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Enlightening Neuroscience: Microscopes and Microscopy in the Eighteenth Century

Brian J. Ford

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 within 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 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

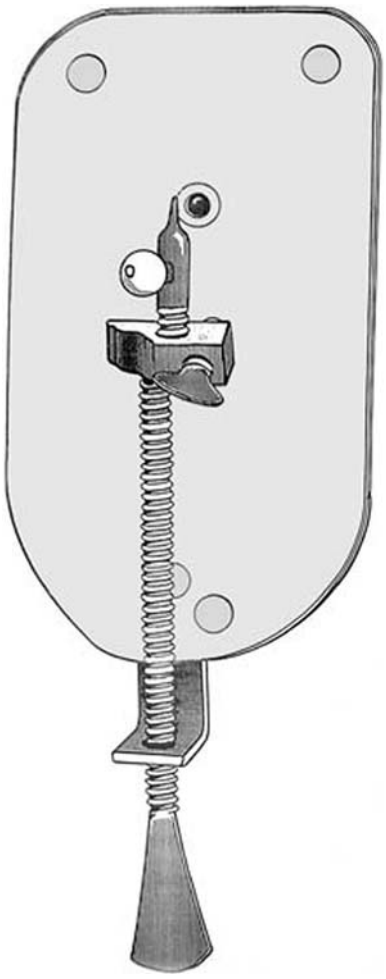

FIGURE 1. Antony van Leeuwenhoek produced microscopes, sometimes with plano-convex or aspheric biconvex lenses. The body plate and attachments were made by Leeuwenhoek at his home. These microscopes were still used for high-power microscopy by Home and others into the early nineteenth century

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

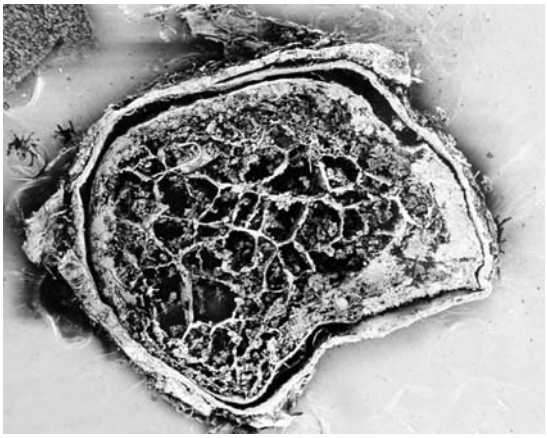

FIGURE 2. In 1674 Leeuwenhoek sent to London the first microscopical sections of nerve tissue. They were discovered by the author among the Leeuwenhoek papers of the Royal Society in 1981, and this electron micrograph was taken at Cardiff with a JSM 840A scanning electron microscope at 2kV. Field width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

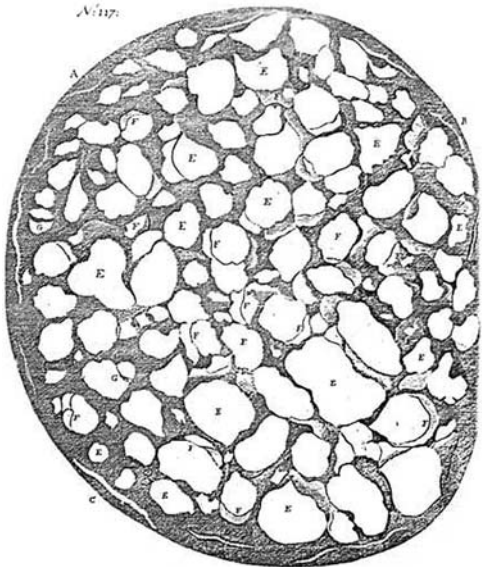

FIGURE 3. Leeuwenhoek's (unnamed) limner prepared pencil drawings of optic nerve and sent them to London. The studies were copied by engravers to produce this full-page image for publication in *Philosophical Transactions of the Royal Society*

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 Schravesande 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 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 Schuyl; 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). Borreli (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,

