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Enlightening Neuroscience: Microscopes and Microscopy in the Eighteenth Century

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Origins of Microscopical Neurology

Little has ever been written on the history of microscopical neurology. The topic is ordinarily ignored – indeed the terms ‘microscope’ (and microscopy), ‘neuron’ (or neurone), ‘cell’ and ‘histology’ are missing altogether from the index to the overview of the history of neurology by Riese (1959).

Microscopy was born in the years prior to the eighteenth century and nerve specimens were among the first to be examined. The late sixteenth century saw the first descriptions of a recognisable microscope and questions of priority persist, since the study of magnification and of refraction – which preceded the practical application of lenses in scientific instruments – was already a matter of some antiquity (Disney, Hill, & Watson Baker, 1928). The first microscope to be pictured was a compound instrument in 1631, and during the first few years these microscopes were utilised in the quest to unravel the structure of familiar objects – the sting of a nettle or a bee, the wings of a butterfly or bird. We must bear in mind that these were truly macroscopic, rather than microscopic, investigations. Observers were exploring everyday specimens, searching for details the eye could almost discern. Only when the high-power microscope emerged could investigators progress to the most far-reaching development in natural science – the recognition that there were forms of life, and marvellous structures, the existence of which nobody had previously recognised.

The first great pioneer of the microscopic – perhaps better *macroscopic* – world was Robert Hooke (1635–1703) who was appointed to be curator of experiments at the Royal Society of London in 1662. On 25 March 1663, Hooke was enjoined to begin a series of demonstrations with a view to publication, and on 1 April he was instructed to bring at least one microscopical observation before each meeting of the fellowship (Gunter, 1961). Hooke obtained a compound microscope magnifying some 40× from Christopher Cock, a London instrument manufacturer, and his studies with this instrument laid the groundwork for modern science. Hooke’s pictures of flies and fungi, of seeds and spiders, needles, gnats and nettles, served to set natural philosophy afire. His large folio book *Micrographia*, published by the Society in 1665, gave readers a vivid insight into what he had seen (Hooke, 1665).

That much is well known to historians of science, but a crucial section of the Preface to his great work has been overlooked. In this key passage he described how to manufacture a microscope of much higher magnification. On page 22 of the (un-numbered), pages of the Preface appears a recipe for a microscope capable of magnifying hundreds, rather than tens, of times. This kind of instrument gives clear views of much smaller cells – bacteria, spermatozoa, erythrocytes – and could be made without specialist equipment. Curiously, Hooke never published an illustration of this microscope. But his description was seized upon by a convert to the cause who went on to make legion discoveries with this unrefined type of microscope, and who soon began a study of bovine optical nerve (Ford, 1991).

The enthusiastic newcomer was Antony van Leeuwenhoek (1632–1723), the draper of Delft, Netherlands. He became acquainted with Hooke's book on a visit to London about 1668, when the second edition of *Micrographia* had been published and the book was enjoying extraordinary popularity, and began with studies of whiteness in bodies like chalk (which Leeuwenhoek had encountered on his voyage up the Thames). By 1673, Reinier de Graff (1641–1706) was writing to the Royal Society about this 'most ingenious person' and his remarkable microscopes. They were diminutive instruments, little more than postage-stamped-sized rectangles of metal (typically brass or silver) between a perforation in which was held a small ground lens, little larger than the head of a dressmaker's pin (Fig. 1). Specimens were held on a tapered metal holder projecting from a small stage, itself about a centimetre long, and screws mounted on the plate allowed the user to adjust the position and the focus of the specimen. Solid specimens – insects, flowers, leaves – were held with wax on the end of the pin. Liquid materials, including aquatic microorganisms in pond-water, were confined with a flat capillary tube that was itself glued to the stage pin.

This design was explicitly set out in Hooke's *Micrographia* and the results that Leeuwenhoek obtained with it are remarkable. His earliest reports, sent to the Royal Society in 1673, were of specimens referred to by Hooke. As a rule, Leeuwenhoek's early accounts were sent in refutation of what 'a certain learned gentleman' had recently published. During the following year Leeuwenhoek continued his innovative investigations and on 1 June 1674 he sent to London his first selection of prepared microscopical specimens. Three of them – cork, elder pith and the white of a feather – were in direct response to observations Hooke had published in *Micrographia*.

