. One textbook describes aphakic spectacles as creating "a monumental change in his [or her] life to which adaption comes slowly—and for some never" [4] p. 247. For Ridley and other knowledgeable eye surgeons, the dissatisfaction of aphakic correction was a discouraging reality of everyday practice. The typical aphakic patient had to adjust for to a 25% image magnification, reduction in peripheral field of vision, and the loss of about 20% of visual field due to a ring scotoma [5]. This roving scotoma results in peripheral objects suddenly appearing in the field of vision when gaze is shifted, a phenomenon lightly referred to as a "jack-in-the-box" surprise. Aphakic spectacles transformed the external word into one with exaggerated diagonal dimensions, giving objects a pincushion appearance. The aphakic eye also needed to move an additional 40% more than a phakic eye because of rotational magnification. For patients with unilateral aphakia, the situation was more bothersome because the optical disparities between eyes usu-

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M.F. Marmor, D.M. Albert (eds.), *Foundations of Ophthalmology*,
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ally prevented single binocular vision [5]. The solution to the optical conundrum of aphakia is to place the corrective lens (i.e. artificial lens) at the nodal point of the eye, which according to Allvar Gullstrand's (1862–1930) reduced schematic eye, is in the posterior chamber where the crystalline lens resides.

Harold Ridley's original contributions to the concept and development of the first artificial IOL are uncontested. Although he alone is credited with what is acknowledged as the standard treatment of surgical aphakia, the original idea that a cloudy cataract could be replaced with an artificial lens is lost in history. Reference to an artificial intraocular lens has been found in the memoirs of Casanova (1725–1798), who attributes the notion to an oculist named Tadini. According to Casanova, Tadini admitted that he only thought about replacing a cataract with a glass lens, but never actually accomplished the feat [6]. In 1795, a German oculist known as Casamata reportedly placed a glass lens in an eye after cataract extraction only to have it fall back into the vitreous [7]. The accuracy of the claim is impossible to validate. Medical technology, much like aerospace engineering, can be preceded by science fiction, which undoubtedly has a role in advancing true scientific creativity. The idea of an IOL is not that complicated. In 1940, an English surgeon named John Foster wrote an amusing article for the Leeds Medical Society Journal in which he mentioned the possibility of a glass lens replacing a cataract. Although the comment was not meant to be taken seriously, it contained an element of futuristic fantasy [8]. A Yugoslavian doctor named V. Cavka took a slightly different approach to curing aphakia. He transplanted a human lens into a 32-year-old man with traumatic cataract in 1954 [9]. He placed the donor lens in the posterior chamber without sutures then closed the surgical wound. He reported that the lens remained clear for 6 months, but no further follow up exists.

Ridley would seize the opportunity to turn science fiction into reality. Since his revolutionary surgery, artificial intraocular lenses have improved the quality of life for tens of millions of patients. The ostensibly straightforward solution to the tribulations of aphakia, however, was anything but simple or trouble-free. Profession-wide acceptance of IOL surgery did not occur for over a quarter century after Ridley's revolutionary procedure, and the first IOL was not approved by the Food and Drug Administration until December, 1981 [10]. Ridley's implant surgery was initially condemned by a vocal group of his peers and academicians. Unlike the vast majority of modern medical advancements, IOL surgery occurred largely outside of academic institutions—in the private sector [11, 12].

The story of IOL-implant surgery touches on common themes surrounding invention and discovery, yet it also deals with more contentious issues related to human experimentation and entrepreneurship. Replacement of a cataract with an IOL seems so logical from a twenty-first century perspective that the consternation the surgery caused and the protracted period of refinement are difficult to understand without an appreciation of the professional attitudes and norms associated with medical research of commercial products following World War II.

"Revolutionary Rather than Evolutionary"

Ridley was born in the summer of 1906 in Leicestershire, England. He developed an interest in ophthalmology at an early age [13]. His father was a general surgeon who limited his practice to eye surgery after developing arthritic complications of hemophilia. A quiet but good student, Ridley attended Pembroke College, Cambridge before receiving his medical training at St Thomas' Hospital (Fig. 1). In 1931, he continued at St Thomas' Hospital in general surgery before securing a temporary position in the eye department for 6 months. After completing his qualifying examination, Ridley began training at

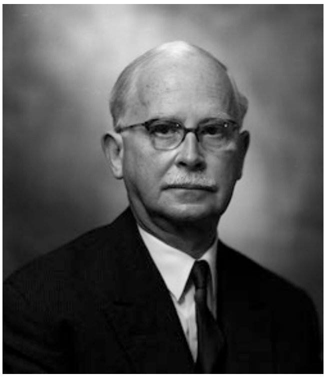

Fig. 1 Harold Ridley at age 65 (Courtesy National Portrait Gallery, London)

Moorfields Eye Hospital in 1933. Five year later, he was appointed full surgeon and permanent consultant at Moorfields, but had little opportunity to establish a practice before the outbreak of World War 2.

During the war, Ridley was stationed in West Africa, where he learned a considerable amount of topical medicine [3]. Later in the war, he served in Calcutta and Rangoon. During this time he developed interests in onchocerciasis, ocular leprosy, and vitamin A deficiency. When he returned to London after the war, St Thomas' Hospital was badly damaged. In 1946, he established a practice on Harley Street, not far from St Thomas' and Moorfields, where he practiced general ophthalmology until his retirement in 1971. Like other physicians of his era, a considerable portion of his practice in the late 1940s involved the care of military veterans.

Popular accounts of the invention of the IOL highlight how Ridley got the idea by observing the lack of inflammation associated with fragments of Perspex (also trade name Plexiglas, or poly-methyl methacrylate [PMMA]) lodged inside the eyes of injured pilots [14]. The story is generally correct, but with two caveats. First, regular surveillance of the biocompatibility of the plastic involved just a single aviator: Flight Lieutenant Gordon "Mouse" Cleaver, a member of the 601 Squadron [13] p. 104–121. And, second, Ridley had thought about the possibility of an artificial IOL years before he first witnessed Perspex embedded in the eyes of pilots. Nonetheless, Ridley had the perceptiveness to appreciate the clinical utility of a biologically inert plastic.

On August 14th, 1940, Cleaver was returning from a combat sortie when his aircraft, a Hawker Hurricane, was shot down by bullets that shattered the sidewalls of the cockpit (Fig. 2). Having not worn googles, shards of Perspex penetrated both eyes. Remarkably, he was able to parachute to safety, landing in southern England. Cleaver was triaged at Salisbury infirmary then evacuated for further care. The injury to the right eye would leave it permanently blind, but the left eye was salvaged despite numerous splinters of Perspex. During the ensuing years, Cleaver would have 18 operations on his left eye, including many at Moorfields Eye Hospital [13] p. 121. It was during this prolonged period of treatment and convalescence that Ridley met Cleaver and noticed how well the eye tolerated the plastic polymer. Cleaver would receive the Distinguished Flying Cross for service during the Battle of Britain.

Ridley had seen other pilots with Perspex embedded in their eyes during the war, but the notion of an artificial implantable lens had existed in his mind long before he encountered these men [15]. He told David Apple (Ridley's official biographer [13] p. 22) that the first thoughts occurred in the 1930s. Subsequently, the subject was discussed at various times with his father and with Professor Arthur Cyril Hudson (1875–1962), with whom he had trained [13] (p. 104). Ridley apparently never wrote down any of his idea about the challenges of implanting a foreign object in the eye; nor did he present the subject at any professional meeting prior to his groundbreaking surgery [15]. There is no evidence that Ridley made any systematic inquiry into a suitable substitute for a glass lens.

The artificial IOL stayed forefront in Ridley's mind after the war, but it was serendipity in slow

Fig. 2 Hawker Hurricane used in the Battle of Britain, the type of aircraft flown by Lieutenant Gordon Clever when he was injured by shards of Perspex (Photograph courtesy of Adrian Pingston, July 2008. Photograph in the public domain)

motion [16]. He relates the final impetus to pursue the lenticular prosthesis was the innocent comment of a medical student, who asked during a routine cataract extraction in 1948 whether Ridley planned to replace the cataract with another lens [13] p. 130? This question have come from a person without any experience in ophthalmology may have worried Ridley that the idea could occur to others. Stimulated to take action, he first needed to decide on what type of material to use for the lens. The logical choice was Perspex, based on his observations during and after the war. The next decision was what type of extraction to perform. Since the artificial lens would have to remain fixed in the visual axis, the ultimate fate of the surgery depended on insights into maintaining the maximum strength of supportive tissues. No one had dealt with this problem before him, and there was insufficient information on the biomechanical properties of the anterior hyaloid to draw an informed conclusion. Ridley had learned both intra and extracapsular cataract extraction techniques when training under the supervision of Professor Hudson and Geoffrey Doyne (1886–1959) [13] p. 45. The extracapular procedure seemed preferable because it left the posterior capsule and zonules for IOL support.

In the fall of 1949, Ridley collaborated with Rayner & Keeler, Ltd. to fabricate a disc-shaped artificial lens made of PMMA [17, 18]. John Pike, the senior optical scientist at Rayner & Keeler Ltd., created a biconvex lens to correct aphakia based on the metrics of Gullstrand's schematic eye and the known optical properties of PMMA. He used high-grade polymer supplied by Imperial Chemical Industries. The lens was made by compression molding, and designed to correct an average adult eye to theoretical emmetropia when placed in the coronal plane behind the iris (Fig. 3). Ridley spearheaded and oversaw every aspect of the project, but never had any financial interest in the commercial product [13] p. 20.

The lens was 8.35 mm in diameter and 2.44 mm thick. The asymmetric biconvex lens (steeper posterior curve) had a refractive power of 24 diopters in aqueous solution. Before polishing, a peripheral groove was cut in the lens to assist in handling. (Decades later, David Apple performed scanning electron microscopy on an original Ridley IOL. He found that the polished surface of the lens exceeded current standards of manufacturing quality [13] p. 136.)

Prior to surgery, the lens was sterilized in 1% cetrimide for half an hour, using a specially designed rack also manufactured by Rayner & Keeler, Ltd. The rack held lenses in a fixed anterior-posterior direction to assure correct orientation inside the eye.

Ridley had personally selected the nurse to assist him that day. In the era before surgical microscopes, she was experienced in holding the flashlight steady without obstructing the operative field. Following expression of the lens nucleus and cortical clean up, pre-placed sutures

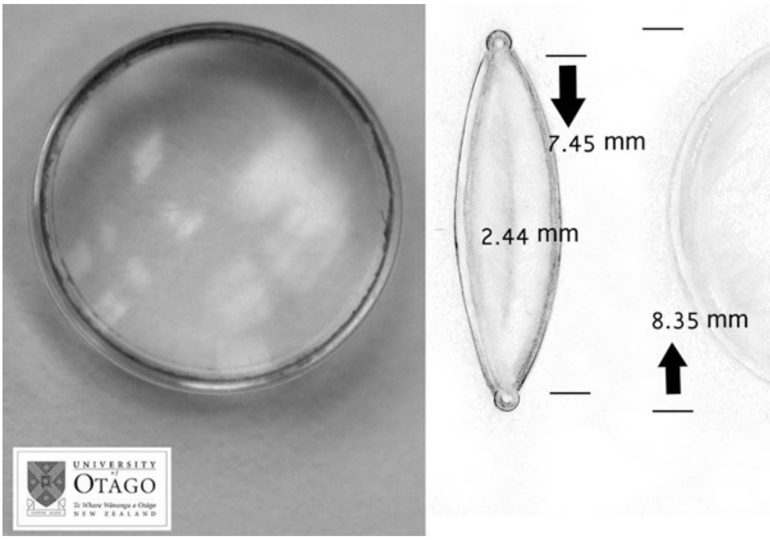

Fig. 3 Photograph of an early Ridley lens on the *left*. (Courtesy of University of Otago, Department of Medicine. Photograph used with permission.) The diameter and thickness of first acrylic intraocular lens on the *right* (Author's illustration)

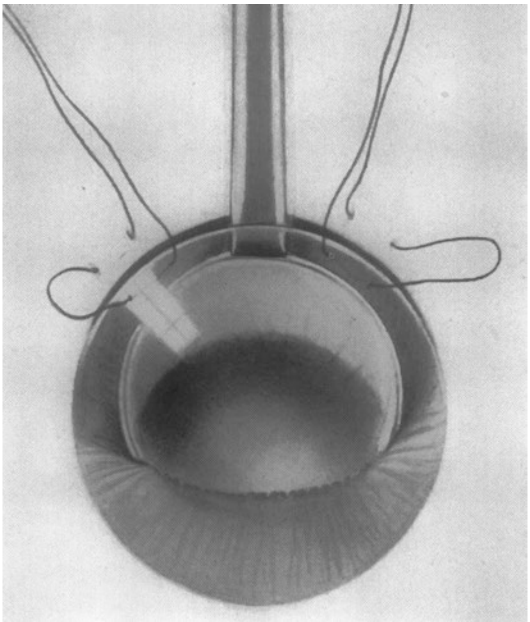

Fig. 4 Illustration from Ridley's seminal paper in British Journal of Ophthalmology [28] showing insertion of acrylic lens using lens-insertion forceps (Courtesy of British Journal of Ophthalmology, with permission.)

were draped away from the path of lens insertion. After thoroughly rinsing the artificial lens with sterile water, Ridley used a special lens-insertion forceps and iris hook to guide the lens behind the iris employing a "slight side-to-side movement" through the pupil (Figs. 4 and 5) [17, 18]. He then centered the lens by applying gentle pressure to the external cornea and sclera. Iris prolapse complicated the surgery, but the iris was eventually coaxed back into the anterior chamber. A small peripheral iridectomy was performed and penicillin instilled into the anterior chamber. He decided against a topical miotic (standard care at the time). Both eyes were patched for 48 h.