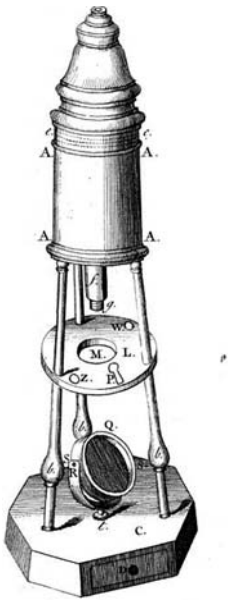

FIGURE 4. This typical compound microscope of the seventeenth century was described by Henry Baker (1743 plate III). Originally designed by Marshall and adapted by Culpeper, this model was designed by Edward Scarlett jr., Master of the Spectacles Company 1745–46

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

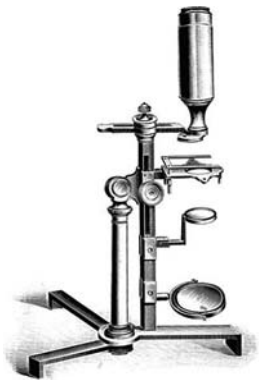

FIGURE 5. W. and S. Jones' 'Most improved' microscope characterises the brass and glass instrument of the late eighteenth century. It was produced in 1790 and influenced designs that were prevalent in the early nineteenth century

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.

FIGURE 6. Nerve fibres envisioned as tubes, published by Descartes (1662, Fig. vi). The appearance is close to that of myelinated fibres; the tube-like interpretation may lie in the artefact of refraction during observation

First, the single lens was constrained in a hand-held barrel design which was fitted with a lateral handle. Designed by an instrument manufacturer, it became known as the Wilson screw-barrel microscope. Before long an advanced design began to appear, in which the microscope was mounted on a brass stand. This made it easier to use; the stand usefully occupied the distance between the observer's eye when seated, and the height of the table on which the device was standing. Such microscopes were widely used by natural philosophers, and the development of the simple microscope (which permitted good magnifications at adequate resolution) proceeded in parallel with that of the compound instrument. Because of the simplicity of design, the specification, description and *modus operandi* of the simple microscope was rarely mentioned by their many users.

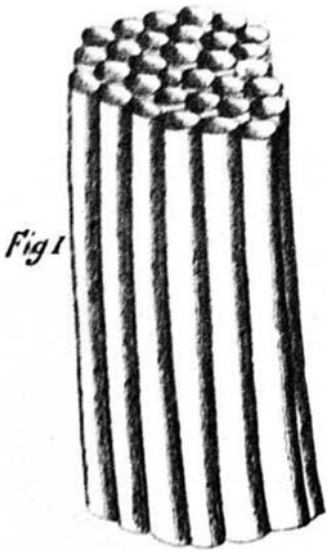

FIGURE 7. Tubular nerve elements were portrayed less ambiguously by Ledermüller (1761, Fig. 1). In this portrayal of nerve fibre bundles, a hollow appearance is clearly conveyed. This interpretation was erroneously published until the 1840s

In Britain, the compound microscopes of the early eighteenth century had changed little in design from the type designed by Christopher Cock and used by Hooke in the 1660s. The Marshal microscope typifies the trend; its lenses produced an image of only moderate quality and it was the brass pillar and intricately tooled leather coating of the body tube that made it an object of desire. These were desk-top adornments as much as serious scientific instruments and they suffered from design difficulties – thus, it was almost impossible to observe wet preparations in a watch-glass. To this extent, the design of the instrument imposed limits on the level of inquiry that the investigator might pursue (Ford, 1985).

