Chapter 1

General Introduction & Outline of the Dissertation

History

The term "autopsy" derives from the Greek words "autos" (self) and "opsis" (eye), meaning "to see with one's own eyes." It is a medical procedure with a long history.

Hippocrates (approximately 460 - 370 BC), a prominent figure in the establishment of Western medicine, played a pivotal role in the development of autopsies. Departing from earlier animistic and supernatural beliefs, he based his understanding of symptoms, diseases, and treatments on a morphological understanding of the natural substrate.

In Alexandria, about a century later, Herophilos (approximately 335 - 280 BC) and Erasistratos (304 - 250 BC) conducted the first autopsies. Despite prohibitions imposed by Church father Augustine (354 - 430), knowledge in the realm of pathological abnormalities continued to expand. The Byzantine physician Aëtius of Amida, author of the "Sixteen Books of Medicine", drew from writings in the library of Alexandria to describe the solid consistency of tumors and cachexia as clinical symptoms of uterine carcinoma.

By the 12th century, written references to autopsies emerged, and in 1209, Pope Innocentius III decreed that unexplained deaths should be further investigated by experienced physicians. Antonio Benivieni (1443 - 1502) was one of the first to underscore the importance of autopsies in determining the cause of illnesses. More than 150 years later, Théophile Bonnet (1620 - 1689) published the seminal work "Sepulchretum sive anatomia practica ex cadaveribus morbo denatis," which compiled a comprehensive collection of disease-related abnormalities known at that time.

Subsequent years witnessed an increase in autopsies and an improved understanding of disease mechanisms. Herman Boerhaave (1668 - 1738) in the Netherlands emphasized, among other things, the significance of comprehensive clinical histories, while Giovanni Battista Morgagni (1682 - 1771) in Italy solidified the acceptance of the connection between morphological organ abnormalities and diseases through his work "De Sedibus et Causis Morborum per Anatomen Indagatis." Maria Theresa (1717 – 1780), the sovereign of the Austro-Hungarian Empire, ascended to power during the mid-18th century. Under the influence of Gerard van Swieten, a long-time student of Herman Boerhaave, Maria Theresa signed a decree, mandating autopsies for every hospital death. Although the decree's strict adherence has waned over time, it theoretically is still in effect in Austria. It is conceivable that these practices influence the relatively high autopsy rate in nations previously affiliated with the Austro-Hungarian Empire.

Matthew Baillie (1761 - 1823) contributed to the field with "The Morbid Anatomy of Some of the Most Important Parts of the Human Body," expanding knowledge of macroscopic abnormalities. Concurrently, Marie Francois Xavier Bichat (1771 - 1802) discovered the existence of tissues within organs. Johannes Müller (1801 - 1858) in Berlin delved into the microscopic level of diseases, advancing the understanding that diseases could arise at the tissue level. Pathologist Carl von Rokitansky (1804 - 1878) integrated assessments of both macroscopic and microscopic abnormalities.

The refinement of autopsy procedures, standardization, and various dissection methods were further developed by Rudolf Ludwig Carl Virchow (1821 - 1902) and Francis Delafield (1841 - 1915). In subsequent years, autopsies continued to contribute significantly to the progression of medicine. It can be said that the foundational work of these individuals and others was indispensable for the development of Western medicine as we know it today. [1].

By performing autopsies and closely examining organs and tissues, pathologists have helped to identify and classify various diseases, establish diagnostic criteria and refine disease classification systems. Autopsies have provided indispensable deeper understanding into the underlying mechanisms of diseases, which in turn have helped to identify potential targets for intervention and development of new treatments. Even now, the autopsy is a great source to investigate tumor heterogeneity, and new diseases such as COVID-19 [2-6]. Autopsies have been instrumental in medical education and training by offering a unique opportunity for medical students and staff to enhance their understanding of anatomy, disease processes and clinical correlations through real-life cases [7]. Investigating real-life cases allows for verification of clinical diagnoses and treatment outcomes, helping to improve patient care via quality control [8, 9]. Furthermore, autopsies have contributed to epidemiological studies by providing valuable data on disease prevalence, incidence and risk factors. Finally, in the case of young patients, certain deaths may be attributed to an inherited genetic disorder, and understanding this information could provide valuable benefits to the deceased person's family members.

Laws and regulations

While international medical guidelines exist for classifying deaths, the laws and regulations surrounding death vary between countries.

In the Netherlands, when someone passes away from natural causes, the attending physician is responsible for completing the necessary death administration (Wet op de Lijkbezorging, Art. 7). This includes a form for the registrar of births, deaths, and marriages, as well as a form for the cause of death registry. A natural death is defined as a death resulting from an illness or occurring during properly conducted medical treatment. In hospitals, it is typically the attending physician who fills out the forms, while outside of the hospital, it is usually the family physician. If the attending physician is unavailable, the acting physician may complete the paperwork.

