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How Rudolph Virchow changed the approach to autopsy of the brain

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Abstract

Anatomical studies of the brain and successive analyses of this organ were performed in ancient times. Indeed, notes found in the Edwin Smith Papyrus mention that the Egyptians identified the meninges and gyri millennia ago. Their successors examined the content of the skull, examined it and illustrated it in greater detail. Alexandrians (Herophilus and Erasistratus) described the cerebral ventricles and blood circulation and supply to the brain. More accurate depictions emerged during the Renaissance with Leonardo da Vinci (1452-1519), Charles Estienne (1504-1564) and Andreas Vesalius (1514-1564), followed by Thomas Bartholin (1616-1680), Franciscus Sylvius (1614-1672) and later scholars. The present study focuses on neuroanatomy and is devoted to the study of nervous system structures by the eminent pathologist Rudolph Virchow. When reorganizing the procedure and reporting of the post-mortem examination, including a meticulous autopsy of the brain, neuropathology was a discipline yet to be developed. He pioneered a new approach to the autopsy and analysis of its results, aiming to benefit not only the patients but also clinicians and pathologists.

Key words: *Rudolf Virchow, pathology, neuropathology, history, autopsy, brain, spinal cord, nervous system.*

Introduction

Not so long ago we celebrated the bicentennial of the birth of Rudolph Virchow (1821-1902): a polymath, scientist, researcher and physician who moved pathology into a completely new era. His life was dedicated to many activities and, apart from being a practising physician, he was a fervent politician, member of Parliament and historian. Virchow's wide interests resulted in many discoveries and over 2,000 scientific writings. He also started the famous medical journal *Archiv für pathologische Anatomie und Physiologie und furlinische Medizin*, renamed *Virchow's Archives* after his death [1,2,4,7,10]. By developing the idea that diseases originate in cells, subsequently affecting tissues and organs, Virchow disproved the still commonly accepted humoral theory of medicine, and *Die Cellularpathologie* (1858) is considered the cornerstone of modern pathology.

The aim of this paper is to show how such an illustrious pathologist and perseverant researcher reshaped the autopsy as a medical procedure, with emphasis on the dissection of the brain and spinal cord, and how his work initiated a change in clinicians' attitudes towards the practice of autopsy [1,4,7,10].

Rudolph Ludwig Karl Virchow was born in 1821 in Schivelbein, Pomerania (now Świdwin, Poland). He

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graduated from the Friedrich-Wilhelm Institute in 1843 and, being an outstanding student, was exempted from military service and appointed to an internship at Berlin's Charité Hospital. In 1844, he joined the Prosector's Department and became an assistant to Robert Froriep (1804-1861), Professor of Pathology and Prosector, who directed his young co-worker towards scientific rather than clinical activity [1,4,7,10]. Virchow mentions that Froriep performed autopsies "with great manual dexterity" but very rarely. Post-mortem examinations were usually carried out by "random obducents" described as "young men, subsequently styled assistants, who had not yet passed the State examination". Autopsies were performed "irregularly and unmethodically", without systematically inspecting the organs, recording observations or taking tissue samples for microscopic examination. All these failings also encumbered brain and spinal cord analysis [1,4,6,16].

After Froriep's resignation in 1846, Virchow became Head of the Pathology Department and set about changing the whole prosection routine: the training of the obducents; the autopsy procedure; and, last but not least, the collection of tissue samples for histology and/or the pathology museum that he planned to create. Autopsies were to be performed following a strict protocol by select personnel. Regular note-taking and record keeping of the changes in all the organs, not just in those known to be affected, were made obligatory for future investigation and/or research. Details that seemed irrelevant at autopsy often proved significant when supplemented with clinical data, leading to a more complete understanding of the cause of death. The notes and records constituted a valuable case database for students and physicians to consult [1,13]. Thanks to these improvements, clinicians started to see the benefits of exchanging information with pathologists.

Virchow was well aware of the manual of pathological anatomy published by one of the most prominent pathologists of the time, Carl von Rokitansky (1804-1878). His *Lehrbuch der pathologishen Anatomie* described autopsies performed by him or under his supervision and provided a vast amount of gross pathology reference material. Virchow disagreed with the Viennese professor on dissection techniques and the need for the microscope, an instrument that Rokitansky used sparingly. In addition, he was a strong opponent of Rokitansky's doctrine of "crases" and "dyscrases", asserting the influence of proteins on inflammation and the effect of diseased blood components on human tissues. According to Virchow, diseases originated within the cells, and he insisted on the importance of histology, urging his students and fellow pathologists to "think microscopically" [1,4,13].