There was one further specimen: a small packet containing slices of dried optic nerve. This was not stimulated by anything Hooke had described in his *Micrographia*; these were examples of Leeuwenhoek's independent investigations. These are the first specimens from Leeuwenhoek's original research and they also served to launch the microscope as a tool of neurological investigation. Clifford Dobell, whose well-researched biography of Leeuwenhoek remains one of the most detailed

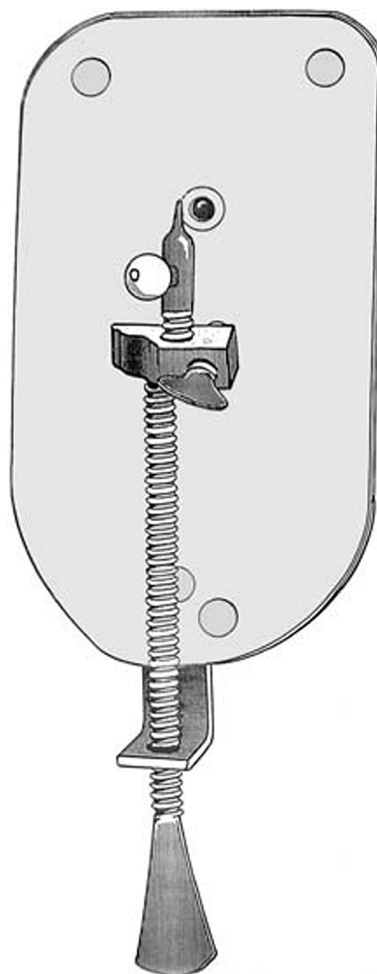


FIGURE 1. Antony van Leeuwenhoek produced microscopes, sometimes with plano-convex or aspheric biconvex lenses. The body plate and attachments were made by Leeuwenhoek at his home. These microscopes were still used for high-power microscopy by Home and others into the early nineteenth century

such works in the history of science, noted in 1932 that the specimen packets "have remained intact to the present day" but did not investigate what they might contain (Dobell, 1932). The presence of the optic nerve specimens in the Leeuwenhoek papers was noted by F. J. Cole, who in 1937 published a pioneering paper on Leeuwenhoek's zoological researches, but most writers did not refer to them (Cole, 1937). For example, a lengthy celebratory publication on Leeuwenhoek's researches was published in *Natura* in 1932, to commemorate the tercentenary of his birth, and – although this aimed

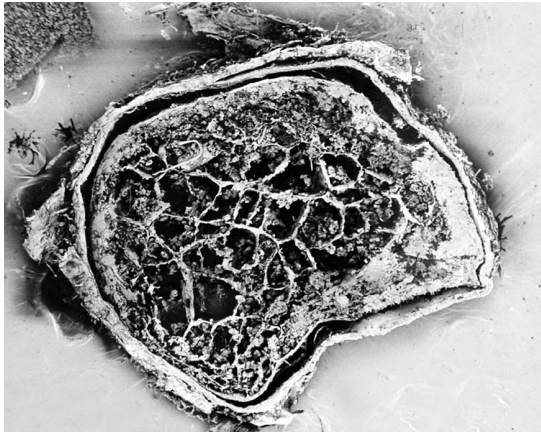


FIGURE 2. In 1674 Leeuwenhoek sent to London the first microscopical sections of nerve tissue. They were discovered by the author among the Leeuwenhoek papers of the Royal Society in 1981, and this electron micrograph was taken at Cardiff with a JSM 840A scanning electron microscope at 2kV. Field width = 4 mm (Ford, 1982)

to present a full chronology of all his researches – there was no mention of the surviving specimen packets. The definitive Dutch collection of the Leeuwenhoek correspondence (1932–present) mistakes some of his specimen packets for ‘drawn rectangles’ and misses others altogether. Although these extraordinarily well-prepared specimens represent the roots of modern bioscience, they remained lost to contemporary science. By the time I submitted them to both optical and scanning electron microscopical examination in 1981, they had lain essentially undisturbed for 308 years (Ford, 1981) (Figs. 2 and 3).

Early Microscopical Investigations

Microscopical investigation of the nervous system began with Leeuwenhoek's studies in 1674, when he made his first preparations of bovine optic nerve. His letter dated 7 September 1674 describes how he was encouraged to observe nerve specimens: 'I communicated my observations [of optic nerve] to Dr of anatomy Schravensande and he mentioned that since ancient times there has been some dissention among the learned about the optic nerve and that some anatomists affirmed [it] to be hollow; and that they themselves had seen the hollowness, through which they would have the animal