The death of an individual does not necessarily mark the end of medical care. While the deceased person cannot be helped any further, the impact of the death extends to loved ones, and there may be lessons to be learned. The clinical autopsy serves as the final and most comprehensive medical examination performed on a deceased person. It is not merely a favor to the next of kin; it is their right. Consent from the next of kin or the deceased is required to conduct this examination, which can be obtained verbally or in writing (Wet op de Lijkbezorging, Art. 72). The autopsy needs to be performed by a medical doctor (Wet op de Lijkbezorging, Art. 75). Next of kin may have to consider ethical, religious, and financial aspects when deciding on consent for performing an autopsy. Hospitals typically have a budget allocated for autopsies, but if the body needs to be transported to the hospital, the costs are often borne by the next of kin. After all, health insurance coverage ceases upon death in the Netherlands, including reimbursement for postmortem medical procedures.

In the past, certain clinics and training programs used to adhere to a minimum autopsy rate as a quality criterion. However, this requirement has gradually diminished in some clinics. Nonetheless, several hospitals in the Netherlands recognize the significance of conducting a "death review," whether or not it includes autopsy findings, as a quality measure. For instance, at Maastricht University Medical Center+, a Committee on the Investigation of Deceased Persons (Commissie Onderzoek Overleden Patientën, COOP) reviews all deaths. Additionally, open publication of standardized hospital death rates, known as the Hospital Standardized Mortality Ratio (HSMR), promotes transparency and quality control.

Non-natural cause of death

If the attending physician in the Netherlands has doubts about a natural death, they should promptly contact a forensic physician. The forensic doctor will then arrive at the scene to personally examine the body. In cases of deaths occurring outside of healthcare facilities, tactical investigators and forensic specialists typically aid in the investigation. All non-natural deaths are discussed with the prosecutor, although further investigations are usually initiated only if there is evidence of a criminal offense, and occasionally if a realistic criminal scenario can not be excluded. One such follow-up investigation is a forensic autopsy (Wet op de Lijkbezorging, Art. 73).

A forensic autopsy necessitates the expertise of a forensic pathologist, as clinical pathologists are typically not trained to investigate non-natural causes of death. In addition to determining the cause of death, a forensic pathologist is involved in securing forensic evidence and interpret findings to answer forensic relevant questions. In the Netherlands, a forensic autopsy employs similar techniques to its clinical counterpart but also includes the examination of additional body parts, such as the neck. Furthermore, forensic pathologists commonly utilize postmortem imaging techniques and toxicology analysis.

Although this dissertation primarily focuses on clinical autopsies, some insights can be applied within a forensic context.

The autopsy procedure

During a clinical autopsy, the procedures and techniques may vary depending on guidelines and preferences. In the Netherlands, a complete clinical autopsy typically involves the following steps:

1. External Inspection: After a minor external inspection, the body is prepared for further examination.

2. Incision: A large Y-shaped incision is made, running from the shoulders to the base of the sternum and continuing across the midline to the pubic bone. The location for this incision ensures it is not visible during burial, unlike some other countries where the incision is made from the symphysis up to the chin. Next, the skin and muscles are peeled back to expose the underlying organs.

3. Dissection Techniques: There are several dissection techniques used, depending on the pathologist's preference and the case at hand:
   a. Virchow's Technique: This technique involves removing each organ separately from the body for individual examination.
   b. Ghon's Technique: The organs are removed in three "blocks" - the thoracic, abdominal, and cervical block.
   c. Letulle's Technique: All organs are removed as a single block.
   d. Rokitansky's Technique: This technique involves assessing the organs in situ without their removal. It is less commonly used but may be advantageous for cases involving infectious agents.

4. Organ Examination: The pathologist examines each organ individually, noting their size, color, texture, and any abnormalities.

5. Histopathological examination: In the Netherlands, it is standard practice to take small tissue fragments from most abdominal and thoracic organs for histopathological analysis. These tissue samples are processed, embedded in paraffin blocks, thinly sliced into sections, and stained for microscopic examination. The pathologist examines these slides under a microscope to identify cellular changes, diseases, or other microscopic abnormalities.

6. Additional Investigations: During the autopsy, other tissues and fluids may be collected for additional microbiological, genetic, or cytological investigations. This allows for a comprehensive investigation of the deceased individual. In the Netherlands, it is common procedure to ask relatives for additional consent to examine the skull and the brains.

7. Organ Replacement: At the end of the autopsy, the organs are returned to the body as much as possible. However, in certain cases, organs may need further processing, evaluation by an expert, or preservation for educational purposes. The goal is to keep the number and duration of organ removal to a minimum, respecting the wishes of the next of kin. Lastly the body is carefully closed.

