Application Note

From macroscopic to microscopic anatomy: How the Use of Microscopes in Medical Education is Evolving.

Review and Outlook

Seeing beyond

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In today's medical education, students acquire detailed knowledge of the microscopic structure, form and function of cells, tissues and organs of the human body. This fundamental knowledge is a prerequisite for understanding their characteristics as well as for recognizing disease-related changes. It is key to justifying a medical diagnosis, including treatment. But it was not always like this: medical education has evolved over the centuries. This article gives a brief historical outline of developments in anatomy education. It also describes analogue, digital and virtual microscope techniques in use today.

First anatomical studies

How is the body built? How do diseases develop? Is bloodletting suitable for healing people? Human beings have always been interested in learning more about the structure of their body and seeing with their own eyes what is hidden inside. But for eons there was only one way to satisfy this curiosity: opening up and dissecting bodies.

The first anatomical studies can be traced back to the 17th century BC. Hippocrates, Aristotle and Praxagoras of Kos in the 4th century BC are just some of the well-known names that recall the origins of biomedical investigations. But it was the rulers of the Ptolemaic Empire who first officially allowed the opening of corpses for anatomical studies with the naked eye. Thus, Alexandria became the center of medical knowledge with a first anatomical school in the 2nd century BC. Alexandria was also famous for its huge library and experienced educators. Herophilos of Chalcedon worked there and is said to have conducted the first scientific investigations on dead human bodies and animals. Thus, he is considered the father of anatomy.[1]

One of the most famous physicians of antiquity is Claudius Galenos, also known as Galenus or Galen (129 – 199 AD). He too studied human and animal bodies in Alexandria. Back in his hometown of Pergamon, Galen cared for gladiators as a sports and wound doctor. In doing so, he was treating fresh injuries and so was able to describe the human body scientifically. Galenos became one of the most famous among the scientific greats. He had compiled much of the ancient medical knowledge in his works and his findings influenced anatomy for several centuries.[2,3]

Even though the opening of corpses was crucial for gaining further knowledge, it came into disrepute with critics coming from church as well as from medical theorists. The dead body could be viewed the dwelling place of the soul, they argued, and its dismemberment put its final rest in danger. Subsequently, there came a time when, officially, no practical anatomical examinations took place in medical education and knowledge was based exclusively on theoretical treatises. In consequence, there were no new biomedical findings within that period and anatomical research stagnated until the beginning of the 12th or 13th century.

Figure 1 *Fasciolo di Medicina, depiction of Anatomy lecture, 1493; https://bodyworlds.com/about/history-of-anatomy/*

Figure 2 *Head study, Leonardo da Vinci*
https://de.wikipedia.org/wiki/Leonardo_da_Vinci

However, curiosity and the thirst for new insights remained and the school of Salerno revived the Alexandrian tradition: anatomical studies could be carried out again. The anatomical act was of great interest to both scholars and the public. During the anathomia, the professor sat in his chair and read from Galen's works while a craftsman or surgeon dissected the corpse. There was not necessarily a direct connection between the lecture and what was revealed on the dissecting table.[4]

Another impetus for anatomy came from art. Among others, the schematic representations by Botticelli, Leonardo da Vinci and Michelangelo deserve mention here.

The next great milestone in medical history is the work of Andreas Vesalius (1514 – 1564), also known as Vesal. Vesalius was the first to combine practical dissection with theoretical knowledge in one person. His groundbreaking findings shook up the teachings of Galenos that had been valid up until then. When he found out that Galenos had presumably gained his knowledge about human anatomy from anatomical studies on animals, he corrected Galen's deductions with his own findings and became known for his main work, *De humani corporis fabrica libri septem*. For this, he is seen as the founder of modern anatomy.[6]

The anatomical act became a public spectacle and public interest was enormous. Because only the dead bodies of convicted criminals could be dissected, there was something sinister about the whole business. Anatomic theaters were built to accommodate the crowds and admission fees were charged. The higher the fee, the better your seat for following the dissection with your own eyes.