According to David Apple, Ridley instructed his nurse to record the procedure in the surgical logbook as "extracapsular ext" without mention of the intraocular lens implant [13] p. 145. This choice would later create confusion as the patient returned to the surgical suite on February 8, 1950

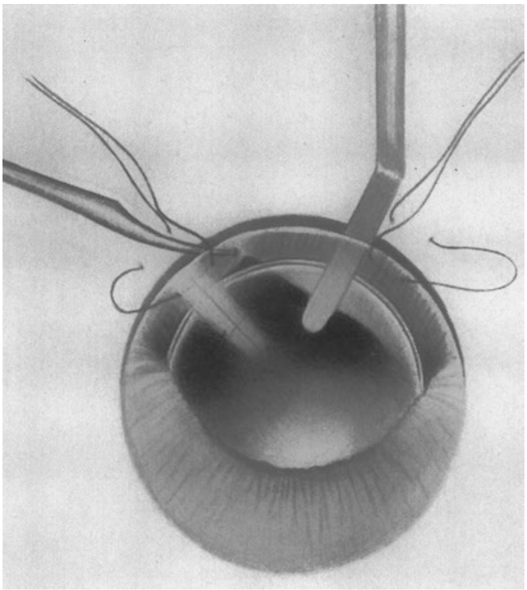

Fig. 5 Illustration from original British Journal of Ophthalmology paper [28] showing iris hook being used to place upper portion of acrylic lens beneath the iris (Courtesy of British Journal of Ophthalmology, with permission.)

Fig. 6 Plaque in St Thomas's Hospital that commemorates the first lens implant cites February 8, 1950 rather than November 29, 1949. This confusion was caused by surgical log entries that lacked sufficient detail. Some believe the later date log entry of "lenticular graft" represented a lens exchange [29] (Image from Wikimedia Commons. Image is in public domain.)

for a "lenticular graft," suggesting a two-stage procedure [3]. Apple questioned Ridley about this discrepancy, as well as his surgical nurse. Both confirmed the implant was inserted at the first surgery [13] p. 148. The reason the patient was taken back to the operating room 3 months later, however, remains unclear, but some contend it was for a lens exchange to correct residual myopia [19]. (The designer of a plaque commemorating the first surgery at St Thomas' Hospital fell victim to this mix-up, mistakenly listing February 8, 1950 as the date (Fig. 6)).

Postoperatively, the patient did well, although she was left with considerable myopia (roughly 14 diopters). This surprising refractive outcome told Ridley that perhaps the index of refraction of PMMA was not accurately known. Adjustments in lens curves were expedited so he could proceed with more surgeries. Ridley continued to perform surgeries in secretly at both St Thomas' Hospital and Moorfield's Eye Hospital. He intended to withhold results of his experimental surgery for 2 years so that he could refine the procedure, analyze the results, and obtain longer follow up [13] p. 151, [19]. When one of his surgical patients mistakenly scheduled an appointment with Frederick Ridley, a London ophthalmologist unrelated to Harold, further concealment of the procedure was impossible. Should the clandestine operation been reported to certain authorities, it could have had serious repercussions [13] p. 151. Ridley submitted papers describing the results of his initial surgeries (series included from 25 to 27 eyes) in rapid succession to The Proceedings of St. Thomas' Hospital, Lancet, the Ophthalmological Society of the United Kingdom, and British Journal of Ophthalmology [17, 18, 20, 21]. Initial public reactions to the surgery were measured, but what was said behind closed doors may have been highly critical. Ridley requested that Dave Apple, who was given access to his private letters and personal communications, refrain from publishing the "many relentless attacks of his clinical judgement and integrity."[13] p. 60. This would indicate that discussions found in journals and at meeting did not reflect the true extend of negative reaction.

According to persons close to Ridley, he performed about a 1000 lens implants within several years after the initial procedure [3] p. 286. In 1954, Ridley published an update on 140 operations [22]. With follow up as long as 3½ years, he was confident that the polymer would be well tolerated in the eye, yet admitted that longer observation will be needed to establish safety. He wrote that the procedure had "undergone little change since the operation was first described [22]. Among the 140 patients operated on, 18 had undergone intracapsular extraction and 10 of those were deliberate (planned). In all ten cases of planned intracapsular surgery, the acrylic lens was "inserted perfectly," but in seven it underwent spontaneous dislocation into the base of the vitreous. Because of these unfortunate outcomes, he abandoned the intracapsular technique.

Topical medications used during surgery were limited to cocaine for pain control and adrenaline for pupil dilation. Homatropine was avoided so that the effect of miotics, if needed, would be greater. He determined from experience that the acrylic lens could be fit through a 3 mm pupil. During this phase of the learning curve, Ridley also realized that staged insertion of IOLs was usually unnecessary except in situations when previous ocular trauma compromised the general integrity of the eye. Vitreous loss occurred in three of 140 surgeries. He reported no infections or serious hemorrhages. Assorted complications included iritis, occlusion of pupil, glaucoma, and postoperative diplopia. Lenses that dislocated in vitreous were not retrieved, except for one traumatically dislocated lens that was recovered. An unforeseen problem was opacification of the posterior capsule, which required needle capsulotomy in two patients.

Postoperative refractive surprises were uncommon once the original lens power was modified. In the 1954 series, one patient was left with 6 diopters of cylinder, but the average postoperative refractive error was 1.75 diopters. Nearly two-thirds saw 6/9 (20/30) or better. Ridley optimistically concluded that "The verdict of 3 ½ year experience is that the intra-ocular acrylic lens operation has a definite place in ophthalmic surgery." He went on to caution, however, that "no other operation in ophthalmic surgery more accurately reflects the degree of skill and care of good surgery." [22]

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When Ridley implanted his first acrylic lens, medicine and surgery was witnessing a variety of miraculous inventions and discoveries. In 1941, penicillin had been transformed into a practical life-saving drug; in 1943, Willem Kolff (1911–2009) brought a woman out of coma using the first hemodialysis machine; in 1944, the first antihistamine was available for human use; that same year Alfred Blalock (1899–1964) successfully surgically corrected the Tetralogy of Fallot; in 1948, cortisone was discovered. The list goes on. The technological advancements were impressive and depended more on non-medical expertise than ever before. There was also a concern that society might not be able to adequately address the ethical dilemmas being created by science in the unprecedented nuclear age. Surgery was not immune from this apprehension.

Since the time of Hippocrates, medical and surgical research was an inseparable part of clinical practice. The activities of physicians were assumed to always be in the best interests of patients, including experimental therapies. Ridley implanted his first IOL 15 years before the World Medical Associated adopted a formal code of ethics for clinical research known as the *Helsinki Declaration*, when the norms surrounding human experimentation were lax. Ridley characterized the surgery as "revolutionary rather than evolutionary" [13] p. 287. He also hid the experimental surgery from his superior and peers, believing secrecy was essential until he could obtain good results [13] p. 133. He choose St Thomas' Hospital for the first surgery, because it would have been harder to conceal the surgery at Moorfields [3] p. 286. Ridley later admitted the need to hide the procedure from "powerful colleagues" who might show hostility to the idea of placing a foreign object in the eye [3] p. 284 From a late twentieth century perspective, the rationale for secrecy may seem objectionable, but intentionally disguising experimental surgery as routine cataract extraction could have bothered some of his colleagues even when the norms surrounding human research were slack.

There has always been ambiguity in how to characterize new types of surgery or technological advancements in surgery. Are they therapy or experimental research or something different? [23] This gray zone lies between the extremes of well-established standards of care with proven efficacy and novel procedures or techniques with unknown risks [24]. Implanting a foreign object in the eye was consider audacious in 1949. Some persons disapproved of the surgery because no animal experiments had been done to test the safety of PMMA [13, 25]. Perhaps one of the most influential ophthalmologists of this era, Sir Stewart Duke-Elder (1898–1978), thought the surgery irresponsible [19]. Those close to Ridley saw the professional relationship between the two men deteriorate to the point that Duke-Elder became an "archenemy" [13] p. 48. Ridley may not have foreseen the challenges of replacing an established form of surgery with an excellent safety profile with one having functional benefit but beset with complications. In America, the prominent ophthalmologist Derrick Vail condemned the surgery, and advised others to not perform it [26].

Moving Forward

Although Ridley weathered the tumultuous early stages of experimental surgery, his fundamentally straightforward solution to curing surgical aphakia still took over a quarter century to refine before it was adopted as standard care. The prolonged period of development has been attributed to the piecemeal approach to research, the relative lack of academic involvement, and the dearth of governmental funding [11, 13] p. 4 [27]. The ambiguous relationship that biomedical researchers had with industry over intellectual property after the war contributed to the slow pace of research and development.

Financial support in England for research in cataract surgery was non-existent after the war. The commercial development of penicillin, which was a major war-time priority, is a prime example of the strained relationship biomedical researchers had with industry. Alexander Fleming (1898–1968) had discovered the antibacterial activity of the penicillin mold in 1929, but it was the efforts of Ernest Chain (1906–1979) and Howard Florey (1898–1968) that brought the therapeutic utility of the drug to clinical fruition. When Florey came up against a technological impasse in terms of large-scale production, he consulted commercial companies in America for help [28]. By the autumn of 1941, the laboratories of Merck and Company, E. R. Squibb and Sons, and other major pharmaceutical companies had begun producing substantial amounts of penicillin [29]. The combined efforts of British physicians and U.S. industry in bringing the greatest miracle drug of the twentieth century to market should have served as a model of medical-industrial cooperation, but it did not. Florey and many of his academic colleagues were bitter about being left out of the financial windfall. The acrimony surfaced when Florey commented he had not received a penny for his work while American drug companies, according to his estimate, had made about $20,000,000 [28] p. 247. Many university faculty in Britain were indignant that the monetary reward for penicillin would benefit companies outside the United Kingdom. This experience, and others like it, would sour the relationship between academia and industry on both sides of the Atlantic for decades [28] p. 251.

In the United States, the financial disincentives related to government sponsored medical research progressively increased after the war, reaching a critical stage in the late 1970s. According to federal regulations, any patent or intellectual property that resulted from federal grants belonged to the U.S. government. There was no financial incentive for academicians to work on projects with potential commercial value. Throughout this period, the acrylic lens that Ridley had designed would be subject to multiple modifications and repeated trials in humans before being ready for widespread use. Research was conducted in the private sector without government support. It was inefficient and time consuming, and relied on trial-and-error, which had the potential to inflicted considerable patient morbidity in the process [12, 30]. One high-profile surgeon had to remove about 250 of 493 angle support lenses he implanted [31].

The potential benefit of IOLs was apparent to many forward-thinking surgeons by the 1970s. Implant research and development began to accelerate in the United States after 1975, when the original manufacturer in Britain engaged in a joint venture and technology agreement with companies in America [32]. Legislation in the form of the Bayh-Dole Act of 1980 changed regulations dealing with ownership of new technology under federal grants, but this legislation came too late to have a major impact on the early phase of IOL development. The lion's share of the work had already been accomplished by surgeons in private practice [11, 12, 33, 34]. The Bayh-Dole Act, however, would influence future research for it encouraged federally funded studies by universities and small businesses by allowing ownership of inventions and intellectual property rather than belong to the U.S. government [35].

Giving Birth to Biomaterial Science

When Ridley began his experiment he ventured into the unexplored field of biomaterials. Ridley appreciated that few materials possessed the properties required of an IOL. The material must have an appropriate density and weight to remain suspended in the visual axis, and also be optically transparent, durable, and biologically inert. Finding a suitable material other than glass that satisfied these criteria involved considerable luck.