8. Documentation and Report: Throughout the autopsy process, the pathologist meticulously documents their findings, observations, measurements, and test results. They compile this information into a detailed report, which includes the cause of death, contributing factors, and any significant findings. The attending physician

receives the report and discusses the results with the family members.

Discrepancies between clinical diagnosis and autopsy results

As discussed before, autopsies allow for verification of clinical diagnoses and treatment outcomes, helping to improve patient care via quality control. Goldman et al. have been important pioneers, showing major discrepancies (Class I and II) between the clinical cause of death and the autopsies results in multiple eras from 1960 [10]. According to Goldman, Class I discrepancies refer to diagnostic errors that could have altered clinical management and potentially resulted in longer patient survival, whereas Class II discrepancies would not have influenced the treatment and survival. His results have been reproduced throughout the last 35 years in various settings [11-19], but with similar results: despite medical advances, important discrepancies between clinical diagnosis and the autopsy remain. These discrepancies were investigated in the Netherlands up to 2013 [20].

Decline of autopsies

The autopsy rate in the Netherlands is exceptionally low, even compared to other European countries experiencing a decline [21]. Worldwide there has been a decline of the autopsy rate [22-27]. The reason for this declining autopsy rate is probably multifactorial [28-31].

Firstly, the decision-making process involving the attending physician and the next of kin is crucial [32]. A study in the Netherlands showed that for physicians in 51.5% of cases, the decision not to request an autopsy was based on the conviction that the cause of death was already known [33]. Similarly, this was the most common reason (51.0%) cited by next of kin for not granting consent. Another significant factor for both physicians and next of kin was the perception that the deceased had a lengthy history of illness (9.6% and 29.5% respectively). Contrary to popular belief, the fear of mutilation of the body was not the primary reason for avoiding autopsies. Religious objections are also often not insurmountable, as neither the Koran nor the Bible explicitly forbid autopsies [34]. In practice, obtaining consent from next of kin for an autopsy, when sensitively explained by a caring doctor, generally presents few difficulties [35].

Secondly, the role of the pathologist, who carries out the autopsy, is essential. The outdated notion of pathologists working in the hospital basement is far from reality. Pathology

encompasses the scientific study of diseases, their causes, processes, and effects, focusing on understanding disease origins and potential treatments. Dutch clinical pathologists in general allocate less than 1% of their time to performing autopsies. Instead, they fulfill a vital and active role in diagnosing diseases and providing essential information for possible treatment. This involves the meticulous examination of tissues (organs, excisions, biopsies, fluids) through macroscopic and microscopic assessments, as well as conducting additional investigations such as (immuno)histochemical staining, immunofluorescence, electron microscopy, and molecular diagnostics. Although their work is often unseen by patients, pathologists regularly engage with physicians in various settings, including Multidisciplinary Meetings, where their presence is a training requirement for some medical specialties. It is worth noting that within the field of pathology, there are several subspecialties like hematopathology and dermatopathology, but autopsy pathology is not currently one of them. Consequently, it is highly likely that within a pathology department, there are few or no pathologists who possess a strong passion for and experience in performing autopsies. Furthermore, with the declining number of autopsies and an increasing workload in other areas, conducting an autopsy often becomes an additional task on top of their daily diagnostic responsibilities. As a result, long turnaround times occur, which can diminish the clinic's interest and learning opportunities, ultimately leading to a downward trend. This cycle results in pathologists being unable to provide adequate support to practitioners due to limited resources and a shift in focus, which in turn reduces the likelihood of autopsy requests from practitioners [36].

Financial aspects may further support the decline in autopsies. Since health insurance coverage ends upon a person's death, there is no reimbursement available for autopsies, as they are performed after death. Instead, autopsies are regarded as a service provided by the hospital to the deceased person's next of kin. In practical terms, hospitals allocate a budget from which the pathology department receives reimbursement for conducting autopsies. From a direct financial standpoint, hospitals have limited motivation to actively encourage or prioritize autopsies. Furthermore, the overall cost of performing an autopsy, excluding facility maintenance and site expenses, surpasses the reimbursement received from the hospital by the pathology department, which typically amounts to several hundred euros. Consequently, the pathology department also lacks financial incentives to promote autopsies. Note, however, that the above reasoning fails to acknowledge the significant value that postmortem examinations may bring to the overall quality of healthcare.

Another factor contributing to the lower autopsy rates compared to neighboring

countries is the consent regulations. As described before, an old law allowing autopsies to be conducted on any deceased individual in a hospital without requiring consent from the next of kin may have resulted in higher autopsy rates in Austria, Hungary, the Czech Republic, and parts of Poland.