Limiting the post-mortem to organs macroscopically affected was unacceptable to Virchow, as was the practice of inspecting organs *in situ* without removing them from the body, though it must be said, he himself analysed some organs this way (e.g. the heart). He strongly upheld that an investigation into the cause of death should include a thorough examination of the whole body. In the chapter "Method of performing [autopsy]", Virchow wrote "In a systematic and scientific performance of an autopsy, nothing is more difficult, and at the same time more important, than the insight into the reasons for pursuing a definite order of sequence in every detail of the examination" [16]. In this manner, he was following the same approach as Giovanni Battista Morgagni (1682-1771), who in 1761 had published his seminal work *De Sedibus Et Causis Morborum Per Anatomen Indagatis* (The Seats and Causes of Diseases Investigated by Anatomy). However, Morgagni did not have the technical means to reach a deeper understanding of the causes of disease, since microscopes were still not regarded as scientific instruments. Initiated by Marie-Francois Xavier Bichat (1771-1802) with his doctrine of tissues, histopathology was further developed by Virchow half a century later [2,11,13,15].

Rudolph Virchow's outspoken liberal views and his uncompromising report on the typhus epidemic in Upper Silesia brought him into conflict with the authorities, which ended with his forced resignation from Berlin's Charité Hospital in 1848. The department was taken over by his close friend, Benno Heinrich Reinhardt (1819-1852), with whom Virchow had founded *Archiv* für *pathologische Anatomie und Physiologie und für Klinische Medicin* a year earlier. Reinhart died prematurely of tuberculosis, after which Rudolph Virchow ran the journal alone [1,6,15].

Virchow was also instrumental in the writing and enforcement of special regulations concerning the post-mortem examination, including medico-legal ones, issued in 1858. During his lifetime some of these regulations became outdated, if not obsolete; hence, a revised version was issued in 1875 [13].

Autopsy of the brain

Knowledge of anatomy, including anatomy of the brain, has existed since ancient times. The first analysis of brain tissue was performed and noted in ancient Egypt, with descriptions of the superficial elements such as gyri or meninges (Edwin Smith Papyrus). Their successors went further, examining the content of the skull. Alexandrians (Herophilus and Erasistratus) described the cerebral ventricles and blood supply vital for the brain. More accurate depictions emerged later during the Renaissance with more and more accurate drawings by Leonardo da Vinci (1452-1519; Fig. 1),

Charles Estienne (1504-1564; Fig. 2), those commissioned by e.g. Andreas Vesalius (1514-1564; Fig. 3), followed by Thomas Bartholin (1616-1680), Franciscus Sylvius (1614-1672), Thomas Willis (1621-1675) and many other scholars. But in this paper, we will focus on the work of the eminent pathologist from the 19th century.

Despite his attempt to standardize the procedure of the autopsy as a whole, in his *Post-mortem Examinations* Virchow writes that "there are many cases in which deviations from [...] method is not merely allowable, but also absolutely necessary. The individuality of each case must often determine the plan of examination. [...] For this purpose, however, a full and intimate acquaintance with the reason why the plan or rule has been laid down is quite imperative" [13].

Regarding the brain autopsy, he suggests that the pathologic-anatomical examination has to take a course peculiar to itself, different in many respects

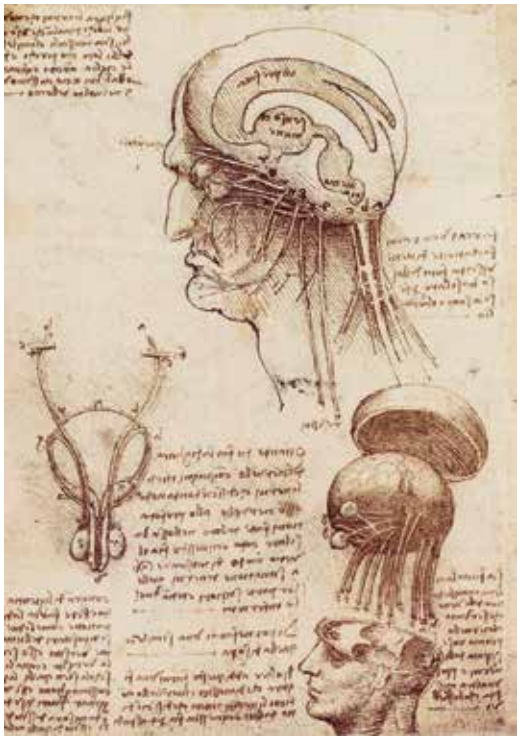

Fig. 1. Leonardo Da Vinci – Brain Physiology. Ca 1510. Source: Wikimedia Commons.