Over the next centuries, anatomical knowledge was supplemented and refined by other anatomists. It is not possible to name everyone at this point without diminishing their individual discoveries. What they all had in common was that their knowledge was based on macroscopic observations. Naturally, as all examinations were carried out with the naked eye, the eyesight of the observer became a limiting factor.

Although these early anatomists could describe body structure in detail, deeper insights into structure, form and function beyond the resolution of the eye remained hidden.

How microscopes evolved traditional anatomy

Everything changed with the use of microscopes by Marcello Malpighi (1628 – 1694), anatomist and pioneer of microscopy, along with Robert Hooke (1635 – 1702) and Antoni van Leeuwenhoek (1632 – 1723).[7,8,9] Robert Hooke is credited with making the first drawings of cells in 1665. He drew a thin cage-like disc, the chambers of which he described as microscopic pores and cells. Using magnifying optical instruments, it was now possible to enlarge the smallest details in such a way that the structure of cells and their organization in different types of tissue and organs could be studied. Microscopes thus opened the door to morphological studies. Since tissue samples are often colorless, examinations were limited at that time. This limitation was overcome with the help of stains such as madder or carmine. Likewise, microtomes were being developed to produce thin specimen sections.[10] The thinner the tissue section, the more translucent the sample and the better the result of the microscopic examination. Thus microscopic anatomy was born and it soon became an independent discipline in medicine and biology. The term histology became established from around 1819 and can be traced back to the anatomist August Franz Josef Carl Mayer (1787 – 1865).[11,12,13]

Rudolf Albert v. Koelliker (1817 – 1905, anatomist in Würzburg) was responsible for the division into four types of tissue (epithelial, connective and supporting, muscular and nervous tissue), which is still valid today.

The further progress in histology is associated with the development and systematization of staining techniques by Paul Ehrlich (1854 – 1915). The application of the Golgi staining method

Figure 3 *State Optician School Jena: microscopy room, around 1922; Archive of ZEISS Microscopy*

enabled Ramon y Cajal, for example, to demonstrate the cellular structure of the brain and nerve tracts. For their work, Santiago Ramón y Cajal and Camillo Golgi were awarded the Nobel Prize in Physiology or Medicine in 1906.

Just as more dyes were gradually discovered, and dyeing and cutting processes were refined, microscopes were also continuously being developed. Different manufacturers were hard at work on this and, as a result, it was primarily the craftsmanship of the builders that determined the optical quality of the microscope. A standardized manufacturing process for high quality microscopes—based on scientific calculations rather than trial and error—was largely absent at the time. This was to change in 1846, when Carl Zeiss founded his optical workshop with a declared goal of producing the best microscopes in standardized high quality. Early on he recognized the genius of young Ernst Abbe, who would later become co-owner of the ZEISS company, as a scientist who could provide the scientific framework for lens production.

Thus a global organization had its beginning and the lens system optimized by Ernst Abbe shifted the center of microscopy development to Jena in Germany. The high quality product and high standard of manufacturing laid the foundations for large-scale use of microscopes in medical education. By 1900, microscopes were already widespread in science and, during the years to come, they became the standard indispensable tool for medical studies in histology, pathology, microbiology and other disci-plines.[11] The quality of microscopes continued to improve. Meanwhile, the processes for lens calculation, production and coating were being optimized alongside the technology for glass production.

No other instrument has enabled such fascinating insights into tissues, cells or other types of specimen. The first look through the microscope was—quite literally—an eye-opener for many young students in training, and this is still the case today. "Microscopy is the oldest imaging technique in medicine and still a key method in medical diagnostics. It triggered a revolution of diagnostic concepts as part of its introduction into medicine (Virchow's 'cellular pathology') and is still being continuously developed and improved today."[14] Thus, microscopy equipment are used now during surgery and for endoscopy on the one hand, and electron microscopy and super resolution techniques have contributed to the fundamental understanding of cell organelles.