No microscopes of the eighteenth century were as good as those made by Leeuwenhoek, and his diminutive instruments continued to be in demand for high-power microscopical research. In a letter written on 20 August 1738, Lord Jersey commended the Leeuwenhoek microscopes for use in research on the structure of spermatozoa. Another enthusiast was Henry Baker (1698–1744), an enthusiastic amateur who wrote on the microscopy of the eighteenth century, often with more verve than veracity. Almost all of his writings were in the

form of a simple rehash of what others had done before. His pictures were re-engraved from higher-quality originals that had previously been published. In one of his books (Baker, 1743) we find his account of Leeuwenhoek's work on the nervous system:

"Mr LEEUWENHOEK endeavoured to discover, by his *Microscope*, the *Structure* of the *Nerves*, in he Spinal Marrow of an Ox; and saw, with great Delight, that minute hollow Vessels, of an inconceivable Fineness, invested with their proper Membranes, and running out in Length parallel to one another, make up their Composition . . . He observed farther, that the Vessels in the Brain of a Sparrow are not smaller than those of an Ox; and argues from thence, that there is really no other Difference between the brain of a large Animal and that of a small one. . . ."

He published wise comments on the innervation of the insect eye (1743, p. 227). 'It is also reasonable to believe', Baker stated, 'that every *Lens* [of the compound eye] has a distinct Branch of the Optic Nerves administering to it: and yet, that Objects are not multiplied, or appear otherwise than single, any more than they do to us, who see not an Object double though we have two eyes'. The use of the microscope to unravel the problem of innervation is itself noteworthy, as is this prescient description of how compound eyes must surely function.

He also shows simple microscopes, for they remained the prime instruments of microscopy at higher powers, and described the Leeuwenhoek microscopes which were still being used by the investigators. Many workers were making the smallest lenses as spheroidal globules of glass, whereas Leeuwenhoek had pursued lens-grinding and had made fine biconvex lenses. Even as the mid-eighteenth century approached, Baker (1743, p. 7) was referring to the Leeuwenhoek microscopes with some sense of admiration, for they remained the best available:

"Several Writers represent the Glasses of Mr. Leeuwenhoek made use of in his Microscopes to be little Globules or Spheres of Glass, which Mistake most probably arises from their undertaking to describe what they had never seen; for at the Time I am writing this, the Cabinet of Microscopes left by that famous Man, at his Death, to the *Royal Society* as a legacy is standing upon my table; and I can assure the World, that every one of the twenty-six Microscopes contained therein is a double convex Lens, and not a Sphere or Globule."

Leeuwenhoek's supremacy continued even into the following century. Sir Everard Home (1756–1832), who worked on (and freely plagiarised) the papers of the anatomist John Hunter (1728–1793) took the Leeuwenhoek microscopes back to his apartment and used them for high-power microscopy in the 1820s. These delicate, silver instruments were probably destroyed in a disastrous fire at Home's apartment in the Chelsea Hospital, when he decided to burn the potentially incriminating Hunter manuscripts and set fire to his home in the process. No other microscopes have so long served a role in the history of science.

Microscope Design

Baker provides good evidence of the microscopes that were in vogue for this kind of research. His book (1743, p. 16) illustrates a 'double reflecting microscope' – i.e., one with an objective and a field lens or eyepiece, which could be fitted with a plano-concave substage mirror. The model he depicted was produced by Culpeper and Scarlet, being 'an alteration and improvement' of the design by Marshal.

The design was produced in many models by Edmund Culpeper from about 1730 onwards. Culpeper is believed to have served time as an instrument maker under Walter Hayes, who according to Clay and Court (1932) was well established as a maker of mathematical instruments from 1650 until his death in 1686. It seems that Culpeper then continued Hayes' business. In the eighteenth century, Culpeper began to produce a microscope of which the major design feature was the abandonment of a single pillar to support the body tube, in favour of a tripod design. This facilitates the alignment of objective, specimen and mirror and was altogether a more sturdy microscope. Yet, although it can be seen as an improvement upon the Marshal design, it was not a new concept. Microscopes from the seventeenth century were thus constructed; indeed the earliest known drawing of a microscope (dating from around 1590) depicts this same design principle. In time Culpeper microscopes became widely available. They were fitted with lenses ground from soda

glass and had body tubes that were decorated with an ornate covering, typically shagreen. The design was widely adopted by manufacturers across Europe, and they became popular possessions of the wealthy.