Fig. 2. Charles Estienne – De dissectione partium corporis humani. 1545. Wellcome Library, London. Wellcome_L0030444.

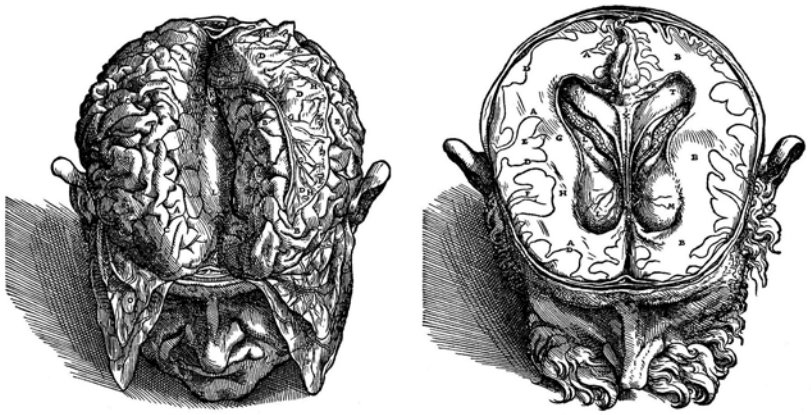

Fig. 3. Andraeas Vesalius – the brain and ventricles. De humani corporis fabrica libri septem. 1543. Centre d'Études Supérieures de la Renaissance Tours. License Creative Commons.

from that adopted in descriptive anatomy. "It is of the greatest consequence that the incisions should be even and smooth, in an organ like the brain, where the separate portions are of so great importance, and where one part is distinguished from another by peculiarity of function. How could we possibly demonstrate small foci of softening or induration upon an uneven, crushed or torn surface? And these two are exactly those changes most frequently occurring in the brain. Therefore, I say to my students, 'Smooth though wrong incisions rather than correct and uneven ones!' It is true that with an incision made in a wrong direction we can scarcely tell what we are about, but an incision badly made is entirely worthless" [13].

When describing the dissection of the brain, Virchow bases his method on a thorough investigation not only of the brain substance but also of the ventricle system, so that the organ after dissection could be analysed "like a book" bound in the pia mater which envelops the cerebral vessels. The study of the ventricles and meninges was crucial at gross examination as well as under the microscope [1,13]. He begins with opening the cranial cavity and exposing the dura mater, the great longitudinal sinus, pia mater and cerebral hemispheres. He warns against forcefully detaching any adhesions between the skull cap and dura mater, because of the risk of tearing or crushing the brain tissue, which would jeopardise disease detection [7,16]. The brain surfaces, meninges and blood vessels should be grossly inspected, and the status of the circle of Willis and carotid arteries checked before further steps are taken (Figs. 4 and 5).

Virchow advises that incisions in the hemispheres be made from within to without, and recommends cutting between existing cuts to obtain increasingly thinner slices for a more detailed analysis of the brain tissue. In another paragraph, he states that "It is true that in other cases and in other organs – for example, always in the brain – we must make a larger number of cuts in order to be sure that nothing has been overlooked. [...] In the case of the brain, we can never positively assert that it is quite normal, unless we divide it into quite microscopic portions, according to the new method of Herr von Gudden". Virchow insists that 5 mm-thick slices are of no use, as "in the interior of such sections there is always plenty of room for foci of morbid material sufficient to produce paralysis or convulsions. However great the number of these incisions may be - and it is necessary here to make numerous cuts – the relationship of the parts may always be closely preserved, in consequence of the connection between each separate portion and the peduncle of the cerebrum" [13]. Virchow repeatedly stresses that whatever procedure or number of cuts is performed, it is mandatory to avoid destroying the organ so that it can be reassembled at the end of the procedure.