ZEISS now offers versatile microscope technologies to support modern teaching, be it face-to-face, online learning or virtual education. The following chapter describes in more detail the various solutions for teaching and learning in medical education.

Figure 4 *Digital Classroom, University of Exeter, UK*

Figure 5 *From hand to brain: drawing are still an important tool in education.*

Face-to-face teaching and learning

For decades, face-to-face lectures have been a cornerstone of university teaching. In medical education, microscopic anatomy is often taught in practical exercises, done directly at the microscope. Educators and students are on site at the same time and in direct communication. The training is carried out as real-time microscopy of fixed and mostly stained sections on glass slides.

Traditionally, the specimen is first examined with the naked eye. This allows staining and important structures to be recognized and regions of interest identified before the slide is placed under the microscope. The object is examined first at the lowest magnification. Once the microscope image is in focus, the object can be visualized under increasing magnifications.

It is also considered important to give students a comprehensive knowledge of methods and diagnostics. For this purpose, individual observation skills are trained by having students draw and sketch what they see here and there under the microscope. Detailed sketches are only possible if those details are accurately recognized and understood. Close observation is a prerequisite for being able to produce detailed hand drawings which follow the hand-to-brain rule and support sustained learning of what is seen. At the end of the course, students might be expected to sketch a histological object, identify it by its visual characteristics and justify a diagnosis.

Classically, students use upright microscopes in the histology training course. These microscopes—for example, ZEISS Primostar 3—are factory-equipped with a standard set of objectives and optimized for reliability, durability and ease of use. Fixed Koehler microscopes are especially useful when the focus is on the specimen and the microscope is used as a tool for visualization only. If, in addition, the student is being taught the technique of microscopy as preparation for everyday life as a medical doctor, full Köhler microscopes are the instrument of choice.

To visualize ultrastructures of organelles (e.g. *mitochondria, cilia*), electron microscopic images are used in the lecture and also in the practical course. The basics of electron microscopy are taught and insights into high-resolution methods and (fluorescence) staining techniques are provided.

Both, electron and superresolution microscopy give valuable insights into the inner structures of cells and therefore boost the knowledge in anatomy and cell biology.

This is the century of digitalization in education. On one hand, as the technological development of the world wide web evolves, so too do digital cameras, digital media, apps and software, enhancing the use of digital elements in teaching. This trend has made an impact on microscope-based education and, in turn, influenced further developments in the digitization of microscopy. On the other hand, digital media are second nature for the generation of digital natives. Universities have already managed to capitalize on this trend and offer modern teaching and blended learning concepts to support their students' education and to reach out to the next generation of students.

Electron microscopy provides information on the structure of mitochondria, myelin, synapses and other cellular components not resolved by light microscopy.

Figure 6 *The drawing function of ZEISS Labscope enables the students to draw their microscopy images and easily share and save their results.*

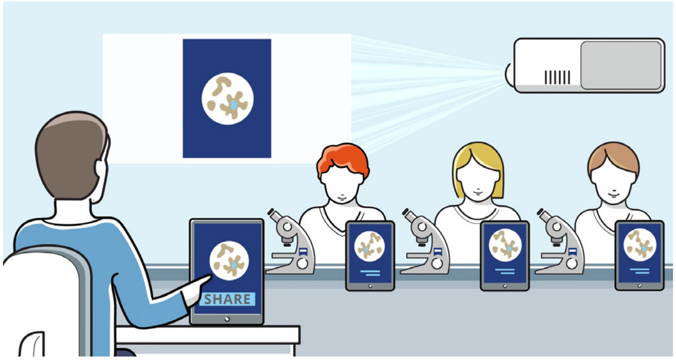

Figure 7 *ZEISS Labscope Teacher puts the lecturer in charge of all connected microscopes in the network of the digital classroom.*

The use of software introduces further possibilities for interactive teaching. Using the ZEISS Labscope app has the potential to improve learning by offering benefits for teachers and learners alike. In a digital classroom with connected microscopes, teachers enjoy enormous time savings as they can view all microscopes in the network with a single glance on their mobile device. This allows personalized training by providing individual assistance where needed. But most importantly, that valuable time can be used for teaching content, which lies at the heart of the educator and in the center of teaching.