Surgeons had experimented with only a few biomaterials before World War II. Experiences were limited because of the inability to adequately sterilize prostheses before implantation and because once implanted inflammatory responses were difficult to control and could be highly destructive. Themistocles Glück, a Professor of surgery in Berlin, fashioned a hip implant using an ivory ball and socket joint that was fixed to bone with nickel-plated screws in 1891 [36]. Although his work was unsuccessful, hip replacement surgery seemed poised to led the way in the development of biomaterials [37]. Philip Wiles of Middlesex Hospital in London attempted the first total hip replacement in 1938 using stainless steel components fixed to bone with screws and bolts [36, 38]. The surgery failed, leading to other futile attempts with rubber, glass, and plastic [37]. The desired structural and physical properties of biomaterials vary depending on prerequisite functions of the tissue they are to replace. The one thing these materials have in common is the ultimate need to be tested for function and compatibility in human subjects.

In terms of materials for IOLs prior to 1950, glass was the only option, which because of its relative density was unacceptable [17]. The development of light weight, clear and chemically inert materials other than PMMA, such as polycarbonate, silicone and hydrogels, were years to decades in the future.

Protracted Era of Refinement

Given the general state of knowledge about the biocompatibility of PMMA, toxicity of most antiseptics, and unknowns related to mechanical support, the results of implanting the first artificial lens likely exceeded expectations. The surgery required an impressive degree of skill if one considers that it was performed with relatively basic equipment and without the advantage of a surgical microscope, using a lens that weighed in air more than four times that of moderns IOLs. As news of the procedure spread, public responses were mixed. An anonymous review on Ridley's work in the British Medical Journal in 1952 thought 2 years was too short a period of observation to offer a final judgement [39]. The tone of the essay, however, was positive, stating that "the optical benefits conferred appear on both theoretical and practical ground so encouraging that the operation deserves the most serious consideration." [39]

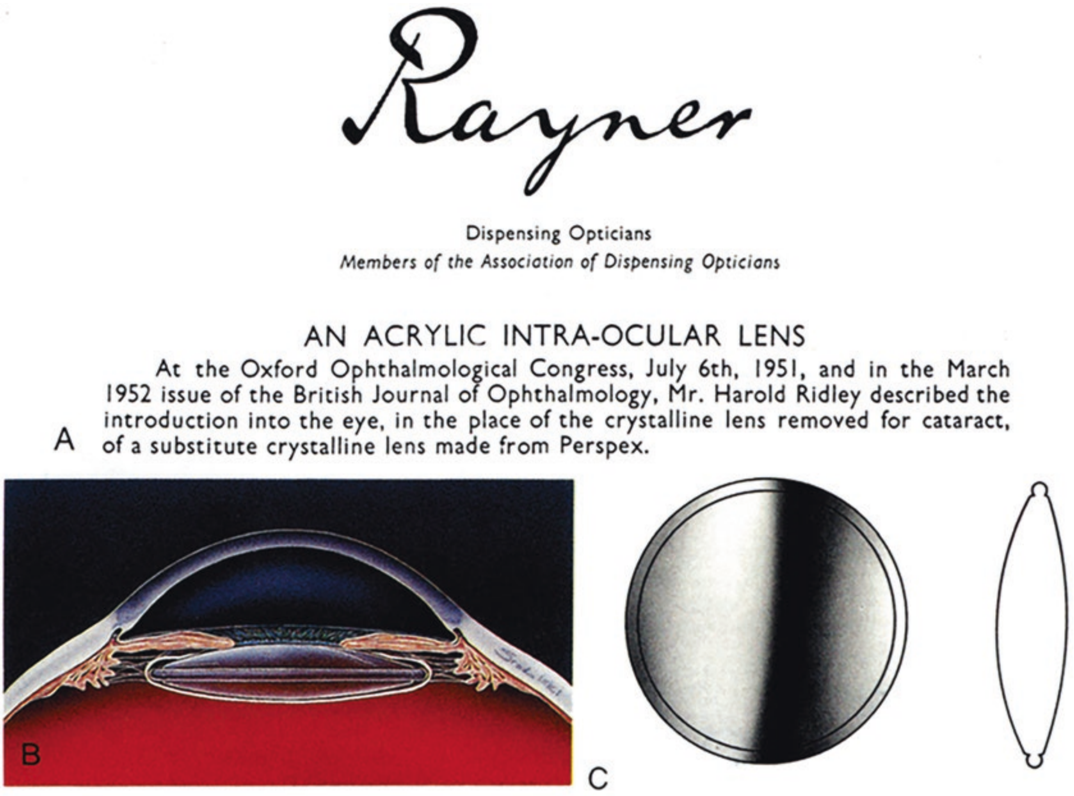
Relatively few surgeons were willing to try the surgery, however. Reasons varied from a reluctance to implant a foreign object in the eye to a lack of experience with the extracapsular extraction technique. Ophthalmologists that questioned whether Ridley had gone too far argued that a proven, safe alternative was already available. As time passed and more complications emerged, and criticism turned to rebuke. In later years, Ridley described this period as personally painful [3]. Few surgeons could duplicate Ridley's results. As the litany of complications associated with pseudophakia grew, the safety and predictability of aphakic spectacles became more appealing.

In 1954, Warren Reese of Wills Eye Hospital in Philadelphia reported his experience with the Ridley procedure in 29 eyes [40]. During the introduction of his Academy presentation, Reese remarked how much opposition existed towards the Ridley operation, particularly among older ophthalmologists [40]. He acknowledged the technical difficulty in performing the surgery and confirmed the opinion that intracapsular extraction should not be used when inserting an IOL. Although he did not provide details in terms of visual outcome, Reese felt “that the Ridley operation will take its place in ophthalmic surgery because of its efficacy in enabling the patient to use both eyes after operations for unilateral cataract.” [40]

John Finlay and Hunter Romaine of New York Eye and Ear Infirmary, who also spoke at that year’s Academy meeting, were more pessimistic [41]. They reported a series of 11 cases, the first two of which were performed by Ridley himself, presumably as a means of instruction. Clinical outcomes were discouraging. Two patients lost vitreous, two developed glaucoma, three developed occluded pupils, and all had varying degrees of iritis [41]. The authors believed the implant surgery was too hazardous to perform except in the context of research, and then only in selected situations.

Because funds for research into IOLs was lacking, and a general interest in the subject was absent in academic centers, research and development was haphazard. Most human studies testing new lens design involved small numbers of patients, were uncontrolled, and prone to bias [12, 25, 31]. Anecdotal experiences carried considerable weight. Because some patients were delighted with the results of unilateral IOL surgery, the indications for surgery morphed into bilateral aged-related cataracts. But problems persisted, particular with lens support. Ridley lived with the fear of litigation, knowing, for instance, that the late dislocation of acrylic lenses was a persistent concern [3].

Among surgeons testing implant surgery, many found postoperative inflammation more



Rayner

Dispensing Opticians

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AN ACRYLIC INTRA-OCULAR LENS

At the Oxford Ophthalmological Congress, July 6th, 1951, and in the March 1952 issue of the British Journal of Ophthalmology, Mr. Harold Ridley described the introduction into the eye, in the place of the crystalline lens removed for cataract, of a substitute crystalline lens made from Perspex.

Fig. 7 Ridley’s original lens received restrained commercial promotion. An illustration from 1950s brochure displays the acrylic lens after surgical implantation (Illustration courtesy of Rayner Intraocular Lenses Limited, © 2016.)

severe than the scant literature on acrylic lenses suggested. Investigators Binkhorst and Flu proposed that the quaternary ammonium compound (cetrimide) used to sterilize the lens may be contributing to this problem [42]. Their concerns that the chemical disinfectant could not be effectively rinsed from PMMA was supported by studies demonstrating reduced inflammation with alternative methods of sterilization [19, 42].

By the late 50s, a small minority of surgeons were performing implant surgery. Any early enthusiasm for the original artificial lens had waned (Fig. 7). A handful of surgeons including Peter Choyce (1919–2001), Cornelius Binkhorst (1928–2015), Jan Worst (1928–2015), and Svyatoslav Fyodorov (1927–2000) continued to make refinements in surgical technique and modify the design of lenses. By this time Ridley was cautious in promoting IOL surgery. He admitted that inserting lenses in the posterior chamber had grown out of favor and that serious complications had dogged some surgeries [43]. The host of early and late complications associated with IOLs were indeed troublesome, but he stressed that pseudophakic vision was superior if these deficiencies could be eliminated. Several late complications unique to posterior chamber lenses made Ridley experiment with anterior chamber implants, although he was worried about secondary corneal injury [43, 44].

Celebrated eye surgeons at the Wilmer Institute in Baltimore reported as late as 1975 very conservative and "strict selection criteria" for IOL surgery [45] p. 922. Although other leading American surgeons echoed this same guarded approach, repeated shortcomings of IOLs placed in the anterior chamber and iris plane drove private-sector research to experiment further with lenses placed in the lens capsule [12, 46] p. 107. When the Food and Drug Administration gained regulatory authority over medical devices in 1978, it forced manufacturers to verify claims of safety and effectiveness [47]. By the 1980s a tipping point had been reached (Fig. 8). Key modifications in lens design and sterilization techniques improved the safely profiles of IOLs that nearly guaranteed their commercial success. Critically, after 25 years of use, PMMA still appeared to be chemically inert inside the eye.

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Ridley wrote a comprehensive update on IOL surgery in 1960, finding only one case of sympa-

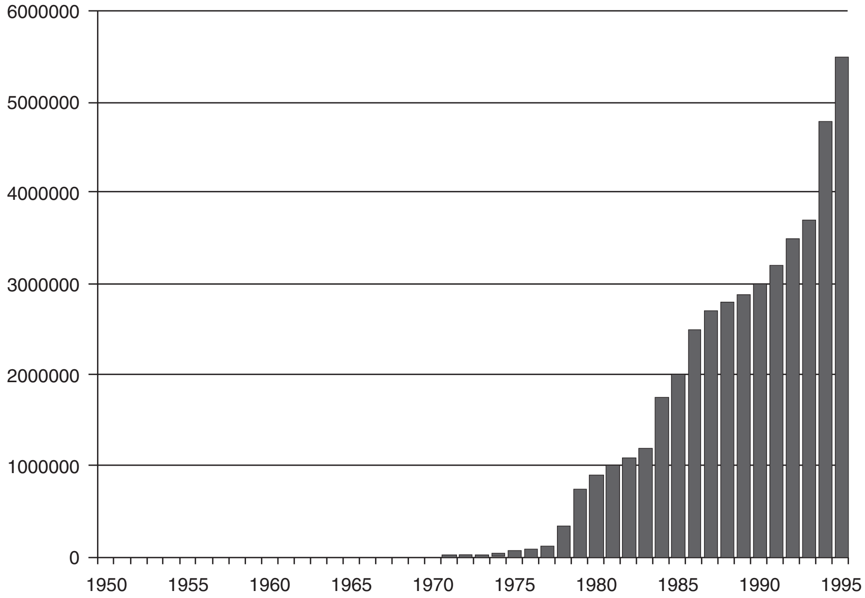

Fig. 8 Graph showing annual number of implants used worldwide from 1950 through 1995 with vertical units of one million. Implant surgery accelerated after technology transfer agreement occurred in 1975. Estimates based on multiple sources [13] p. 11 [48–52], (Courtesy of Wyatt Saxon, with permission.)

thetic ophthalmia among 750 operations [43]. Few details concerning clinical outcomes were available from this large series. The review lacked the particulars of visual acuity and residual refractive error that his seminal paper on 140 cases contained in 1954 [22]. To friends he mentioned having performed about 1000 implant surgeries in the first several years after the invention [3]. The disparity in surgeries reported in the literature has not been resolved, but may be related to the early upheaval he faced [3, 19, 22]. Ridley's middle career by any measure was stressful.

