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Scale in the history of medicine

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A R T I C L E   I N F O

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A B S T R A C T

This is a history of medicine that takes its point of departure in the specimens of human bodily material used to produce medical knowledge. An ordering principle of scale prompts a material and epistemic history of 18th-21st century medicine that highlights shifts in interest towards smaller and smaller units of study: from organs in pathological collections, over microscope slides, to samples in biobanks. The account reveals a set of connected scales of the site of disease, time of diagnosis, size of cohorts, number of disease categories, and technologies of investigation. Moreover, the principle of following the scale of specimens demonstrates the continued importance of physical specimens in medicine, it synthesizes studies of important epistemic objects of medicine such as the organ specimen, the microscope slide and the blood sample, and it draws new historical connections from pathological collections to biobanks.

1. Introduction

This history of medicine takes its point of departure in the matter of medicine. More specifically it offers a history of the specimens of human bodily material collected to produce medical knowledge. Medical doctors, teachers and researchers have, especially from the 18th century and onwards, preserved and investigated collections of human material: preparations of embryos and organs, microscope slides, cell and blood samples. These collections constitute material and epistemic traces of the development of medical knowledge. The present account will follow the specimens and use the principle of scale to synthesize the ways they have been investigated and collected into a history of medicine that ties together different sites and periods across medical history and establishes new connections.

The principle is deceptively simple: to organize a medical historical account according to the size of specimens. Ordering specimens according to a scale, it becomes clear that such an organization establishes a kind of material chronology that follows the body parts that enjoyed the lion’s share of attention. The scale takes its starting point in whole bodies dissected in anatomical theatres. It continues with preserved organs and slices of tissue in anatomical and pathological collections. And it ends with samples of blood for molecular analysis kept in biobanks. The scale thus highlights a history moving towards smaller and smaller basic units of disease from humoral imbalances in the whole body to lesions in organs, lesions in cells, and molecular variations.

This is relatively well-charted territory in the history of medicine. As we shall see, however, ordering specimens on a size-scale brings out an additional set of interconnected scales in medical science and practice. A scale of time emerges from the moment when a disease can be diagnosed on the basis of a specimen as this comes earlier and earlier relative to death: from ascertaining the final diagnosis at the autopsy table to detecting a disease risk in a blood sample from a newborn. Another set of scales materialises in the increasing numbers of specimens from still bigger cohorts of patients used to establish more and more refined categorisations of disease. And last, the technologies employed to investigate specimens increase in size and become more deeply integrated with the specimens.

The principle of a scale of specimens was first developed as a concept for the research-based exhibition The Body Collected at Medical Museion (see Fig. 1), which focused on the specimens of human bodily material used to generate medical knowledge (Tybjerg 2015, 2016, 2019). The scalar organization worked well for this context because the historical account emerged from the objects themselves rather than being imposed on them. The exhibition principle was also generative for the history of medicine, which is the concern of the present paper. The scale, for instance, brought out connections between 19th century pathological collections and modern biobanks, it demonstrated the importance of
specimens in modern biomedicine, and it materialized ongoing connections between collections, hospitals and laboratories.

With its interest in specimens and their connections to medical knowledge, the present account draws on the work of the philosopher of science Hans-Jörg Rheinberger, who investigated the nexus between the material practices and the epistemic history of medicine and science (Rheinberger 1997, 2010; see also Landecker, 2018). In an article on specimens (or preparations as he denotes them), he points out that the material objects of study have often been sidelined in studies of medical and biological knowledge. “(The) things around which the knowledge process unfolds”, he writes, “were relegated to the margins of history. Yet they play a decisive role in the development of knowledge” (Rheinberger, 2010, p. 233). In the following, I redress their relegation by shifting specimens to the centre of history. I present an epistemic and materially informed history of medicine that strings together several important studies of how specimens shaped medical knowledge as they were excised, prepared, stained, stored and categorized in museums, hospitals, labs and biobanks, and how medical knowledge shaped them in turn. All these periods and practices are brought together by the scalar organization of specimens to form a connected history and to extend Rheinberger’s historical epistemology across a longer historical timespan.