Some decline in autopsy rates may be due to the emergence of postmortem imaging techniques. Postmortem imaging techniques provide a non-invasive investigation, which can easily be reassessed. Among the various techniques explored [37-52], post mortem coronary tomography (PMCT) has shown particular promise due to its cost-effectiveness, efficiency, and widespread availability in modern hospitals [53-56]. The addition of contrast agents may further increase the effectiveness of PMCT. However, it is important to note that many publications on this topic primarily focus on forensic cases, which may limit their applicability to clinical cases [57-77]. In forensic settings, PMCT is commonly utilized to investigate bone abnormalities (e.g. fractures), abnormal air configurations (e.g. pneumothorax), and the presence of foreign objects (e.g. bullets). A large systematic review and meta-analysis concludes that distinct postmortem imaging modalities can achieve high sensitivities for detecting various findings and causes of death, which should lead to a reasoned use of each modality [78].

The final possible reason for the decrease in autopsies relates to the lack of education about autopsies in basic medical training and continuing medical education. Each year, numerous newly graduated physicians complete their training without ever having witnessed an autopsy. In many cases, they have never even had any contact with the pathology department. Subsequently, their training usually pays little to no attention to autopsies and their value. Consequently, these physicians are expected to engage in a procedure that they are unfamiliar with in terms of both the procedure itself and its significance. The significance of autopsies in modern medicine can only be truly appreciated by ensuring that the next generation of doctors have the opportunity to personally experience the valuable educational benefits of examining the body after death [79].

Aim and outline

The primary objective of this dissertation was to enhance our understanding of the value, the current state and potential future of the clinical autopsy. To accomplish this task, we aimed to understand the factors influencing the autopsy rate, the added value of medical

autopsy as well as novel methods.

The study in **Chapter 2** addresses the development of the autopsy rate in the Netherlands over a span of 25 years in different age categories and by sex. In this study, data was used from the nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA), along with death statistics provided by Statistics Netherlands (CBS). We investigated the overall autopsy rate, as well as the influence of sex and age on the autopsy rate.

The study in **Chapter 3** was conducted to delve deeper into factors influencing the autopsy rate. The relation between the clinical cause of death, a diagnosis of cancer and the autopsy rate, within an elderly population, will be presented utilizing a large cohort study (NLCS).

Chapter 4 aims to investigate whether the decrease in autopsy rates can be attributed to the diminishing relevance of autopsies due to improved medical care, focusing on the occurrence of major discrepancies between clinical diagnoses and autopsy findings, using the Goldman criteria. It will be demonstrated that Class I discrepancies have not decreased, despite technological advancements.

The study in **Chapter 5** aims to determine the proportion of discrepancies in clinical diagnoses and postmortem findings in a specific patient population: patients with sepsis and septic shock who died within 48 h after admission to the Intensive Care Unit (ICU).

As post-mortem computed tomography (PMCT) offers a non-invasive method to examine a deceased, it might overcome reluctance of next of kin to give consent for post-mortem examination. Therefore, it might be a solution for the declining autopsy rate. On the other hand, it might even further decrease the need for an autopsy. To investigate whether new modalities such as PMCT enhance the number of significant clinical findings, the study in **Chapter 6** was conducted.

The effectiveness of PMCT determining the cause of death in a clinical population was addressed in **Chapter 7**. Both chapter 6 and 7 highlight the possibilities, as well as the limitations, of PMCT when compared to the autopsy.

By incorporating histological examination to PMCT through needle sampling, a potential limitation of PMCT to autopsy may be negated. Therefore, in **Chapter 8** the sensitivity and specificity of needle sampling, when compared to autopsy derived tissue, was investigated.

Lastly, in an effort to enhance the overall quality of medical autopsies, **Chapter 9** proposes

international guidelines put forth by the autopsy working group of the European Society of Pathology. Only by looking at ourselves, we may be able to revive the medical autopsy.

Chapter 10 summarizes our main findings in the general discussion. It explores future perspectives and discusses the impact of this dissertation on medical and forensic science, healthcare and the society.

Lost in Time

"Lost in time" generally refers to something or someone that has been forgotten or disconnected from the present, often implying a sense of irretrievability, fading relevance or disconnection from the current context.

"Lost in time" may refer to people, customs, events, or ideas that were once significant but have been disregarded or no longer hold significance in the present day. To describe something as "Lost in time" suggests that it has faded from memory or relevance over the years, becoming obscured or overlooked. Underlying causes may be the passage of time, changing societal values, or shifts in cultural norms.

The phrase "Lost in time" can evoke a sense of yearning for what once was, nostalgia even, as if something valuable has been abandoned.

Do autopsies belong to a bygone era, lost in time? Have they gradually diminished in relevance, been overlooked, and forgotten? Are our societal values and cultural norms shifting, rendering the autopsy a relic of the past? Over the years, a number of publications have portrayed the decline of autopsies while underscoring their enduring significance. Are these authors driven by nostalgia, or do their arguments hold some truth? And if indeed true, does our society still place importance on this?

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