Microscopes were widely utilised by the Italian natural philosophers. Dell Torre (1776) produced the first studies of peripheral nerves, which were delineated as rows of threads. Felice Gaspar Fontana (1730–1803) carried out extensive investigations of the stimulation of the nervous system using pressure, electricity and venom, and supplemented this work with microscopical observations of the nerves. He was able to observe the neuraxon and the myelin sheath many years before the findings of Remak and Schwann.

Alexander Monro *primus* turned his attention to the microscopical structure of nerves in 1732:

"The nervous Fibrils, which when examined with the best Microscope, appear only like so many small and distinct Threads lying parallel, without any Appearance of being Tubes: But in their Interstices and Membranes innumerable Branches of Vessels may be observed; the open Orifices of which, when seen in a Nerve cut transversely, are in hazard of making us believe, that we have discovered Cavities of the nervous Canals."

McHenry (1969) reports that Monro *secundus* (1783) described nerve fibres as 'one nine-thousandth of an inch' in diameter (approximately 3 μm) and of twisted, solid appearance. Wade (2004) reports that William Porterfield came up with similar dimensions in the same year: Porterfield proposed that the nerves were about '1 part in 7,200th inch' (approximately 3.5 μm). Wade reminds us that nerves were variously reported to consist of 'bundles of fibrils, filaments, capillaments, threads, or villi (as they were variously called)'. Only the microscope would eventually lead us to a proper understanding of the fine structure of the nervous system.

These pioneering investigations of the microscopy of the nervous system were largely prosecuted with simple microscopes that utilised a single magnifying lens. The development of simple microscopes led to a variation on the Marshal/Culpeper theme, for instruments with a single lens did not lend themselves so readily to a tripod construction. Tripod microscopes were easier to align, and typical simple microscope designs retained a lateral pillar to support the lens mount, stage and substage mirror. Early examples were produced by John Cuff (1708–1772) and the lesser known James Ayscough (*c*. 1718–1759) whose design was an early example of a microscope that could be used as a simple or compound instrument. Makers of these microscopes included the two George Adams (father and son, who published in 1746 and 1787), Francis Watkins and Benjamin Martin. Jean Baptiste Amici produced a range of microscopes in Italy, and attempted to solve the problem of achromatism. He believed the task was impossible, and went on to produce reflecting microscopes that were based on the proposals by Sir Isaac Newton. In France, Dellebar's 'Microscope Universal' was based on the design popularised by Adams and Martin, being introduced to France by Lalande in 1762 (Montucla, 1802). Clay and Court (1932) report that Samuel Gottlieb Hoffman produced a similar microscope in Germany in 1772.

Binocular microscopes, which we take for granted in the modern laboratory, were little used during this period. The first was described by Chérubin d'Orléans about 1680, and consisted of two unrefined compound microscopes fitted side by side in a rectangular case. True binocularity was not obtainable, for two reasons. First, the lenses were individually made by hand and could not be accurately matched. Secondly, because such instruments produce an inverted image – movements of the specimen are reversed when observed – the image is inverted, and so is the binocular appearance. Thus, depressions appear proud and hills are seen as holes. This topic was considered by Charles Wheatstone, who published the first design for a successful binocular compound microscope in 1852. He coined the term 'pseudoscopic' for the effect.

The observation of unstained, fresh nerve fibres would have been undertaken by innumerable microscopical investigators using instruments of this kind. And not only nerve fibres: the neuron is widely believed to have been first identified by Purkyně, whose work certainly led to the first published figures depicting the neurons that now bear his name. There is, however, a widely overlooked report of a microscopical observation reported by Prochaska (1779). He pressed specimens of neural material between glass slides, in order to break up the cohesion and see what sub-units he might discern. He concluded that the nerve tissues were made up of innumerable globules. We cannot now

be certain whether he was observing cellular particles or ground nerve fibres, though it is feasible that Procjaska was the first to observe discrete neurons.