As a young surgeon, Ridley engaged in a variety of investigative activities from studying tropical disease to employing television technology in ophthalmology. After the tumult of his implant procedure, he never regained this intellectual vigor. Ridley's bibliography in the 1960s includes some follow up papers on IOL surgery, and various articles and presentations about the early years of implant surgery [13] p. 291–295. The annoying and persistent inquires surrounding his revolutionary surgery apparently took a toll. Based on hours of personal interviews, Dave Apple portrays Ridley as having been professionally marginalized, placing most the blame for this on powerful academicians [13]. A small circle of colleagues took up Ridley's cause, pursuing implant research outside academic centers. Their respect for him never diminished. Ridley retired from Moorfields in 1971, telling friends it was not "fully voluntary or very amicable" [13] p. 50. He confessed privately that he was "put out to pasture" [13] p. 50

Conclusions

Restoring vision lost from cataract by replacing it with a clear plastic lens may be elemental in concept, but in terms of a human experiment it is a bold endeavor. If Ridley had not developed the IOL someone else was bound to. Ridley's innovative leap in recognizing a suitable material and demonstrating surgical feasibility was remarkable in that he achieved a high degree of success working essentially alone with limited—albeit critical, support of industry consultants. Given the obstacles he faced in design and manufacture of the lens, and the unknowns of placing a piece of plastic inside a human eye without previous experimentation or practice, the project was ripe for failure. The degree of success he achieved is testimony to Ridley's ability to anticipate problems, attention to detail, and surgical skills. When others could not duplicate his clinical outcomes and various lens deficiencies appeared, a haphazard approach to refinement and development of implants followed, due, in part, to the lack of a functional relationship between medicine and industry.

Extracapsular cataract extraction with insertion of an IOL is now one of the safest and most predictable of all surgeries. Dozens of incremental modifications in lenses were needed to achieve this goal, but it was Ridley who jump-started the technology. Ridley lived long enough to experience recognition for what he had accomplished. Among his many honors were the Gullstrand Medal from the Swedish Ophthalmology Society in 1992, the Gonin Medal in 1994 from the Club Jules Gonin, and conferred Knighthood by Queen Elizabeth II in 2000. In 1989, Ridley experienced another tangible reward of his invention when he underwent cataract surgery. The IOLs used to restore his vision, although substantially modified from the first acrylic implant, were possible because of his initiative 40 years earlier to cure aphakia [14].

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Arnall Patz and Norman Alston: Oxygen and Retinopathy of Prematurity

Monte D. Mills and Graham E. Quinn

The Emergence of a New Disease: Retrolental Fibroplasia

Retinopathy of prematurity (ROP) is an iatrogenic disease, unknown prior to the development of neonatal pediatrics and resuscitation of premature infants. Early in the twentieth century, deliveries mostly occurred at home; at that time, infants with significant prematurity (less than 34 weeks gestational age) rarely survived, and techniques for thermoregulation, respiratory support, and infection control, and nutrition for premature infants did not exist. Infant incubators for isolation and thermoregulation of premature infants, which were initially a popular attraction at carnivals and fairs including Coney Island, entered hospitals and became a component of pediatric care in the US during the 1920s [1]. The Sarah Morris Station for Premature infants, at Michael Reese Hospital in Chicago, was considered to be the first pediatric hospital unit in the US devoted to the care of prematurely born infants, and was established in 1922 by Julius Hess [2]. As neonatology developed as a specialty, the unique medical problems and need for specialized treatment of premature infants became apparent. In addition to the problems of thermoregulation, prevention of infection, and nutritional support, it was quickly recognized that the youngest and smallest premature infants frequently succumbed to respiratory failure. Supplemental oxygen delivered directly into the incubators improved early infant survival, and became a frequently used treatment for premature infants [3, 4] (Fig. 1).

Suddenly, beginning with a report in 1942, and apparently without precedent, a new syndrome of bilateral blindness associated with premature birth was recognized in many centers treating premature infants. The severe ocular abnormalities were first reported by Theodore L. Terry, an ophthalmologist at the Massachusetts Eye and Ear Infirmary who noticed an unusual cluster of 5 infants treated in Boston who were born prematurely and were observed several months later to have blindness with an opaque membrane behind the lens [5, 6] (Fig. 2). Within a few years, this abnormality, subsequently called "retrolental fibroplasia" (RLF) and now described as ROP stage 5 (the most severe stage, with retinal detachment and blindness [7]) was recognized and reported in many more infants in Boston, across the US, and in the UK [8–10]. By 1944, Terry had personally seen 100 cases and learned of a total of 200 additional cases [11], all in infants born prematurely and surviving their early months only to develop vascular fibrosis behind the crystalline lens, retinal

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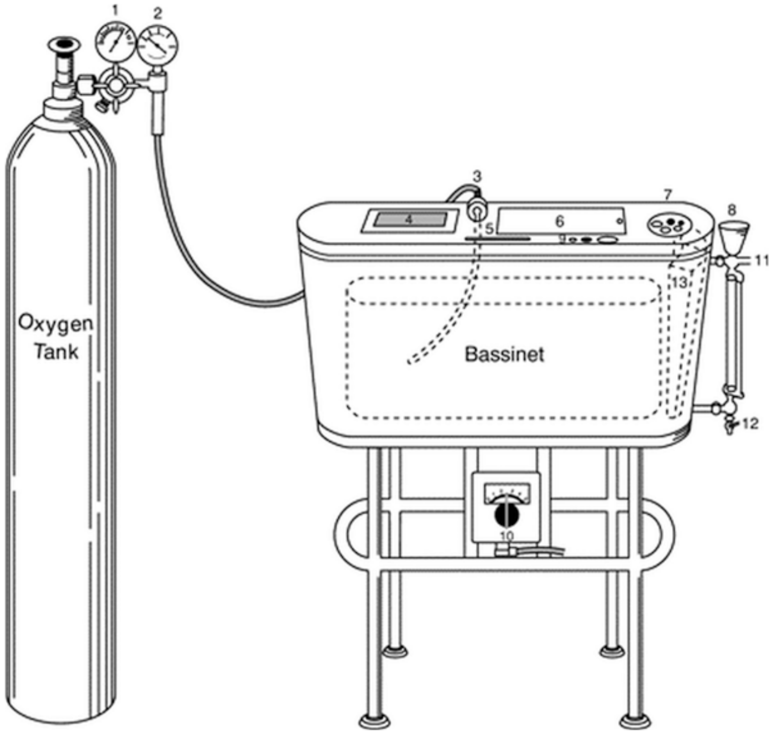

Fig. 1 Hess Premature Infant Incubator, showing oxygen directly piped into enclosed incubator. From Dunn PM, Arch Dis Child Fetal Neonatal 2001 [2]

Fig. 2 Drawing of the ophthalmoscopic appearance of retrolental fibroplasia, with white vascular membrane behind the crystalline lens. From Terry, Trans Am Ophthalmol Soc. 1942, with permission [5]

detachment, and untreatable permanent blindness. Ophthalmologists in medical centers with neonatal units across the US, and around the world, recognized RLF as an epidemic of a previously unknown blinding ocular condition, occurring exclusively in premature infants. It has been estimated that in the US, as many as 10,000 infants were blinded by RLF prior to 1954 [8], these children composed 30% or more of the blind preschool children in the US in the late 1940s [10]. An epidemic of blindness affecting prematurely born infants was recognized, but the specific causes, beyond prematurity, was not known. The suddenness of the recognition of this new condition, unknown prior to 1942 but with dozens of reports of large case series within a few years, was startling. Even in retrospect, Hess reported very few cases in birth cohorts prior to 1940, even though supplemental oxygen was in use at that time [12].

Theories and Speculation

As the epidemic of RLF was recognized in centers with developing neonatal treatment units, various theories of the pathogenesis of the eye abnormality were proposed. Terry initially believed the abnormality was related to a form of congenital ocular malformation seen in full term newborns [11, 13, 14], known then as "persistent tunica vasculosa lentis" and now called "persistent hyperplastic primary vitreous" or "persistent fetal vasculature" [15]. This abnormality, which is usually unilateral and not associated with prematurity, has superficial resemblance to severe retinopathy of prematurity (ROP) but is a congenital abnormality, present at birth. Terry and others did not immediately recognize this fundamental difference: that ROP was an acquired condition, not present at birth, but developing after preterm birth. This error was repeated in publications by Algernon Reese and Frank Payne from the Institute of Ophthalmology at the Presbyterian Hospital, New York [16].

Other investigators hypothesized different prenatal influences were causing RLF, again without recognizing the acquired nature of the condition (Table 1). Theodore H. Ingalls of the Harvard School of Public Health, a pioneer in epidemiology, observed that infants developing RLF had more frequent history of placental problems, twinning and multiple births, prenatal maternal infections, and possible fetal hypoxia. Ingalls hypothesized that fetal hypoxia associated with these prenatal conditions, as well as potentially postnatal hypoxia, were the likely causes of RLF [17].

Terry, continuing his investigations in RLF, noted the ocular abnormalities similar to RLF were seen in newborn rats whose mothers were fed a diet deficient in vitamin A, and speculated prenatal vitamin A deficiency could contribute to RLF [14].

Although some investigators, including Reese, continued to insist that RLF could be present at birth [32], conclusive evidence that RLF was acquired postnatally was developed in a series of cohort studies with early consecutive eye examinations during the first months of life [24, 33, 34]. By examining infants sequentially during the first months of life using the indirect ophthalmoscope, the progression of abnormalities from immature avascular retina thorough early stages of vascular abnormality and progressing to severe ROP with RLF, was first described in detail. These investigations also first identified and documented the frequent spontaneous improvement seen in many cases which did not progress to RLF [35, 36].

As the postnatal nature of RLF was recognized, investigators began to focus on postnatal factors as potential causes. If RLF is acquired postnatally, identification of a postnatal cause would also potentially allow development of effective therapy.

One of the most obvious and first recognized, was light exposure. First suggested as a possible cause by Terry in 1944 [13] light exposure was speculated upon as a potential factor, and the subject of the earliest clinical trial for RLF. In 1949, Hepner reported RLF developing in 4 of 5 premature infants blindfolded from birth for the first

Table 1 Early hypotheses and reported associations of retrolental fibroplasia (Severe ROP)

	Hypothesis/association	References
Prenatal factors	Persistent primary vitreous/PHPV, present at birth	Reese [16, 18]
	Infantile hemangioma of the skin	Reese, Greenhouse [19, 20]
	Prenatal fetal hypoxia	Ingalls [17]
	Maternal deficiency vitamin A	Terry [14]
Postnatal factors	Light exposure	Terry [5]
	Vitamin supplementation	Kinsey [21, 22]
	Iron supplementation	Kinsey [21, 22]
	Transfusion	Mallek [23]
	Vitamin E deficiency	Owens [24–26]
	hypoadrenalism	Reese, Blodi [27–29]
	Postnatal hypoxia	Szewczyk [30, 31], Ingalls [17], Kinsey [21]

several months [37], and concluded that light exposure did not play a role in the pathogenesis of ROP. The role of light in development of ROP continued to be controversial, leading to several clinical trials, none of which has demonstrated a relationship [38–41].

Water-soluble vitamin solutions became available and were used in neonatal units beginning in the 1940s, at the time of the first epidemic of RLF. V. Everett Kinsey and Leona Zacharias reported a temporal association between introduction of vitamin supplementation and RLF in several hospitals in 1949 [21]. Similarly, iron supplementation became widespread during the same period that RLF was initially recognized, leading to a hypothesis that iron supplementation could be causative [22]. Early association studies identified blood transfusions as a potential cause of RLF [23], although this association was never studied experimentally.

Similarly, a possible relationship between vitamin E deficiency and RLF was investigated in a small, controlled series by Owens and Owens [25]. Subsequent larger studies did not confirm the benefit of vitamin E supplementation [22, 34, 42], although the role of vitamin E deficiency in RLF continues to be controversial [43, 44].

Premature infants were presumed to have hypoadrenalism. During the decade of the initial RLF epidemic, the first treatment for hypoadrenalism, ACTH, became available as a treatment. After small case series demonstrated promising results with administration of ACTH in infants with early stages of ROP [27] a randomized trial of ACTH for early progressive RLF was organized. This randomized trial did not show a difference in the development of RLF, but the ACTH treatment group had greater mortality [28, 29], and the use of ACTH for RLF was abandoned.

Despite the intense interest in identifying a cause, and potentially a cure, for RLF, the association of supplemental oxygen was almost completely overlooked as a potential factor in the disease. As ophthalmologists and pediatricians developed experience with the condition, it became more apparent that RLF was most likely in the sickest, most premature infants: those less than 2000 g at birth, less than 34 weeks gestational age at birth, and those with the most respiratory, GI and infectious complications during their early postnatal life. The epidemiological studies of Kinsey identified oxygen use as an associated factor [21], but their interpretation was that the oxygen use reflected the severity of prematurity, and they chose instead to investigate nutritional supplementation.