Other paragraphs emphasise the importance of a minute analysis of the ventricles and describe the method to be followed. "My opinion is that, the examination of the brain, after the membranes have been finished, should commence with the opening of the ventricles, since, apart from any tearing or squeezing

Fig. 4. Brain – general view with meninges partly moved up.

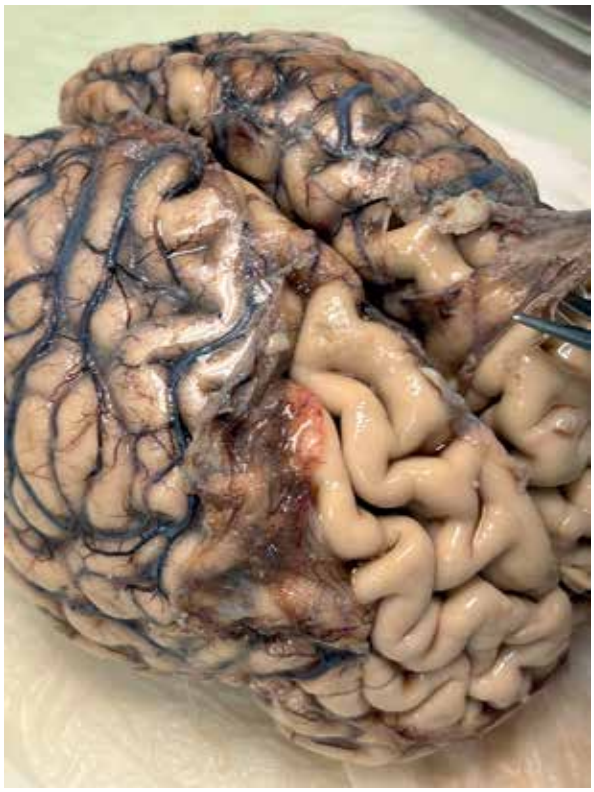

Fig. 5. Brain – closer view of the meninges.

caused by manipulation, the very weight of the organ increases the liability to laceration as time goes on, and the consequent risk of the escape of the fluids. The first incision, therefore, which I generally make into the brain, is carried directly into a lateral ventricle [...] In order to open (completely) the anterior and posterior cornua, or, at least, to demonstrate their condition (for the posterior cornua are more frequently completely or partially obliterated than open), it is necessary to make particular incisions anteriorly and posteriorly. These should not be made vertically, but horizontally, the anterior one higher, the posterior one deeper, in the anterior and posterior lobes of the brain. Only then do we obtain a view of the lateral ventricles in their whole extent, for the entrance, at least, to the descending cornu is also exposed by the incision toward the posterior cornu" [13]. We present it in the following photographs taken in our department (Figs. 6 and 7).

These cuts allowed the obducent to check the content and walls of the lateral ventricles, as well as the condition of the vessels and choroid plexus. The next step was to explore the third ventricle by lifting and cutting the corpus callosum to reveal the septum lucidum and fornix, then detached from the velum interpositum and its choroid plexus (Fig. 8). "After these two latter have been exposed, we have to examine the state of their vessels and tissue. Then the handle of the scalpel is passed from the front, under the velum, which is thus detached from the pineal body and corpora quadrigemina, ...and the third ventricle now exposed. Lastly, with a long perpendicular incision, we divide the corpora quadrigemina and the cerebellum as far as the aqueduct of Sylvius and the fourth ventricle" [13] (Fig. 9). The technique of making incisions from within to without was not applicable to structures such as the optic thalamus or corpus striatum, for which Virchow suggested "fan-shaped radial incisions, whose common starting point is the peduncle of the cerebrum".

As concerns the spinal cord, Virchow advocated transverse incisions, "leaving the pia mater attached on the anterior or posterior surface". He disagreed with his predecessor Froriep, who dissected it along its length with a single straight cut, opening it into two halves. "This certainly made a very elegant section, [...] but, however well it was performed, there were but very few cases in which it was of any use. The natural consequence was that Froriep's attention was directed principally to the membranes and roots of the nerves, and that the commonest and most important alterations in the white substance remained unnoticed" [13].