Imagined Constraint

It is important to examine the real, and imagined, limitations that such microscopes imposed. Constraints on resolution limits and the problem of chromatism did not impose the barriers to progress that it is popular to propose. Compound lens arrays magnify aberrations more than they do specimens, and single lenses impose relatively few perturbations of image quality. I have shown that a Leeuwenhoek microscope can reveal microfibrils as fine as 0.7 μm – a result that is within a factor of four from the theoretical limits to optical resolution. A microscope of these specifications could clearly have revealed most of the epoch-making discoveries that were later to be made with optical microscopes. Chromatic aberration is not the problem we think it is, either; its main effect is to impart spurious colours to minute structural details within a specimen. The popular idea of rainbow-hued blurred images in which little detail can be discerned is unjustifiable, for images from diminutive biconvex lenses can be of surprising clarity and vividness. For example, a micrograph I have taken of an unstained blood smear, using the single-lensed Leeuwenhoek microscope at the Museum of the History of Science at Utrecht University, shows not only the erythrocytes with remarkable clarity, but even reveals the lobed nucleus within a polymorphonuclear granulocyte. Image acuity was clearly no barrier to histological observation (Fig. 8).

The limits lay not with the microscope, but rather with the techniques of specimen preparation.

Once nerve cells could be satisfactorily stained, even a simple microscope of the early eighteenth century could have allowed the presence of the cells to have been demonstrated. When McHenry (1969) writes: 'No real notion of the microscopic structure of the brain could be obtained until the invention of the compound microscope and microtome, along with the development of methods of fixation and staining of nervous tissue' he is only partially correct. In truth, the simple microscope was optically up to the task; it was the microtechnique (and staining in particular) that was lacking. Purkyne's successes were due to his readiness to adopt the latest, newly developed methods of fixation, staining and microtomy.

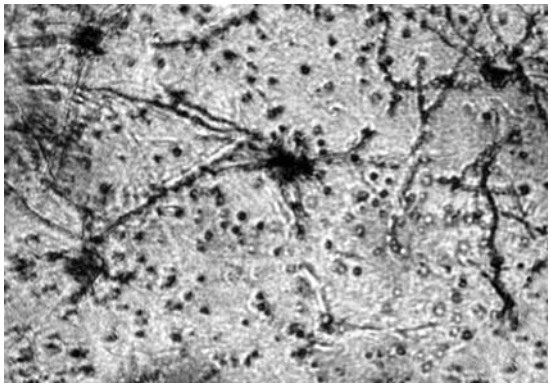

FIGURE 8. Cerebral section stained by the Golgi method and imaged by the author through a single-lensed microscope typical of those in use during the eighteenth century. Discrete neurons and their interconnections are clearly visible. Even primitive microscopes could allow the visualisation of neurons, though these cells remained unseen until staining procedures were available

The Century Turns

It is in strange juxtaposition that I close this outline of eighteenth-century neurological microscopy with the work of Marie François Xavier Bichat (1771–1802) who is regarded as the 'father of histology'. Bichat read medicine and surgery at the University of Montpellier and at the Hôtel-Dieu, Paris. Even in his years as an undergraduate he conducted a prodigious amount of research into physiology, and went on to become a demonstrator, and then lecturer, at the Hôtel-Dieu. He died at the age of 31, just five years after graduating, yet amassed enough research to furnish three truly monumental works: *A Treatise on the Membranes* (1800), *Physiological Researches on Life and Death* (1800), and *General Anatomy* (1802). A web site summarising his work exists at http://www.bium.univ-paris5.fr/histmed/medica/bichat.htm and Bichat's reputation has long been secured in the history of medicine. The study of anatomy and physiology had been traditionally founded upon the bodily humors, or the study of organs. Bichat determined that pathology should better be