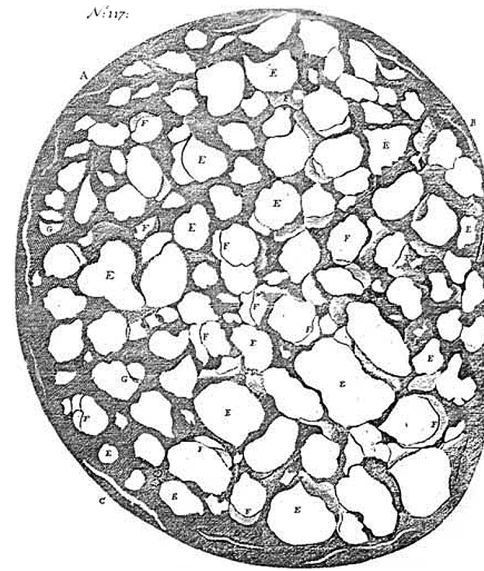


FIGURE 3. Leeuwenhoek's (unnamed) limner prepared pencil drawings of optic nerve and sent them to London. The studies were copied by engravers to produce this full-page image for publication in *Philosophical Transactions of the Royal Society*

spirits that convey the visible species, represented in the eye, pass into the brain. I therefore concluded that such a cavity might be seen by me. . . . I solicitously viewed three optic nerves of cows, but could find no hollowness in them' (Anon, 1932).

This is a crucial moment in the history of neuroscience. The notion of a hollow nerve, analogous to a vessel transporting a fluid, had existed since ancient times. Galen (131–201 AD) viewed the nervous system as the distributive counterpart of the blood circulation, transporting vital spirits from the lung and heart around the body. René Descartes (1596–1650) published an account in which he wrote of the nerves conducting animal spirits between brain and musculature. In one edition of his book (Descartes, 1662) his descriptions are accompanied by an engraving by Florentio Schuyt; this figure clearly shows a cored, perhaps hollow, structure. The diagram was not by Descartes, and was omitted from the subsequent French translation of the book edited by Claude Clerselier (1664) and henceforth.

There had long been a tacit assumption that nerves were hollow until the writing of Andreas Vesalius (1514–1564). He described the optic

nerve – in terms similar to those of Leeuwenhoek – as a solid structure. Yet it was not until the microscope was brought to bear on the topic that the true histological appearance of the optic nerve could finally be determined. On 4 December 1674, Leeuwenhoek wrote to London with an attempted resolution of the earlier theories. ‘I took eight different optic nerves which did shrink up . . . upon which, a little pit comes to appear about the middle of the nerve, and it is this pit, in all probability, that Galen mistook for a cavity’, he wrote. Leeuwenhoek made his transverse slices from dried specimen of bovine nerve, since the fresh material was too soft to be sectioned with a razor.

The drawings that he prepared display the anatomy of the optic nerve remarkably well. When cutting botanical material (including cork from *Quercus suber* and pith of the common elder *Sambucus nigra*) Leeuwenhoek used a rising, sawing motion with the razor edge. When the plant material began to become friable and break up, he cut slightly deeper. In this way the plant sections contained thicker supportive regions interspersed with thinner zones in which histological observations could be made. With the optic nerve, however, Leeuwenhoek writes that he used a single cut (not a ‘sawing motion’), and the resulting specimens were thicker than his plant sections. He sensibly calls the nerve preparations ‘slices’ rather than ‘sections’ since they were >200 µm in thickness.

The nerve fibres comprising the fasciculi are missing from these preparations leaving a lattice of openings that accord well with Leeuwenhoek’s description of a ‘leathern sieve’. This appearance is due to the survival of the perineurium. The nerve sheath or epineurium is unique in the optic nerve because it derives from the pia, arachnoid and dura of the brain and thus has a three-layered structure. The separation of the layered epineurium is well portrayed in the studies of optic nerve that Leeuwenhoek sent to London and are testimony to his acute and accurate observation. It is noteworthy that Leeuwenhoek himself was no draughtsman; he employed a limner to make drawings on his behalf. We are reminded of this in a letter he sent on 25 December 1674 to his correspondent Mr C. Huijgens van Zuijlichem, in which he wrote: ‘I enclose a copy of the optic nerve . . . as I saw though my own microscope, drawn to my order’.

A version of this study was published in *Philosophical Transactions* (Leeuwenhoek, 1675). Leeuwenhoek’s description of the structure of optic nerve is set out in his letter of 4 December 1674:

“I have put before my microscope a piece of such a dried Optic Nerve of a Cow, and how it appeared, and you will see by the picture hereby transmitted unto you. ABCD is the circumference of the Optic Nerve, which did not dry round ways, but somewhat oblong on the side CD. E, and all the places that are left white and clear, are cavities in the dried Nerve which I imagine to have been filaments, and out of which, for the greatest part, the soft globules have been exhaled. F are particles or globules which are in the little holes of the filaments in many places, and such as have not been exhaled”.