The temporal relationship between the introduction of oxygen in treatment of premature infants and the initial epidemic of RLF is clear in retrospect, but was missed by almost every researcher during the decade of the 1940s. Oxygen was introduced as a treatment for respiratory distress during the initial development of the neonatal unit [4, 8, 9, 45, 46]. Along with thermal regulation, nutrition, and antisepsis, oxygen supplementation was considered essential to the survival of premature infants. Julius H. Hess, the founder of the Sarah Morris Premature Center in Chicago, suggested that all premature infants would benefit from liberal use of oxygen in the incubator [3, 4]. A public health manual published in 1939 suggested “For infants that have respiratory difficulties at any time in the neonatal period oxygen administration is always indicated. Oxygen is of great value particularly in the treatment of premature infants. It should be used freely…” [45]. Without methods to standardize its use, standards and protocols varied widely. Oxygen analyzers only became available clinically after 1953 [8, 9]. Continuous capillary measurement of oxygen saturation, and arterial blood gas measurements, were not yet available. The clinical measure of oxygenation used at that time was cutaneous cyanosis, there was no quantitative measure of hyperoxemia. No upper boundary to acceptable oxygenation was recognized, it was presumed that increased oxygen saturation could only be beneficial.

The initial empirical observations leading directly to the recognition of the role of hyperoxemia in the development of RLF care from Australia in 1951. Kate Campbell, one of the first women trained in pediatrics in Australia and a consultant at the Queen Victoria Hospital and Royal Women’s Hospital, Melbourne [47] (Fig. 3), observed and recorded the different rates

Fig. 3 Kate Campbell, MD. From Melbourne Medical School 150 Years of Medicine, http://medicine150.mdhs.unimelb.edu.au/history/kate-campbell-and-blindness-premature-babies, with permission [51]

of RLF seen in three neonatal units in Melbourne. One unit used high concentrations of oxygen, 40–60%, in most premature infants, delivered by "oxygen cot" (piped directly into the enclosed incubator), the other two units used oxygen less liberally, delivered by nasal catheter or smaller, enclosed respiratory funnel device. In infants at the high oxygen nursery, the rate of RLF was 19%, at the other two sites 7%. Campbell concluded that the dose of oxygen was related to the development of RLF, and proposed restricting use of oxygen to the minimum necessary to avoid cyanosis [48]. In the same year, in Birmingham, England, Mary Crosse, using a sequential case series of babies treated before and after a change in the method of oxygen delivery, reported a higher rate of RLF in infants treated with oxygen tent (high concentration), compared with those treated with face mask (lower concentration) [49] and A. C. L. Houlton noted a spike in RLF in Oxford, England, associated with advent of oxygen tent use [50]. These clinical observations identified the relationship between unrestricted use of oxygen and RLF. However, Campbell's report was published in the Medical Journal of Australia, which may have limited the impact of her report on other neonatal research groups outside her country. Publications by Crosse and Houlton added independent data, and likely also were more widely read and understood as direct evidence of the critical role of hyperoxemia in development of RLF.

Fig. 4 Arnall Patz, MD. Portrait of Dr. Patz by Howard Schatz, first fellow on Arnall Patz's Retinal Vascular Service. From Ferris FL, Arch Ophthalmol 2010, with permission

Clinical Interventions to Prevent RLF: The Insights and Investigations of Arnall Patz

Arnall Patz was a resident in ophthalmology at the District of Columbia General Hospital, Washington, DC during the period of the initial epidemic of RLF (Fig. 4). After observing 21 cases of RLF during his resident rotations with Leroy Hoeck, pediatric chief of the nursery, they observed that 18 of the 21 infants had received high levels of oxygen. Together, Patz and Hoeck devised an experiment in which babies were alternately assigned to a high oxygen group (60–70% oxygen for 4–7 weeks, weaned over 1 week) or low oxygen group (40% for ≤2 weeks, weaned over 1–3 days). All the infants were to be examined periodically for the first 6 months of life. Other than the oxygen use, the subjects were to receive similar treatment, group assignment was alternate.

Patz and Hoeck proposed this controlled clinical trial for NIH support. Clearly, as the pediatric chief of the nursery, the support of Leroy Hoeck was very important in developing the clinical trial, even though the outcome measured was the retinal finding. Despite the empirical support for the hypothesis that hyperoxemia played a role in development of RLF, the restriction of oxygen was counterintuitive to many neonatologists. Silverman reports that the research proposal met vigorous opposition from some neonatologists, who were concerned that "... these guys are going to kill a lot of babies by anoxia to test a wild idea." [10]. The initial funding request ($4000) was initially declined, but on re-submission Patz and Hoeck received funding [9, 52].

During the trial, in which the treating clinicians were not masked to the group assignment, additional resistance to the concept of restricted oxygen was encountered from another group: the neonatal nursing staff. Patz discovered that, during the nighttime nursing shifts, oxygen was surreptitiously increased to the infants in the low oxygen group in an attempt to protect the subjects [52]. Despite this opposition, the trial was completed successfully, with 76 infants enrolled.

Of the evaluated patients, the rate of RLF was 61% in the high oxygen group, and 16% in the restricted oxygen group. The severity of RLF was also significantly worse in the high oxygen group, with 28% showing more severe changes (consistent with ROP stage 4–5) compared with no detachments noted in the restricted oxygen group. This difference was statistically significant ($p<0.05$), and was the first clear, well controlled evidence that a postnatal parameter could be modified to reduce the incidence of RLF in premature infants. Patz and Hoeck had also successfully completed one of the first clinical trials of any kind in the neonatal nursery, and with very limited resources was at the forefront of the era of data-driven decision making in pediatric medicine and ophthalmology [53–55].

The conclusions and recommendations of Patz' landmark paper, published in 1952, were not universally accepted. The concept of the benefit of liberal use of supplemental oxygen was widespread among neonatologists. T. S. Szewczyk expressed an alternative relationship between oxygen and RLF: that rapid withdrawal of oxygen after respiratory recovery led to relative hypoxia, and caused RLF. The secular association of RLF, which frequently climaxed at 2–3 months postnatal life, with the withdrawal of oxygen at the same age appeared to support this hypothesis [30, 31]. Hypoxemia during withdrawal of oxygen therapy fit the prevalent conceptual models of neonatologists more closely than any injury from hyperoxia. More evidence of the role of oxygen in the development of RLF was needed, and a disease model which could be manipulated to isolate the effects and timing of oxygen supplementation would help resolve the remaining questions.

Experimental Evidence on the Role of Oxygen in RLF: The Animal Models of Norman Ashton

Clinical investigations in premature infants had demonstrated that RLF occurred in the most severely premature, sickest infants. The patients, who are fragile infants with compromise of every system who require constant care and surveillance, and who have substantial risks of complications and mortality, create a very difficult population in which to investigate and isolate a specific cause of RLF. An animal model, in contrast, could potentially be subject to precise manipulation and detailed histopathological investigation not possible in humans.

Norman Henry Ashton, trained as a pathologist at King's College, London and Westminster Hospital Medical School, was appointed to be the pathologist to the Institute of Ophthalmology, the research institute associated with the Moorfields

Fig. 5 Norton Henry Ashton, CBE, DSC, FRCP, FRCS, FRCPATH, FRCOPHTH. From Zimmerman LE, Arch Ophthal 2001, with permission [56]

Eye Hospital, London, (now the University College of London Institute of Ophthalmology) after completing his military service in 1948 (Fig. 5). As the founding ophthalmic pathologist of the Institute, he was a pioneer in ophthalmic pathology in the UK and Europe, and became interested in the pathology of the retinal vessels. As a surgical pathologist, Ashton was confronted with the epidemic of RLF then occurring in the UK, and was familiar with the characteristic retinal detachment, retrolental fibrovascular membranes, and vitreous neovascularization seen clinically as well as histopathologically.

Recognizing the significance of the observations of Campbell and Crosse (Patz' paper had not yet been published) and the potential for RLF as a model of retinal vascular diseases, and with his background in pathology and animal models, Ashton sought to develop an experimental model of retinal vascular development and RLF. Ashton knew that, relative to humans, kittens are born with immature eyes with retinal vascular development continuing after term birth. The degree of retinal immaturity in a term kitten at birth is similar to that of a premature human, and therefore the kitten could serve as a disease model for RLF. In a series of experiments, Ashton exposed newborn kittens to manipulated oxygen environments, to investigate the relationship of hyperoxemia on the immature retina [57–60].

In the first experiments, kittens were exposed to 60–80% oxygen within 3 days of birth, for varying periods, with examination at 6–8 days of age. Examination of sectioned eyes as well as flat-mount retinal evaluation with India ink intravascular contrast, was performed. The results were dramatic: compared with controls, animals treated with hyperoxia demonstrated dramatic pruning or "obliteration" of preexisting retinal vessels during the initial exposure period (Fig. 6). After withdrawal of the oxygen, the vessels reappeared but remained very abnormal in extent and density, with pruning of normal capillary architecture and loss of normal retinal arterioles and venules. This led to retinal vascular pattern which "resembles that of the histological pattern of an emphysematous lung." Thus, Ashton was able to demonstrate that high levels of environmental oxygen had a specific and unique effect directly on the immature retinal vessels, and that the initial effect was reduction or inhibition of vessels, rather than the proliferation seen in human RLF. Furthermore, he established a relationship between both the degree of immaturity at exposure and the concentration of oxygen, and the severity of the retinal vascular effect [57] (Fig. 7).

Subsequent experiments varying the length of exposure, concentration of oxygen, and length of recovery period, described an initial vaso-obliteration phase (Fig. 8), followed by a vasoproliferation phase. The vasoproliferation phase, seen after kittens were returned to room air, resembled more clearly the findings of RLF, with intraretinal and preretinal proliferation of abnormal vessels. Even in the most extreme treatment group, however, retinal detachment and retrolental membrane did not occur. Despite the significant differences between the kitten model and human RLF, Ashton was able to conclude that "the lesions of the early stage are so exactly similar (to human RLF) that an aetiological relationship seems undeniable." [59].

Ashton then proposed a sequential-effect mechanism for RLF, based on the animal model:

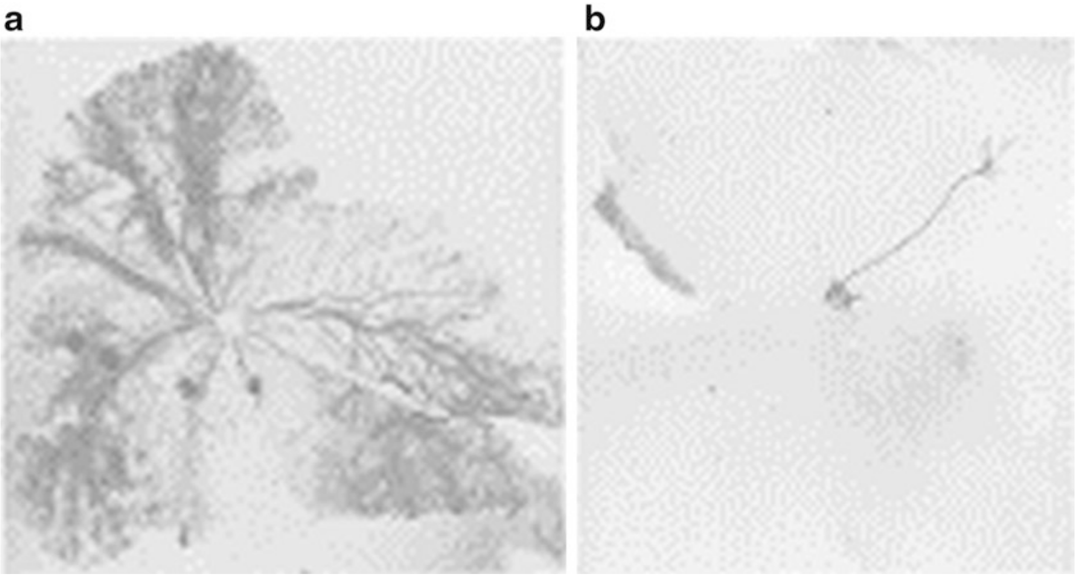

Fig. 6 Flat-mounted retina of kitten with intravascular contrast injection, (**a**): 1 day old kitten with normal retinal development (control), (**b**): 9 day old kitten vasoobliteration and regression of normal retinal vessels after exposure to hyperoxia days 3–9. All retinal vessels have completely regressed to the optic disc; the hyaloid artery and tunica vasculosa lentis remain patent and stained. From Ashton, BJO 1953, with permission [57]