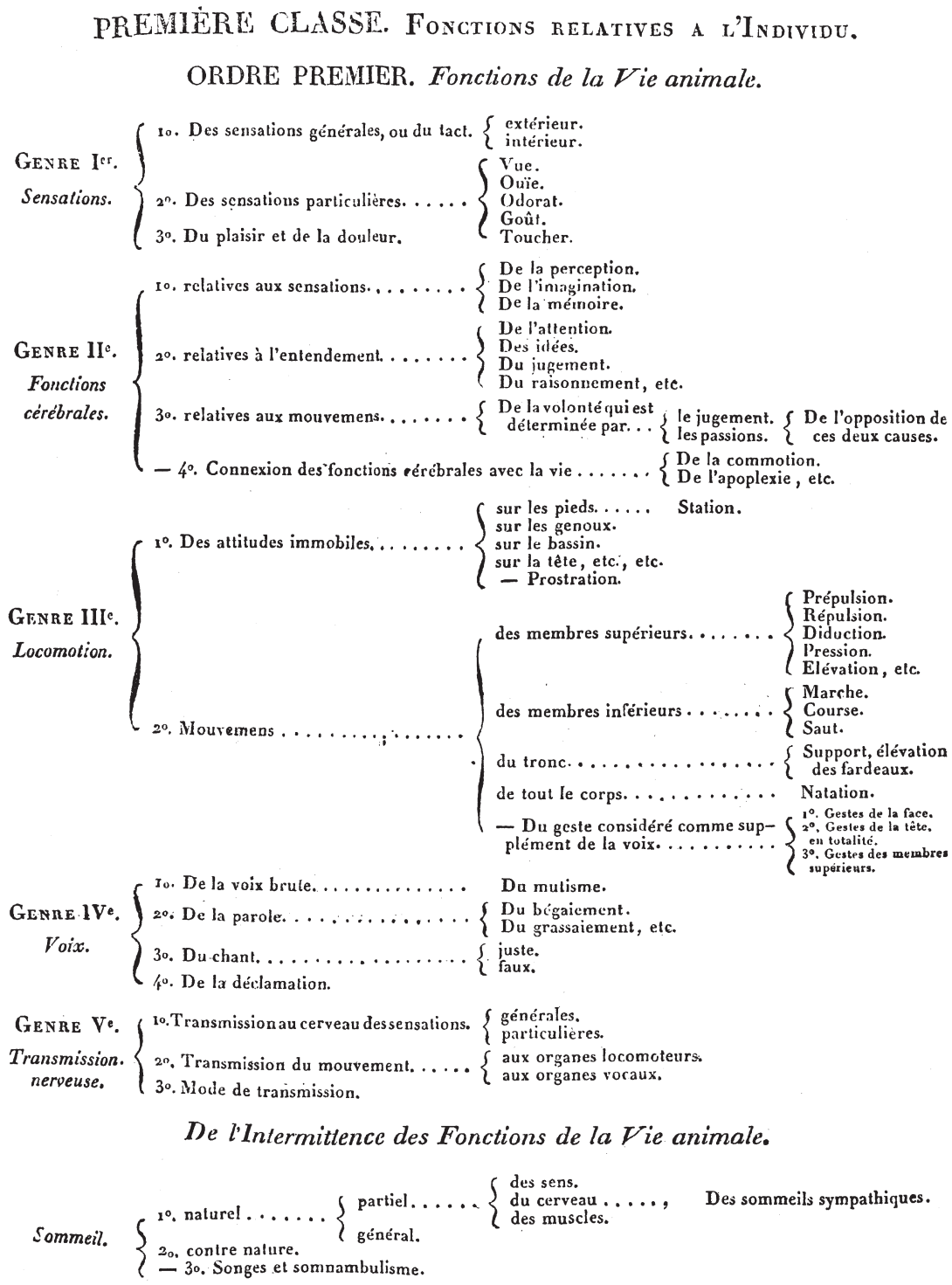

FIGURE 9. Xavier Bichat (1800) published tables of tissue types and their properties which served to lay the ground-rules of the new science of histology. His work was made all the more remarkable by his persistent refusal to involve the microscope in his work

studied through tissue structure and his enthusiasms laid the groundwork for the modern science of histology. In his short career he dissected his way through 600 cadavers and identified 21 basic tissues (Fig. 9).

The paradox lies in the fact that Bichat did not use microscopes. He was unimpressed by them, believing them to distort reality, involve much subjective guesswork and to provide results that were not reliably repeatable. As Otis (2000) has commented, my earlier work has shown that many scientists who made key discoveries in pathology did not use microscopes at all. It is particularly curious that the father of a science which, in the modern world rests firmly on the expertise of the microscopist, himself turned away from microscopy.