Microscope images from any student microscope in the network can be shared on the screens for interactive discussions. Furthermore, each student can create snaps or movies, and learn from the first annotations, e.g. measurements. Mobile devices such as tablets and smartphones are a natural part of life for digital natives. Their use in medical education serves to increase the joy of learning and ultimately creates memory aids for exam preparation.

The Digital Classroom

With the further development of CCD and especially CMOS technology in digital cameras, their use in education is also increasing. There is a growing demand for WiFi-enabled network cameras with different interfaces for connection to the classroom EdTech (educational technology). The connection to e.g. PCs, monitors or projectors opens up the possibility of integrating digital elements into classroom teaching. For example, microscope images can be projected directly onto a large monitor for all to see in real-time and for all to follow the educator's guidance.

Virtual education with digitized microscope slides

With virtual teaching, participants do not have to be present in the classroom or in person on an online call. Instead, virtual slides are linked to subject-specific information and the resulting e-Learning module is posted online.

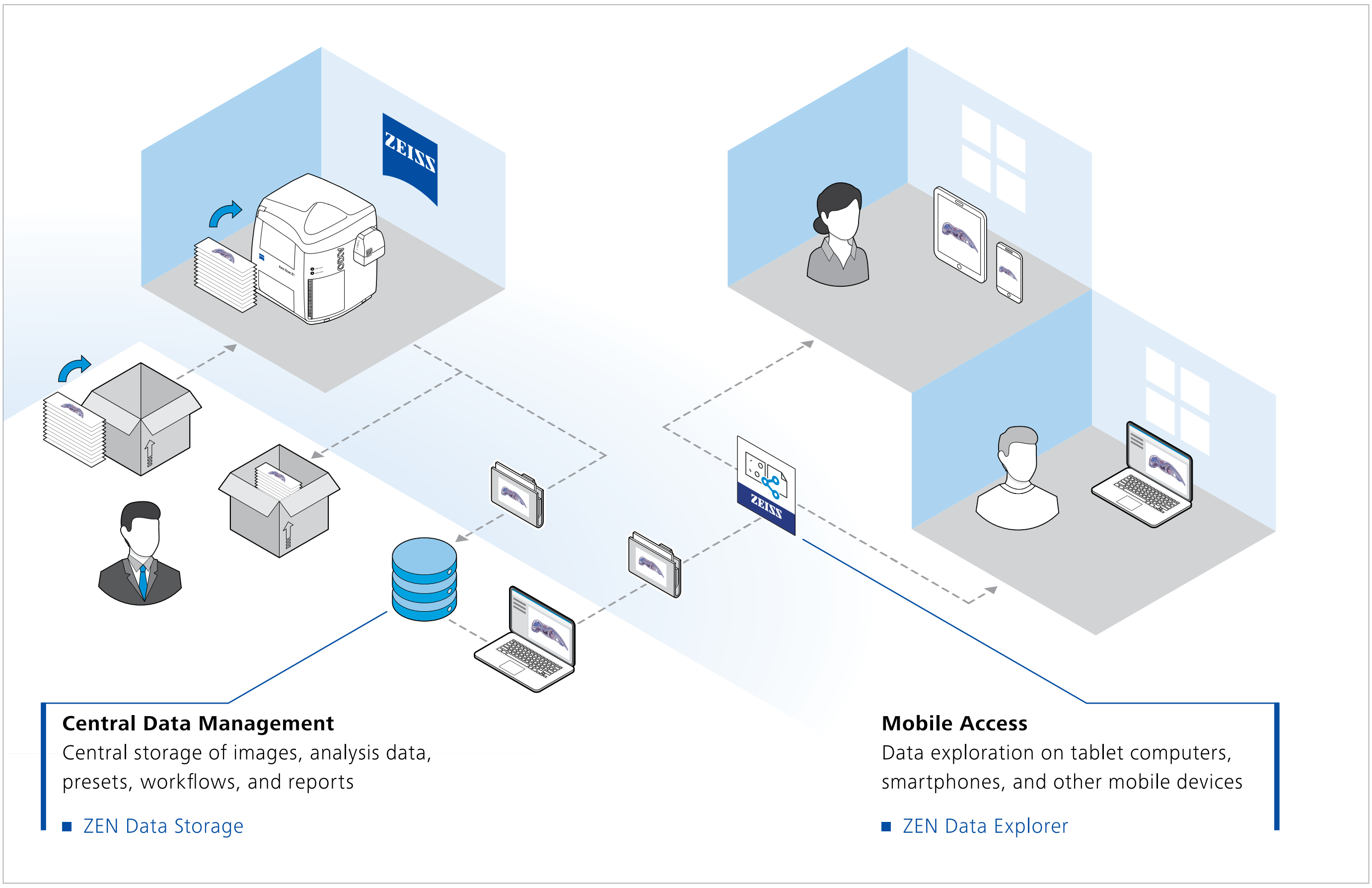

Figure 8 *With ZEISS Virtual Slide Box microscopy sample slides are digitally available to students. They can access all shared slides from home.*

Logged-in students can access the virtual microscope slides with their teaching con-tent at any time and from any location. This allows maximum flexibility in accessing the "virtual microscope" so that students can study the virtual course at their own pace and in their own time. E-Learning modules can contribute to the learning success of medical students both during the current semester and during exam preparation. As there is usually a direct assignment of teaching content to the structures visible in the virtual microscope, students will receive a description of the content in addition to the view of the digitized specimen. Using ZEISS ZEN Data Explorer software as a web browser and app for iOS and Android also allows the virtual image to be edited with annotations by the students who, for example, do measure-ments of cells, tissues and organs.