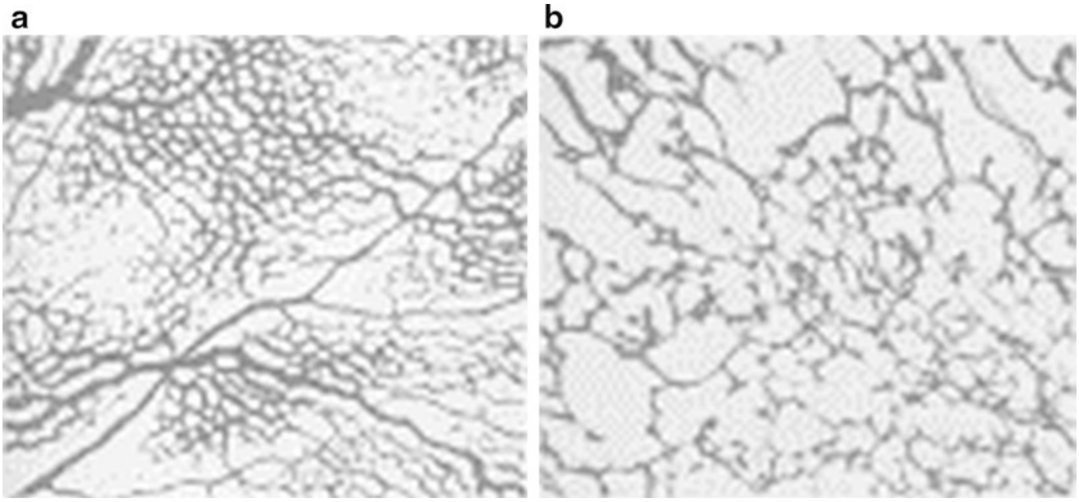

Fig. 7 Flat-mounted retina of 8 day old kitten with intravascular contrast injection, (**a**): normal control 8 day old kitten, showing normal vascular development, (**b**): 8 day old kitten exposed to hyperoxia 4 days, then room air 3 days, at the same magnification, showing abnormal pruning of vascular network with loss of normal appearance of retinal arterioles and venules. "…the picture resembles that of the histological pattern of pulmonary emphysema". From Ashton, BJO 1953, with permission [57]

initial vasoobliteration stimulated by hyperoxemia, followed by vasoproliferation. His experiments seemed to not support the assertion of Szewczyk, that oxygen supplementation during the proliferative phase could reverse the RLF. Ashton concluded that "it is apparent that prophylaxis is by far the most hopeful line of attack and an urgent plea is made for the control of oxygen therapy in the treatment of the premature baby." [58].

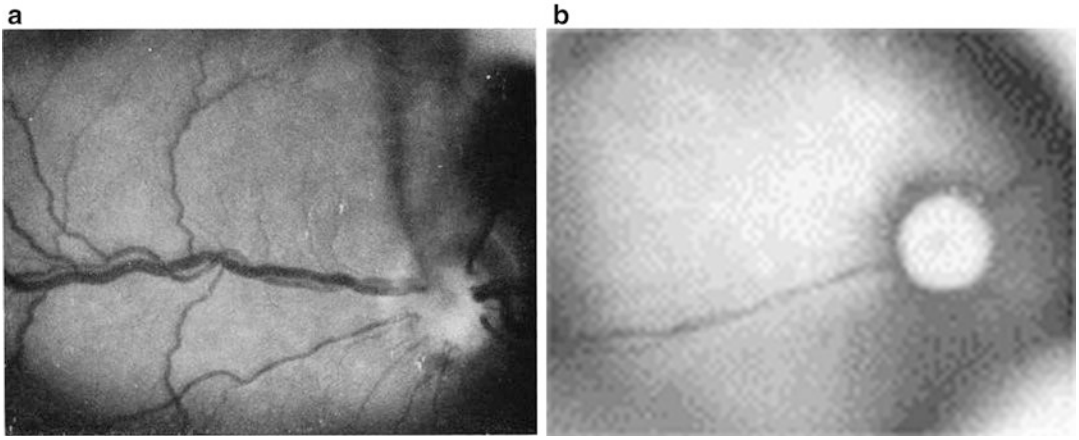

Fig. 8 Clinical retinal photo of 14 day old kitten, (**a**): normal control, with normal vascular caliber, (**b**): retinal vasoconstriction after 24 h exposure to 80% oxygen hyperoxia. From Patz, Surv Ophthalmol 1969, with permission [61]

Why These Insights Were Critical: ROP since Patz and Ashton

The controversy surrounding the use of oxygen and RLF after the report of Patz rapidly coalesced in a consensus for a larger, well controlled, multicenter randomized trial of restricted use of oxygen for the prevention of RLF in premature infants. Planning began in 1952 for this large, multicenter trial. Under the direction of V. E. Kinsey, the National Cooperative Study, sponsored by the NIH National Institute of Neurological Diseases and Blindness (the National Eye Institute was established in 1968) included 18 neonatal treatment sites, where infants were randomized to either "liberal use" (50% oxygen for the first 28 days of life) or "restricted use" (no oxygen, up to 50% only if clinical situation required oxygen). Such was the concern about the risks of excessive oxygen at that time, that the initial randomization was 2:1, in favor of restricted oxygen. Infants were randomized after 48 h of life, insuring that each site could use oxygen freely for initial resuscitation prior to randomization.

The preliminary results of the National Cooperative Study, first published in 1955 [62] reported a dramatic difference in the rate of RLF, with 72% of the liberal oxygen group, and 30% of the restricted group showing RLF. The final report [63] confirmed these results, with no significant difference in mortality between groups. Thus, a much larger, well controlled, carefully observed experiment confirmed the findings of the Patz study [54]: restricting exposure to high levels of oxygen during the first weeks of life dramatically reduced the risk of RLF, without increasing overall mortality.

Even as the National Cooperative Study was underway, clinical practices were modified to restrict the use of oxygen in neonates as a response to the developing understanding of retinal injury and RLF [9]. RLF as a cause of preschool blindness initially peaked in the US in the birth cohort of 1945–1955 (Fig. 9) Manufacturers of incubators modified designs to reduce the risk of high oxygen concentration exposure, and oxygen blenders and systems to deliver controlled, consistent concentrations of oxygen were developed [46]. A consensus classification scheme to allow uniform descriptions and definitions, the International Classification of Retinopathy of Prematurity (ICROP) was developed [7, 64–67]. Clinical trial and data-driven treatment guidelines became the standard of care in neonatal units, replacing expert opinion and guidelines extrapolated from adult medicine. A subsequent "second epidemic" peak incidence of ROP, seen as the second peak in Fig. 9, occurred beginning in the late 1960s for essentially two reasons: increasingly premature infants survived, though

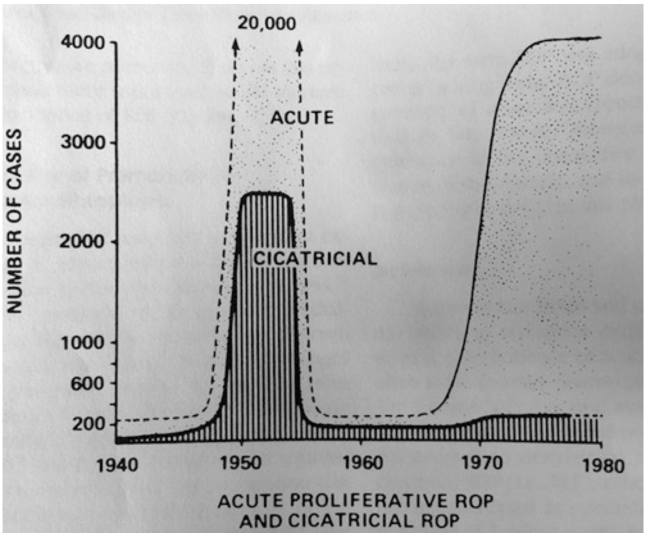

Fig. 9 The incidence of ROP in prematures in the United States, 1940–1980. An initial epidemic of both acute phase proliferative ROP and chronic cicatricial RLF beginning in the 1940s followed the widespread development of neonatology and increasing survival of premature infants. After publication of the Collaborative Study and recognition of the facilitating role of oxygen supplementation, and adaptation of new oxygen protocols, the incidence of both diminished dramatically. A "second epidemic" of proliferative ROP occurred beginning in the late 1960s for essentially two reasons: increasingly premature infants survived, though with higher risks of ROP, and curtailment of oxygen was recognized as contributing to increased mortality and cerebral palsy with oxygen supplementation again gradually liberalized. This second epidemic was not accompanied by such dramatic end-stage cicatricial disease as in the initial epidemic. From Urrea PT, Rosenbaum AL. Retinopathy of prematurity: an ophthalmologist's perspective. In Isenberg SJ, ed, The Eye in Infancy. Yearbook Medical Publishers, Chicago, 1989 [68]

with higher risks of ROP, and curtailment of oxygen was recognized as contributing to increased mortality and cerebral palsy with oxygen supplementation again gradually liberalized. This second epidemic was not accompanied by such dramatic end-stage cicatricial disease as in the initial epidemic.

The success of the National Cooperative Study also demonstrated that large, multicenter trials of interventions could provide answers to clinically relevant questions about complex diseases relatively quickly, and led to a period of large, collaborative multicenter and multidisciplinary studies in neonates, including the landmark Cryotherapy for ROP study [70] and the Early Treatment of ROP study [71].

However, the oxygen story is still evolving even in 2016. Over the last decade, a series of five randomized multinational studies in countries with well-developed neonatal care have been undertaken to determine optimum oxygen target ranges for care of the premature infants. While some of the individual studies showed divergent results, as a group these studies have shown that lower target SpO2 ranges (85–89%) were associated with increased mortality but not increased disability at 2 years of age [72–75]. Thus, there appears to be a tradeoff between optimal restriction of hyperoxemia to minimize ROP; and optimal prevention of hypoxemia to improve survival and prevent cerebral palsy. Considering that treatment of ROP is generally successful, it is unlikely that further refinement of oxygen saturation targets is likely to further reduce the incidence of ROP in countries with well-developed neonatal care.

This is not the case throughout the world, however. Despite strides in our understanding of the mechanisms and risk factors for ROP, this retinopathy continues to be a significant cause of visual impairment in children in developing regions of the world where survival of premature infants is increasing and expert neonatal and ophthalmologic care are scarce or lacking altogether [76–80]. This has led to an increased number of infants who are blind or severely visually handicapped worldwide. An estimated 20,000 preterm infants will become blind or visually impaired due to ROP each year, with an additional 12,300 per year with mild/moderate visual impairment [81]. Almost 2/3 of these children will be in middle income regions and many born at greater than 32 weeks of gestation (in contrast to high income countries, where ROP is seen almost exclusively in prematures less than 32 weeks GA). These data emphasize the continued need for improving neonatal care of premature infants and increased surveillance for potentially blinding ROP.

Retinopathy of prematurity became a model for other retinal vascular diseases, including diabetic retinopathy, retinal vascular occlusions, and sickle cell retinopathy. Animal models of ROP were used to elucidate the biological mechanisms of neovascularization, including the role of cytokines [82] and innovative insights into neovascularization and potential therapies including which have utility in a wide variety of retinal vascular diseases [83]. Treatment of ROP has also benefitted from the recognition of unifying mechanisms of neovascularization in a variety of ocular disorders including age-related macular degeneration (AMD), diabetic retinopathy, and sickle cell retinopathy. Laser photocoagulation and anti-VEGF treatments for ROP are directly derived from successes in treating other retinal conditions.

Individually, Arnall Patz and Norman Ashton both published their key insights into the relationship between hyperoxia and RLF early in careers during which each became a leader in the field of ophthalmic research. Building on insights and hypotheses of observant clinicians including Kate Campbell, Mary Crosse, and A. C. L. Houlton and the interdisciplinary collaboration of Leroy Hoeck, Patz and Ashton applied scientific discipline to develop these ideas. Both had the preparation and insight to not only recognize a potential relationship between hypoxemia and RLF, but to also recognize the need for experimental evidence of that relationship and the importance of carefully controlled experiments (in animals and humans) to investigate and understand the relationships first noticed by detailed observations and the "natural experiments" inherent in clinical medicine. Rather than directing care based on anecdote and narrative, both recognized the need for scientific, evidence-based treatment guidelines to systematically improve clinical outcomes. Patz also benefited from early support and mentorship. The initial studies at D. C. General Hospital could not have been conceived and completed without the support of his collaborator, Leroy Hoeck, who was chief of pediatrics in the nursery and co-author with Patz.

Patz, who conceived and developed his initial clinical trial of restricted oxygen while still a resident, continued investigations and innovations in the diagnosis, prevention, and treatment of ROP and other retinal vascular diseases. He was instrumental in the National Cooperative Study, and was instrumental in the development of one of the most widely used therapies for neovascular retinopathy, laser photocoagulation. In addition to his research, Patz continued to care for patients, specializing in diseases of the retina, and founding the Retinal Vascular Center at the Wilmer Eye Institute, Johns Hopkins University. For 10 years, he served as the Director of that institute, during which time he also served as the President of the American Academy of Ophthalmology.