In the decades following the eighteenth century, a swathe of microscopical discoveries was set to revolutionise neurology. Treviranus was to recognise the neurilemma of peripheral nerves using uncorrected microscopes in 1816; indeed derivatives of the Cuff microscope were used by many investigators elsewhere in biology. Robert Brown carried out his work on the ubiquity of the cell nucleus, and on Brownian motion, using a similar simple microscope made by Bancks in London. We have already encountered Sir Everard Home using the original Leeuwenhoek microscopes for his micro-anatomical studies in the 1820s (*supra*). Indeed, Charles Darwin was still recommending a single-lensed, portable instrument as the microscope of choice as late as March 1848 (Ford 1985) (Figs. 10 and 11).

But from about 1830 achromatic microscopes were to become available. These were grander instruments, objects of desire, finely tooled from brass and easy to use. A burst of activity followed: Ehrenberg recorded ganglion cells in 1833, then Purkyně (1837) identified the neuron and in the following year His portrayed neurons with nuclei and dendrites. In due course Golgi developed in the kitchen at his home the staining system that bears his name and made the neuron visible to microscopists. It is important to note that it was

FIGURE 10. The Czech microscopist Johannes Evangelista Purkyně in his study at Prague during the 1850s. His microscope (right) which has much in common with the designs of W. and S. Jones (Fig. 5) has been identified for the author by Mr James Solliday of the Microscopical Society of Southern California, as being made by Plößl of Vienna

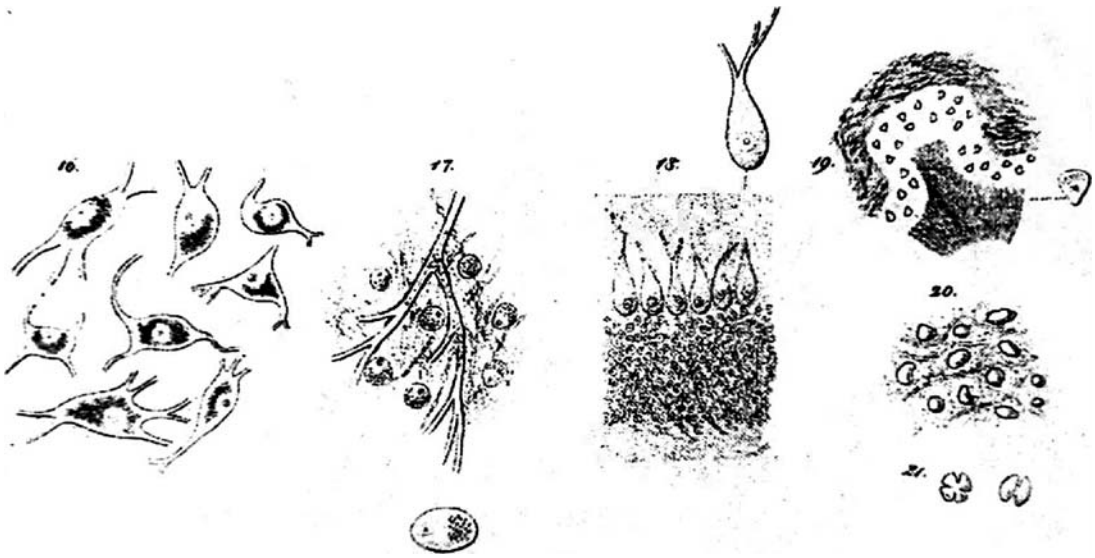

FIGURE 11. The table of nerve cells presented by Purkyně in his lecture to the Prague Congress of 1837 (Anon, 1962). The diagram numbered 18 depicts those now known as Purkyně cells. His talk gave a clear proposal of a cell theory (Körnchen), anticipating the work of Schwann. Purkyně also coined the term 'protoplasm'

primarily the newly developed staining techniques, rather than improvements in the microscope, that made neurological microscopy a reality. After a century in the doldrums, with these exciting new methods of specimen preparation and staining and with the achromatic microscope becoming generally available, microscopy of the nervous system was to embark upon its greatest era of expansion.

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