Virchow not only improved the autopsy procedure but also the instruments used. Noticing that some of the knives did not meet his requirements, he brought in a new design to enhance performance and increase the safety of the obducent. "The modified section knife (*Secirmesser*) which I have introduced differs from the ordinary dissecting knife (*Präparirmesser*), both in the blade and handle. Both these latter are not only longer, but also stronger – that is, thicker and broader. The anterior part of the blade does not form an acute

Fig. 6. Brain – opening of the lateral ventricle and presentation of the choroid plexus.

Fig. 7. Brain – opening and presentation of both lateral ventricles.

Fig. 8. Presentation of the cross sectioned corpus callosum and third ventricle.

Fig. 9. Vertical section of the cerebellum and presentation of the fourth ventricle.

angle, but is rounded off; the very broad surface terminates with a considerable curve in the slightly projecting point" [13].

Thanks to Virchow, microscopic tissue analysis became an integral part of autopsy pathology, and many of his discoveries were made following this approach. He provided a detailed description of the perivascular spaces, microscopic structures that consist of a single or double layer of invaginated pia and basement membrane surrounding small cerebral blood vessels. These fluid-filled spaces were confirmed by the French anatomist and histologist Charles Philippe Robin (1821-1885) and came to be called Virchow-Robin spaces. Subsequent research has shown that they play a key role in the regulation of extracellular fluid flow within the central nervous system and in the drainage of interstitial fluid to the lymphatic system. It is also postulated that perivascular spaces carry out functions similar to those of the lymphatic system in other parts of the body. Their importance lies in the removal of metabolic waste products and the maintenance of fluid homeostasis within the brain [5,14,17,18]. New aspects must also be reconsidered, when these spaces are postulated to interact in the transfer of the drugs [12].

Other elements described by Virchow, as a result of thorough microscopic examination of the brain tissue, were the *corpora amylacae*. For the first time they were described by Giovanni Battista (Giambattista) Morgagni (1682-1771) in the prostate, later to be mentioned by Jan Evangelista Purkinje (17887-1869). Virchow not only identified and described them, but also provided useful techniques to stain and visualize them. Unfortunately, he was unable to explain why these structures appear, why they are mainly found in the brains of elderly patients, and what their clinical significance may be [9].

Conclusions

This paper has illustrated the approach of this remarkable researcher to autopsy and his special interest in the dissection of the brain and spinal cord. His method was highly demanding, requiring considerable knowledge and skill from the obducent, and it is not very common today. The immense contribution that Rudolph Virchow made to the development of pathology will always be remembered. Cellular theory changed the way of understanding diseases. Microscopic analysis became an essential part not only of pathologists'

work, but also of students' curricula. Eponyms such as Virchow's triad, Virchow's node and Virchow-Robin spaces are still present in the medical lexicon today and are likely to persist in the future. His studies on thrombosis and atherosclerosis also laid the foundations for future research [13].

Rudolph Virchow set out a series of procedures necessary to accurately identify the cause of death and created the first template database of clinical and pathological reports, often incorporating microscopic tissue analysis. Though the term "evidence-based medicine" was coined more than a century later, we must not forget Virchow's words: "I aimed at causing the autopsies to be made by one person, at introducing a system of regular notetaking, and of collecting these notes, in order to obtain a useful series of reports" [13].

The information obtained during dissection combined with the clinical data was of immense didactic value. Students attending autopsies were encouraged not only to gain knowledge of gross pathology, but also to "think microscopically" in order to identify the cellular changes that had caused the lesions observed in the cadaver. Virchow's motto was "*nulla dies sine praeparatu*" (no day without a specimen), and these post-mortem examinations allowed him to collect samples from a wide range of lesions, some more and others less common. Being a great admirer of the Pathology Museum created by John Hunter (1728-1793) and having gathered, classified and catalogued more than 20,000 specimens, in 1899 Rudolph Virchow established within Berlin's Charité Hospital one of the foremost pathology museums of the time [3]. His exceptional collection of specimens is still on display today and enjoyed by visitors from around the world.

In 1901, some of Virchow's former students, led by Julius Schwalbe (1863-1930), compiled a bibliography of their master in celebration of his eightieth birthday [6,16]. This opus recorded the prolific lifework of the man and scientist and required almost 120 pages, with an average of about 18 items per page. Such a list, comprising approximately 2,000 titles, "bears witness to the industry, breadth of interest and critical scientific discrimination of the cellular pathologist".

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