Dr. Patz was recognized for his work with ROP, with the Lasker Award in 1956 (presented by Helen Keller), the E. Mead Johnson Award of the American Academy of Pediatrics in 1956, the Lucien Howe Medal of the American Ophthalmological Society in 1991, the Friedenwald Research Award from the Association for Research in Vision and Ophthalmology in 1980, and the Jules Stein Award from Research to Prevent Blindness in 1981. In 2004, President George W. Bush presented Dr. Patz with the Presidential Medal of Freedom, in recognition of his contributions in preventing blindness. Arnall Patz died on March 11, 2010 [52, 84, 85].

Norman Ashton was also just beginning his career in ophthalmic pathology at the time of his groundbreaking experiments investigating the role of hyperoxia on the immature retina. He was the founding pathologist of the Institute of Ophthalmology and Moorfields Eye Hospital where he had served 7 years before his pioneering animal research on RLF, a position he held for 30 years. He followed his first publications related to RLF in the kitten model, with more than a dozen further investigations in the effects of hyperoxemia on the developing retina, and presented this work as the 1957 Proctor Lecture at the Association for Research in Vision and Ophthalmology. His development of a retinal artery contrast perfusion method to examine retinal vascular development, used in the kitten model, also became an effective research tool in investigations in diabetic retinopathy and hypertensive retinopathy. Ashton's interests in parasitic diseases preceded his specialization in ophthalmology, he continued his interests with one of the earliest descriptions of ocular infection with Toxocara canis [86] and studies of toxoplasmosis retinopathy in animals [87, 88] His interests in ocular pathology and animal models led him to describe pathology in turkeys, wallabies, monkeys, and fish, as well as kittens. Working with Sir Stewart Duke-Elder at The Ophthalmology Institute, Ashton became consultant ophthalmic pathologist to ophthalmologists throughout the UK and Europe, and was a founder and founding President of the European Pathology Society.

Norman Ashton founded Fight for Sight (UK) as a charity supporting eye research and education in the UK, and served as chairman of the organization from 1980 to 1991. The foundation continues to be the largest charitable organization supporting eye research and education in the UK [89].

Ashton was recognized for his academic work many times, receiving the Doyne Medal in 1960, the Jules Stein Award for his work on RLF in 1981 (with Patz), and the Helen Keller Prize for Vision Research in 1998. He was recognized for both academic and charitable work by Her Majesty the Queen of England, as a Commander of the Order of the British Empire in 1976. Dr. Ashton died on January 4, 2000 [56, 90].

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Charles Kelman: Phacoemulsification and Small Incision Cataract Surgery

16

Norman B. Medow

Cataract, an opacity of the normally clear lens, is the leading cause of blindness in the world [1]. The treatment for a visually significantly cataract is surgical removal of the lens. In the world, there are estimated to be 20 million cataract operations performed annually [1]. The surgical procedure responsible for 80% of these operations was developed by Charles D. Kelman, M.D. (1930–2004) (Fig. 1). This is the story of how this operation, phaco-emulsification, came to be and of the person who developed it. His thoughts, his ideas, his growth and development are examined so that we can understand how and why this procedure, that revolutionized cataract surgery, was discovered.

It was 1930, the eve of the Great Depression. However, Charlie's father, a penniless immigrant, through hard work and determination, achieved the American dream. Not only did he have a home and a job, but he owned the factory, employed friends and relatives and aided them in achieving success, all by the age of 24 [2]. It was his father who instilled in Charlie the drive to succeed. The seeds were planted. Success in life would be determined by his willingness to accept rejection or failure tempered with the belief that he could do anything he wanted to by persisting. To his strong words of achievement, he added, "but first be a doctor" [2].

Early on in life, Charlie was not interested in academics, much less in medicine. At the age of 4, he realized that he loved music. He learned to play the harmonica, showcasing his talent on a radio show. Soon his father began giving him music lessons on the saxophone and the clarinet. He was taught by the best teachers of the time, professionals who earned a living playing with many of the best bands and recording studios, producing music that all listened to. They also encouraged Charlie in his musical endeavors. He knew he wanted to be a star, and live in the limelight [2].

The conflict between music and medicine haunted Charlie throughout his life. The musical stage, which he loved first, thirsted for and was driven by, was counterbalanced by his father's admonition to first be a doctor and then do whatever he wanted. Throughout high school, Charlie focused most of his attention on music, the high school band and the New York City Orchestra. Although not at the top of his class, he went off to college, accelerated his course work, and graduated early so that he could begin medical school, and his father could see him graduate.

Charlie spent his medical school years in Geneva, Switzerland, learning the basics of medicine, but also enjoying the fruits of Europe, primarily in France and Switzerland. He played in a group called The Swiss Jazz Quartet, which had a weekly radio show. The audition to join

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Fig. 1 Charlie examining a patient—c. 1973. (Photo courtesy C. Kelman).

this group was intense, but once again his credo—persistence—won out. In 1956, just 6 months before Charlie's medical school graduation, his father died of thyroid cancer. Although Charlie's father would never see his son, who he implored to be a physician before anything else, achieve this most important goal, his father's words and thoughts were with him throughout his life.

Returning to the United States, Charlie was not focused on medicine. He was unhappy interning in Baltimore, Maryland and left his internship to spend 6 months traveling with bands, playing the Saxophone and trying to sell his musical compositions He returned to New York and completed his internship in Brooklyn, but was still focused on music. It was the time of Chubby Checkers and the twist. Through Charlie's persistence and indeed some talent, he had a song published. The song, called Telephone Numbers, developed a large following [2].

Along the way, Charlie met Sidney Miller, a saxophone player and ophthalmologist who had a great effect on Charlie's career. He decided to become an ophthalmologist because of Sidney Miller's influence. Charlie found an opening in a residency at Wills Eye Hospital. He travelled to Wills Eye Hospital and met one of the senior physicians, a doctor who took a liking to him and gave him a position as a resident in ophthalmology.

While in Philadelphia, he continued to balance medicine and music. Not only was he a musician, but also a composer of both songs and musicals. He played in local Philadelphia bands and tried to sell his music, all while working in one of the most competitive residency programs in the United States. After completing his residency, he returned to New York and began practice by working for the Health Insurance Plan of Greater New York. He soon found that he disliked routine eye care; glasses and eye examinations were not of interest to him. It was surgery that he wanted. He reminded himself that in show business rejection equals yesterday or today, but tomorrow was all about optimism.

In 1961 Charlie heard about a neurosurgeon named Irving Cooper who was doing studies on freezing areas of the brain in order to control Parkinson's disease and other neurological disorders. Charlie was convinced that he could bring those freezing techniques to ophthalmology. He attempted to meet Dr. Cooper and to convince him to work with Charlie. He wrote many letters, made many phone calls and many visits to the hospital, but received no response. Finally, Dr. Cooper met with Charlie and offered him a job at $100 per week, plus use of his laboratory for half a day per week. Charlie reflected in his biography that he could make a contribution to medicine, be acclaimed and receive wealth and power [2], but the sailing would not be smooth.

Over the next few years, Charlie worked on the use of cryogenics in ophthalmology. One area of research was the use of cryo in retinal detachment rather than diathermy. He wrote a paper on the subject that was rejected by all of the major journals, only to be published in a lesser-known journal with a small circulation [3]. He soon learned that a major medical school had begun research on this same project. Was this serendipity or did the school have advance knowledge of his research? Charlie then developed a means to remove a cataract using the freezing technique. He applied to the American Academy of Ophthalmology Program to deliver his discovery only to find out that a Polish physician, Tadeusz Krwawicz from Warsaw, had published his findings on the development of this technique in a Polish journal before Charlie's paper was even written. Charlie then developed a cryo-stylet for delivering the technique, only to find out that another physician, this one at Manhattan Eye, Ear and Throat Hospital, had developed a smaller disposable version using Freon that would rapidly replace his probe. His academic peers had rejected his priority for cryo on the retina, for cryo extraction of cataracts, and for developing a cryo probe.

Charlie also could not obtain research funding. Colleagues with known grant experience were urged not to join him as a co-investigator. He had dreamed, he had prayed and he had worked diligently only to find out that his ideas were introduced to the profession by others. What was he to do? It was now that his main idea about cataract surgery took shape. Charlie and others felt that cataract surgery had reached its modern day conclusion, whether by intracapsular cataract extraction, extracapsular cataract extraction with the use of instruments or by cryoextraction. The opening was approximately 180° in all of these techniques and the patients had to spend 7–10 days in the hospital with four to 6 weeks of limited activity. Charlie's idea was to remove the cataract through a small opening. By this technique, hospital stay would be minimized, hospital costs would be decreased and the patient's downtime diminished. His ideas included crushing the lens in a small bag while inside the eye and extracting it through this small opening, using disruptive energy to liquify the cataract or by using chemicals to dissolve it. In 1963, to fund his research, he applied to the John A. Hartford Foundation for a grant. Mr. Pete Roy, the Director of the Foundation, realized the potential impact Charlie's work could have on ophthalmology and offered him a three-year $270,856 grant [4]. Manhattan Eye Ear and Throat Hospital took 30% for overhead and appointed Charlie to the title of Director of Cataract Research, building him a research laboratory in the hospital. Although this was a triumph, Charlie was concerned about his ideas being stolen. He learned from personal experience about what could happen to research ideas and was determined not to allow it to happen again. Because of this, he conducted most of his research in secret. He was confident that he was going to change the future of cataract surgery [2].

Most people at the time believed that Charlie's research was focused on cryo surgery, but in fact, it was primarily directed towards removing a cataract through a small incision, although he did not give up on cryo research. His primary experimental model was the usage of cats. His first idea was to use a butterfly net that folded and would bring the cataract into the net, crushing it, and then removing it through the small incision. The incision had to be larger than thought and the lens was not able to be crushed well. This idea was abandoned. His second idea was to use a dental drill to break up the cataract. This produced multiple complications with lens fragments damaging the iris, the cornea and even entering the back of the eye. This was also abandoned. The use of chemicals all caused serious damage to the cornea. It was late in 1966. The grant from the Hartford Foundation was up for renewal. Charlie was running out of time as well as ideas.

Serendipity in medicine is uncommon. The discoverer must make the connection between what he sees and what he can do with the observation. Charlie experienced such a moment of realization while visiting the dentist for a routine check up. The dentist was cleaning his teeth using an instrument that emitted a fine spray of moist air and water while breaking up the tartar that had accumulated. The instrument tip vibrated at 40,000 cycles per second with a very soft buzzing sound being emitted. Charlie experienced no pain or discomfort as tartar was cleaned away. Could Charlie use a similar technique for his own surgical method? Why not the cataract? To test his hypothesis, he ran to the lab and returned to the dentist with a cataract in his hand. Using the ultrasonic cleaner, he watched as the lens was easily liquefied [2]. He knew this was it.

Charlie named the procedure "Phacos" from the Greek meaning Lentil or Lens, and emulsification, to form a liquid, hence Phaco-emulsification. On the heels of this success, Hartford renewed his grant, this time for 2 years for $260,500 [4]. Charlie then contacted Cavitron, the company that made the ultrasonic tooth cleaner. He cajoled, badgered and pleaded with them to make him a probe so that he could develop this technique. Recognizing the business potential should the device prove viable, Cavitron agreed, and he tried it on his first patients, cats. These experiments proved mostly successful. Soon, he felt confident enough with the instrument to operate on his friend's dog.

The instrument had to evolve and encountered many difficulties along the way. Charlie needed to publish his results, but fear of theft ran though his mind on a daily basis. It was then he decided to visit his former Professor, Irving Leopold who was his Chair at Wills Eye Hospital and was now the Chair of Ophthalmology at Mount Sinai Hospital in New York. Dr. Leopold was miffed as to why Charlie brought a dog to the visit with him. Charlie explained that the dog had recently had cataract surgery by phaco-emulsification. After examining the dog and listening to Charlie, Dr. Leopold called his good friend Dr. Frank Newell. Dr. Newell was the Editor-In-Chief of the American Journal of Ophthalmology and he explained to him about Charlie's research and implored him to publish the results of his efforts. In 1967, the paper was published [5]. At the same time, The Hartford Foundation gave Charlie a 3-year renewal of $270,000 [4]. Charlie convinced Cavitron to produce and co-develop the phaco-emulsifier instrument. It was now time for Charlie to operate on a human patient.