Figure 9 *All users of the multidiscussion system see the same image.*

High quality training in histology is only possible with high quality microscope images. ZEISS Axioscan 7 is the microscope of choice for digitizing specimens and creating high quality vir-tual microscope slides. Digitized images—also known as whole slide imaging (WSI)—make it possible to provide all students with standardized image material and equally rare specimens. Using high-resolution scans, it is possible to perform virtual microscopy. Students can navigate and zoom in on the scanned specimen. This provides an overview of the entire histological specimen, and individual cell structures can be enlarged. As digi-tal images generate large amounts of data, proper management is very important. In addition, access rights to the images must be correctly organized. ZEISS ZEN Data Storage is a future-proof solution for data management that is not tied to individual institute employees or individual software versions.

As numerous as the medical courses are, so too are the different microscopes used in anatomy teaching and medical training. They vary in terms of the technology used and the degree of digitization. Microscopes are also used in professional life and in lifelong training programs.

Online live teaching and learning
Under Covid-19 restrictions, school and university closures led to a re-evaluation of digital teaching and learning. In many places, teaching content was delivered via the Internet, with the use of tablets, smartphones and PCs as well as e-learning tools and online platforms. In online live teaching, educators and learners work together simultaneously and synchronously in a teaching call. This provides the opportunity for direct interactive communication. Online live teaching for remote learning is also possible in microscopy-based education and practical exercises on a microscope can make online lessons varied and lively. ZEISS enables live teaching online with camera-ready micro-scopes and Labscope, the educational soft-ware. Teachers establish a connection between their PC and the microscope's camera so that the microscopic image is visible on the PC or laptop screen. Via Skype, Zoom, Microsoft Teams or other platforms, this screen can be shared with the students in the call, enabling all participants to see the micro-scope image simultaneously.