The scalar organization of the history of medicine echoes important insights from Nicholas Jewson’s classic article, “The disappearance of the Sick Man in Medical Cosmology 1770–1870” (1976), which traces social, medical and institutional setups surrounding the patient in successive historical periods. Jewson was primarily interested in changes in the social role of the patient, but he also noted changes in the size of the body parts under investigation, in research methods, in diagnostic techniques, and in forms of therapy (Jewson, 1976, p. 228). It is the body parts, methods and diagnostic techniques that I will shift to the centre, as my primary focus will be on the specimens and their uses. I thus provide a re-reading of Jewson’s article that adds further dimensions and scalar developments in sample size and timing of diagnosis. Where Jewson claims that the patient disappears from the medical horizon in favour of the scientific object, the present account argues that specimens maintain a central role and that they connect the patient, scientific object and technology all the way up to 21st century medicine.

As with every new perspective, the scale of specimens brings both novel insights and new blind spots. It is therefore not intended to replace other histories of medicine. Rather it should be seen as a way to synthesize accounts of specimens from different periods, and to focus on the human bodily material that has not often held centre stage in medical histories. As a consequence, it offers less insight on institutional and professional contexts and on the social history of the disadvantaged, whose bodies were used for specimens against their will.3 Moreover, it sacrifices sensitivity to the particulars of local practices as it moves across hundreds of years. At the same time, it is limited to western medicine and draws mainly on Danish material; the latter parochial choice, however paradoxically helps it concentrate on mainstream medical practice as staying on the periphery side-steps squabbles of national priority.

Summing up, the account presents an epistemic and material history of the last two and a half centuries’ medical knowledge organized according to the sizes of the human specimens. In what follows, it will, in section 2, elaborate the concept of scale, before retelling well-known episodes from the history of medicine centred on the whole body, organs, tissue and molecules. The central argument of the paper in section 3 shows how this new focus reveals several interrelated scales: in the focus on preparing and collecting anatomical and pathological specimens in the 17th to 19th centuries see Alberti, 2011; Knoeff, 2015; Knoeff & Zweijnenberg, 2015; Sturdy, 2006. On investigations of cells and tissue, see Hoeyer, 2010; Landecker, 2010; Löwy, 2010; Löwy, 2013; Close-Koenig, 2013. On blood samples, see Radin, 2017; Bangham, 2020. In addition, some studies trace the preparation and use of specimens in particular collections over longer periods, e.g. Hallam, 2016; Erslev, 2019.

3 The turn towards social history or “history from below” in the 1980’s (Fissell, 2004; Porter, 1985), brought attention to the disadvantaged whose bodies were turned into specimens. From the criminal and poor in the 19th century (Richardson, 1987; MacDonald, 2006) to disadvantaged or misinformed patients in the 20th and 21st century whose bodily material was commodified (Sharp, 2000; Skloot, 2010; Prainsack, 2017). This account views the specimens more from the medical point of view, which has received less attention with the turn to social medicine (Warner, 1995).
of disease, the timing of diagnosis, categories, cohorts and technologies. And last, section 4 will outline how the scalar history establishes material and epistemic connections across the history of medicine and creates new lines of sight.

In conclusion, ordering specimens according to scale appears simple, but under the cover of apparent simplicity, it allows connections to emerge between understandings of disease, diagnostics, collections, technologies, institutions, doctors and patients, and these are all traceable through the excised pieces of human bodies. The history of the collections of human specimens, from large to small e.g. also reveals the slow nature of the development of medical knowledge, which is often obscured by a focus on new theories and discoveries.