John Martin was 79 years old, and blind from glaucoma. The eye was painful and he wanted it to be removed; he also had a dense cataract. Charlie examined him and explained to him what he wanted Mr. Martin to agree to: to allow Charlie to remove his cataract with a new technique and then remove his eye. Mr. Martin unhesitatingly said okay. Quietly, in one of the operating rooms on the 7th floor, isolated from the main group of operating rooms, Charlie removed the cataract in Mr. Martin's blind eye. The operation took 4 h. Phaco time was 79 min. The Iris had been touched a number of times and was ragged. The anterior chamber collapsed onto the cornea injuring the endothelium. The vitreous cavity was breached and lens particles fell into the back of the eye. After suturing the eye closed, the cornea was white, the iris was largely shredded and the sclera/conjunctivae severely injected. Charley sat with Mr. Martin all evening and examined him the next morning discovering that the eye was beyond salvaging. That afternoon the eye had to be enucleated [2].

During the operation on Mr. Martin, Charlie realized that the suction was not well controlled and the anterior chamber collapsed when the line was occluded with lens material. This caused severe corneal touch, time and time again. Charlie found a flowmeter and added it to the machine, which controlled the collapsing of the anterior chamber during the procedure.

Anna Swetze, the second person to undergo the new procedure, was a diabetic with severe retinal hemorrhages. She understood Dr. Kelman's request. This procedure also took approximately 3 h, but no collapses occurred. Four other adults were operated on during this initial phase, bringing the operation time down to 2 h.

Jealousy and competition from outside forces continued to plague Charlie and challenge his work. A senior colleague at Manhattan Eye, Ear and Throat Hospital was so bothered by the invention of Charlie's phaco-emulsification procedure that he developed a rival process. This was a hydro-pulse water jet that injected high pulses of water into the anterior chamber of the eye, hitting the lens in an attempt to mimic the phaco-emulsification energy. This technique never made it to clinical use.

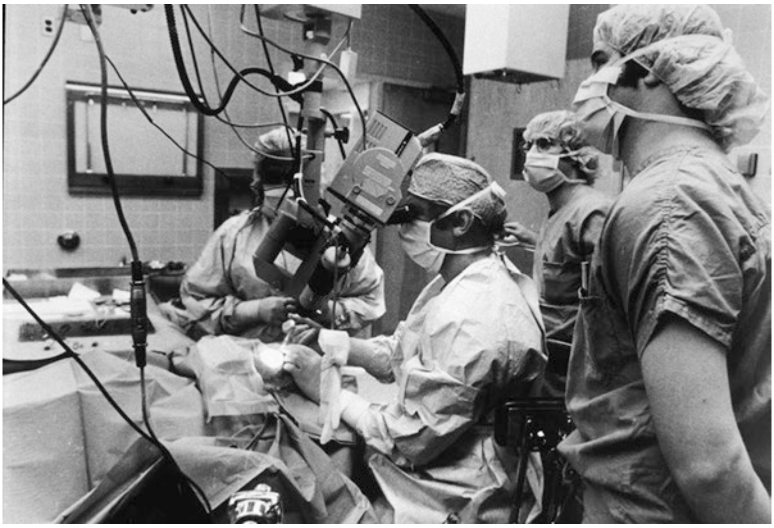

Fig. 2 Charlie in OR—crowded with observers and equipment—c. 1972. (Photo courtesy C. Kelman).

By 1969, Charlie had done 12 cataract operations on patients using his new technique, and the majority were successful. But, all was not going smoothly. A group of doctors at Manhattan Eye, Ear and Throat Hospital called for a hearing to investigate Charlie for what they felt was his doing "experimental surgery". Charlie was accompanied to this inquisition by a well dressed gentleman who the committee thought was Charlie's lawyer. The gentleman stood and introduced himself. "My name is Abe Levin. Dr. Kelman's surgery is no sham, nor experimental, it works! Two days ago, Dr. Kelman operated on me. I have macular degeneration and we both thought that my vision would be poor but, I see well." [2]. At that point, a visual acuity chart was placed on the wall and Mr. Levin read it almost perfectly. His surgery had lasted only 30 min and was a success, not only technically but in terms of his vision. He apparently had a clear area of the macular accounting for his post surgical visual results [2]. The committee adjourned. Charlie's work was allowed to continue.

Soon Charlie developed a thriving practice. Other ophthalmologists were referring surgical cases to him that were either difficult or because they wanted to get to know Charlie. In 1970, Charlie received the First Award for his poster presentation on phaco-emulsification presented at the annual meeting of the American Academy of Ophthalmology and Otolaryngology.

There was light beyond the tunnel, but controversy would continue. In a symposium on cataract surgery in 1971, one of the presenter's papers was entitled Small Incisions, Big Complications [6]. While Charlie was working on phaco-emulsification, he was also looking to make standard intracapsular cryo-extraction possible using a smaller 90 degree incision, slowly molding the lens through this smaller incision. This idea was rejected as only possible in soft immature cataracts.

Charlie developed The David J. Kelman Foundation in honor of his father and used it as a vehicle to put together what was most likely the first major surgical teaching course in the country. Every week, six to eight people would attend an intense 5-day course. They would arrive on a Monday, visit the lab and enjoy some lectures. On Tuesday, they would watch live closed circuit surgery, ask questions and prepare to see the postops on Wednesday and Thursday (Fig. 2). Each night, they enjoyed dinner and music with Charlie and his friends. They came to New York to learn phaco-emulsification but also to taste a bit of New York. Charlie was a master at entrepreneurial endeavors. I was a fellow with him from 1972 through 1973 and recall this time as if it were yesterday. The attendees would arrive and visit the laboratory. Charlie had each of them try the Dextrometer, a device he developed to test the steadiness of the surgeon's hand. There were two different devices. One was two loops of metal that could be set apart at varying levels and various angles so that the surgeon would place the tip of the emulsifier hand piece and pass it through both loops trying not to touch either side of one of the loops (Fig. 3). If he did, a screeching alarm would emanate from under the table, followed by a bloodcurdling cry from the attendees. The other device was a wire that was stretched between two poles placed approximately 14–16 in. apart. A loop traversed the wire held by a handle of wood. The object was to go from one end to the other end without touching the wire. The wire was obviously not straight, but was rather curved in multiple areas. Failure would also result in the alarm going off. Charlie loved to show the group how to do it cleanly and swiftly. The purpose of this test was to show hand-eye coordination, depth perception and performance all occurring under pressure in the presence of their peers (Figs. 4 and 5).

Fig. 3 Dextrometer—c. 1972 (Photo taken by Norman B. Medow).

Soon Charlie was all over the media. Frank Field interviewed him in the operating room on NBC. Newsweek wrote about him as did other media publications. The press delighted in the fact that he played the saxophone [2]. "I knew my life had been changed forever," said Charlie [2].

Charlie had it all … or did he? In his book, Through My Eyes: The story of a surgeon who dared to take on the medical world [2], the 18th chapter is entitled; Can a saxophone player find happiness as an eye surgeon? Although used by Charlie in his book, it was the Saturday Review of April 15, 1972 [7] that used this headline to

Fig. 4 Phaco—emulsification unit—1st production Model—c. 1971 (Photo taken by Norman B. Medow).

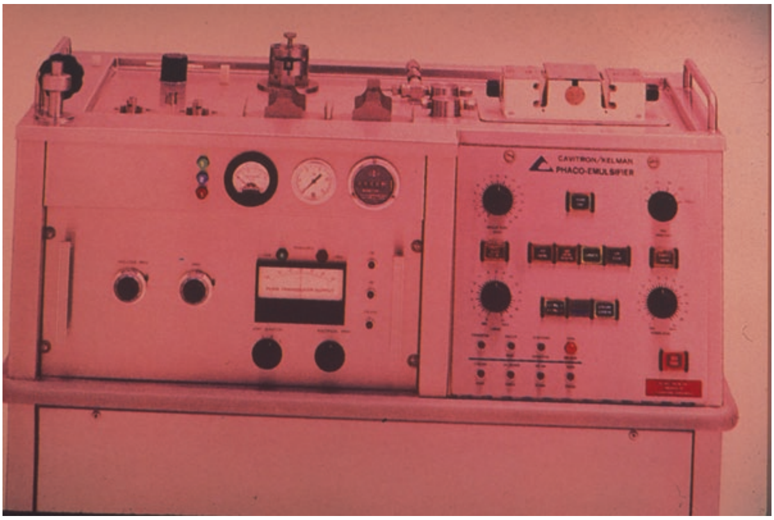

Fig. 5 Charlie holding hand piece of 1st Phaco production model—c. 1972 (Photo taken by Norman B. Medow).

Fig. 6 Charlie with saxophone—c. 1976. (Photo courtesy C. Kelman).

cover Charlie's life. The story was penned in the Rough Rider Room of the Roosevelt Hotel where Charlie played the baritone sax with his musician colleagues in a Friday event called Jazz at Noon (Fig. 6).

In 1972 and 1973, Charlie commuted to his office in NY from his home on Long Island, by Helicopter. Charlie was the pilot! (Fig. 7). The Heliport was just a short 8 min walk to the office. As his practice thrived, he needed more Operating Room time. More than he could obtain from Manhattan Eye Ear and Throat Hospital. To fill his surgical needs, he obtained hospital privileges at Lydia Hall Hospital in Freeport, Long Island. He was now operating in two hospitals.

Over the years, Charlie operated on many famous people. Jan Peerce, William B. Williams, Joe Frazier and Lionel Hampton amongst others, but he wanted to be successful in show business. He tried and tried but would never succeed. He would perform at multiple locations and venues and said at the time he was jealous of Vic Damone singing in Las Vegas [2]. The apex of his trail to musical success was in 1974 when he rented Carnegie Hall primarily to raise money for the hospital (Fig. 8). He rented an orchestra and took voice and singing lessons, which bespoke a hint of an ulterior motive. He practiced his singing and saxophone playing at various clubs on Long Island to prepare for the Carnegie Hall event. Just before the event, he appeared on the Today Show and the Johnny Carson Show, which helped guarantee a full house at Carnegie Hall. He repeated this event a few years later, 1976, always with a smile that said, "I am happy". In his book [2], he says he received calls from well-wishers asking him to consider giving up medicine for show business but his father's words were always there in his mind when he thought about leaving medicine.

Fig. 7 Charlie piloting flying helicopter—c. 1972. (Photo courtesy C. Kelman).

Fig. 8 Charlie in tuxedo—promo for Carnegie Hall Benefit—May 15, 1976. (Photo courtesy C. Kelman).

Phaco-emulsification did not arrive as the standard of care overnight. There were many stumbling blocks along the way, and much opposition from more traditional surgeons, and Charlie had to fight for acceptance of the new technique. The development of IOLs didn't help his cause initially, since incisions had to be enlarged for the lens. However, when flexible lenses could be inserted through a small incision, this hastened the acceptance of phaco-emulsification as the standard cataract surgical procedure. Charlie's research after phaco included his ideas on intra-ocular lens development. He worked on both anterior chamber lenses as well as posterior chamber implants.

The world and his profession had congratulated him on his achievements. Some of the awards he received include; The Ridley Medal by the International Congress of Ophthalmology, The National Medal of Technology Award in 1992 was presented by President George H. W. Bush, The Binkhorst Medal from the American Society of Cataract and Refractive Surgeons—the organization that he was president of in 2002. In 2003 he was awarded the Laureate Award of the American Academy of Ophthalmology. Soon after his death, in 2004, he was awarded the Lasker Award for his contributions to ophthalmology and cataract surgery. The Lasker is considered the American Nobel Prize—a singular recognition! His detractors all learned how to do phaco-emulsification in spite of their negative attitude along the way.

In 1973, Charlie sent out a book to all of the people who had taken his phaco-emulsification course. The book was entitled Jonathan Livingston Seagull [8]. The book is a metaphor for Charlie's thoughts about life. It is a story about a seagull, who wanted more in life than to fight for food. He wanted to learn all about flight and flying. He wanted to fly higher and faster than the other seagulls. He was ostracized by his flock, took lessons and persisted until he was able to achieve his goals. The message in this book mirrored Charlie's drive to succeed despite opposition, which ultimately led him to develop phaco. Show business might have been Charlie's ultimate love, but the world thanks him for his accomplishments in Ophthalmology. In 2003 Charlie estimated that his operation had saved 90 billion dollars between 1985 and 2003 by decreasing the hospital stays of post op patients [2]. I hesitate to extrapolate those numbers through 2016, but it would be staggering. He passed away all too soon, on June 1, 2004 of lung cancer.

Charlie spent much of his life torn between his love of music and his intense curiosity in medicine. Ultimately, he must have realized that his work in ophthalmology and his contributions to the field of medicine brought great joy to the scientific community in which he worked and to the patients affected by cataract surgery through phaco-emulsification. Although Charlie Kelman's legacy exists squarely in the realm of medicine, it was the art of invention—Charlie as the composer, the musician, the innovative creator—that led to the discovery that changed modern ophthalmology.

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Name Index

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