This is an interesting passage, notably for its insistence that the nerve fibres are ‘filaments’. The term comes up again in 1677 when Leeuwenhoek wrote of nerves as comprising: ‘diverse, very small threads or vessels lying by each other’. He speculated whether these ‘conveyed the animal spirits throughout the spinal marrow.’ We should *en passant* note that axoplasmic material can exude from the sectioned extremity of an axon, which might be held to support the notion of the nerve fibre as a hollow vessel that conducted a viscous fluid (Young, 1934). However, there are no records that microscopists of the era examined specimen material of this sort.

Leeuwenhoek’s observations were not the only essays into nerve structure at this time. Comments on the microscopy of nerves were published by the Italian natural philosopher Giovanni Alfonso Borelli (1609–1679). Borelli (1681) reported that nerves were tubes filled with a moist and spongy substance. The first microscopist to move towards a true science of histology was also an Italian: Marcello Malpighi (1628–1694). He served as professor at Bologna, Pisa and Messina, and made some observations of the brain under the microscope (McHenry, 1969). Several years after Leeuwenhoek’s pioneering observations, Malpighi injected blood-vessels to increase contrast, and concluded that the grey matter was made up of cellular follicles and the white matter comprised fine excretory ducts (Malpighi, 1686).

Notions of a hollow nerve, which Leeuwenhoek had satisfactorily dismissed through the use of the microscope, lingered on in the decades that followed. Three years after Malpighi’s book appeared,

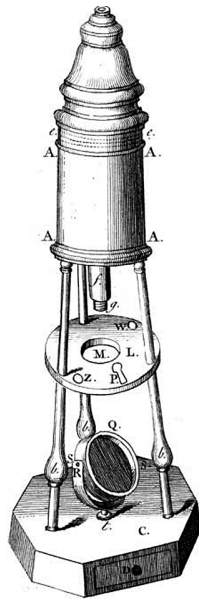


FIGURE 4. This typical compound microscope of the seventeenth century was described by Henry Baker (1743 plate III). Originally designed by Marshall and adapted by Culpeper, this model was designed by Edward Scarlett jr., Master of the Spectacles Company 1745–46

a book was posthumously published by students and colleagues of Theodoor Craanen of Leiden. It included a spurious engraving of hollow nerve fibres bound together with bands like bundles of bamboo (Craanen, 1689). It has been argued that this illustration was included to reinforce Craanen's strictly Cartesian view of nature in which nerve were believed to function as tubes that conducted animal spirits from the brain. Craanen was inclined to allow such preconceptions greatly to influence his interpretation of reality, claiming that "the subtlety of nature surpasses our powers of thought" (Ruestow, 1996) (Figs. 4 and 5).

Eighteenth-Century Microscopy

After the burgeoning interest in microscopy manifest during the latter half of the seventeenth century, a gathering of momentum might logically be assumed. But it was not to be. Microscopy made surprisingly little progress during this century, and neurological microscopy lay largely in the doldrums. Nerve cells are hard to observe in the

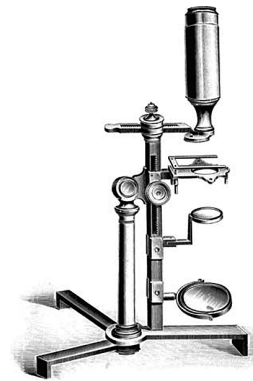


FIGURE 5. W. and S. Jones' 'Most improved' microscope characterises the brass and glass instrument of the late eighteenth century. It was produced in 1790 and influenced designs that were prevalent in the early nineteenth century

freshly harvested state, and attention was instead captured by organisms like *Hydra* and by the intricacies of plant life. Nerve fibres were visible, though the impression gleaned through the microscopes of the period was largely misleading. The refractile myelin sheath was frequently mistaken for a hollow tube, and without a coherent approach to fixation and staining it was impractical to find ways to visualise components of the nervous system.

The notion of hollow nerve fibres was revived for many years. It reappeared throughout the eighteenth century and is typified by a figure published in 1761 by Martin Frobenius Ledermüller (1719–1769) that showed supposedly tubular nerves. The error continued on into the century that followed. Ledermüller's figure was reproduced in the decades following publication, and was still circulating in the middle nineteenth century, the most recent example of republication of this figure that I have traced being by F. A. Longet (1842) (Figs. 6 and 7).

Considerable interest in microscopical revelation was shown by many eighteenth century natural philosophers, though the microscopy of the nervous system was not greatly advanced during this century. Natural philosophers used their microscopes as gadgets, rather than as objects of special importance, and rarely described which instruments they employed for their work. The single lensed or simple microscope utilised by Leeuwenhoek remained a favourite instrument, though the design changed.

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