The pointer function in the ZEISS Labscope app supports distance learning by drawing attention to important points in the sample shown and directing the learners' attention to the selected areas. With Labscope, microscope images can also be captured and sent to learners via email or online tools. After students receive the image, they can use the drawing function to make a digitally-supported hand drawing of the specimen or to do their measurements and annotations.

Face-to-face in-group experience
Face-to-face multi-discussion systems are useful for training future professionals and also for those times when direct consultation on the real slide is important.

In a group session, the important regions in the sample are highlighted with a pointer directly on site and can be examined in detail together. Direct discussion of the object between participants combines what is seen and heard to make a lively experience.

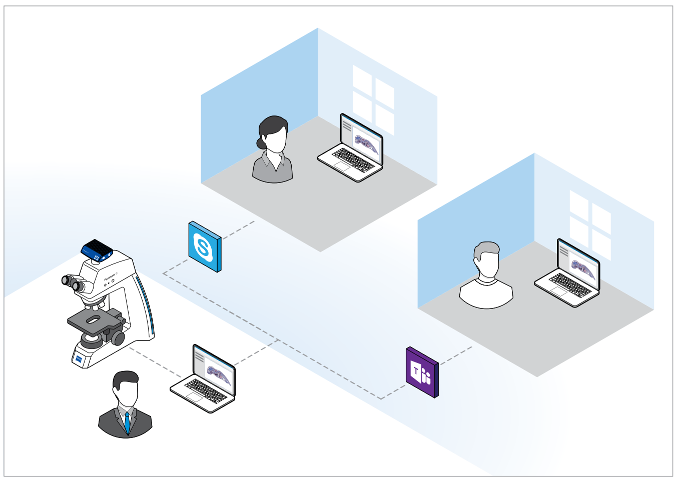

Figure 10 *One way of homeschooling, using ZEISS microscopes.*

In the teaching situation, patterning the specimen and controlling the pointer are done exclusively by the educator at the central element, ensuring that all participants focus on the same slide and the same region of interest.

Users of multidiscussion systems will see the direct image impression on the microscope: image distortions caused by different monitor qualities are eliminated. Since different stains are used in histology, it's important to have optimal visibility of the pointer on each specimen. That's why ZEISS multidiscussion systems allow the intensity and color of the pointer to be varied to white, green or red, depending on the specimen. These systems are often used for professionals in continuing education or in sessions with a limited number of participants. A small group size can make direct exchanges about the sample a very intensive experience. Particularly in everyday laboratory work and in pathology, the safe reading of slides is very important and training on a multidiscussion system can help achieve greater confidence in the assessment of histological sections.

Summary

Microscopy has provided a whole new perspective for understanding the structure of the body. As yet, the morphology of specimens can only be studied with microscopes. Microscopic anatomy is an important cornerstone in medical education. Histology aims to understand the structure and function of body tissue. Only in this way can structural changes in tissues, cells and organs be recognized and conclusions drawn about functional changes and their effects on human health. Training medical students in reading a slide prepares them for later professional life in practice or research.

For decades, hands-on work with microscopes during the histology course has enabled students to examine a tissue section haptically and thus train their eye and memory.

As microscope technology evolves, so too does its use in medical education. Digital transformation is enabling new ways of teaching and learning. The concept of the digital classroom aims to enable students to use their everyday digital devices in medical education as well. In this way, hands-on microscopy becomes a digital experience. At the same time, educators benefit from integrating more interactive forms of teaching into the histology course and promoting group discussions among peers.

Virtual education on digitized slides opens up the possibility of an individual learning experience since access to the virtual microscope is independent of place and time. Especially in exam preparation, additional e-learning modules can support self-study. However, blended learning with hands-on microscopy in combination with online learning elements is the gold standard right now. The hands-on experience with the fundamental knowledge about the use of an optical microscope prepares students of today for the challenges within their professional lives of tomorrow.

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