2. A scale of specimens and disease

Scale has not been used as a historical organizing principle before, but the development towards smaller and smaller units of disease has not gone unnoticed by historians of medicine. Their concern has, however, mainly been with the pioneering efforts to introduce new levels of the body to medical research. Porter offers, for instance, this list of medical first-movers: “Morgagni had highlighted the organ, Bichat the tissue; Virchow had now given pride of the place to the cell”. Bynum extends the scale further noting that “[the] basic unit of medical understanding of disease had become steadily more refined” and listing Morgagni, Bichat, sub-cellular structures and molecules (Bynum, 2008, p. 93; Porter, 1997, p. 331).

I recount, in the following, the same historical developments, but my focus on larger collections of specimens shifts the chronology, because the mainstream medical understanding than of scientific discoveries. Focusing on the rise of molecular biology in the 1930’s and 1950’s, I include the widespread use of slides for categorizing and diagnosing disease in the 20th century. And instead of focusing on the rise of molecular biology in the 1930’s and 1950’s, I extend molecular and genetic understandings into the second half of the 20th and early 21st centuries and see them embodied in the blood samples in biobanks. The scale is thus extended chronologically onwards from the first explorations of a level and includes that level’s integration into medical knowledge and the establishment of larger specimen collections. The size of the specimens most avidly collected in a given period reflects, I argue, an understanding of disease that is turning mainstream. The resource and time-consuming nature of amassing larger collections means that they require institutional support and a broad acceptance of the importance of a particular understanding of disease. The large collections are thus created when specimens at a given level are seen as constitutive of disease, and the collections begin to act as a reference for diagnosing disease and teaching rather than more exclusively as a research resource for exploring disease at a new level. This is therefore more a history of mainstream medical understanding than of scientific discoveries.

At this point, it should be noted that ideas of scale have been implicit in earlier histories of science and medicine with a reductionist slant. Technological capacity to investigate smaller and smaller constituents of the body has, for instance, been seen as a driver of scientific discovery and progress (e.g. Turner, 1967), and more generally the ambition to examine the smallest structure possible has been an important strand in narratives about the Western medical tradition (e.g. Cook, 2006). In addition, reductionist notions that a particular level of the body is privileged are also mirrored in oft-made claims by doctors and scientists that a given level is at the root or is elemental for understanding disease. The present account recognizes the close relation between a history of scale and reductionist accounts, but it is concerned with connecting the different levels, rather than privileging a given level or indicating that disease can be successfully reduced to its smallest constituents.

Relatedly, it is worth emphasizing that the steps on the scale should not be thought of as exclusive. As is highlighted by criticisms of reductionist accounts, the whole body is always present in clinical medicine (e.g. Tracy, 1992; Rosenberg, 2007). Different levels of scale overlap each other and previous levels do not disappear from the medical horizon. They are simply integrated in medical practice. Pathological slides are, for instance, still central in current diagnostics, and lesions in organs are important in surgical treatment and diagnostics with medical imaging. The most newly discovered level in the understanding of disease is, however, at any given time, often seen as the most fundamental level and receives most interest in research, funding, collecting and new treatments in the clinic. To take the example of today’s medical practice, medical collection mania is now centred on samples for biochemical and molecular research, and in the clinic doctors are making early attempts to employ genome-wide testing and precision medicine to decide treatments. But contemporary medicine does not conceptualise disease exclusively in molecular terms.

Having thus calibrated, extended and qualified the scale, I will move to the history of investigating whole bodies, organs, tissue, and blood samples. As stated, my errand is not to challenge the main narratives of these oft-told episodes of history of medicine, but rather to shift the accent towards specimens, extend the periods and indicate how further scales emerge.

2.1. Whole bodies

The whole body is not a level or unit in the same sense as organs or tissue, but is here included more as a point of reference. In the 17th and 18th centuries, medical thinking about disease was dominated by humoral theory, which related disease to imbalances in the bodily fluids – blood, phlegm, black and yellow bile. The fluids were part of a whole body system and while disease could be caused by a local build-up of fluid, the understanding of disease revolved around the body as a whole. In his sociological account of the history of medicine, Jewson related the understanding of disease as individual humoral balances to the clinical encounter with the patient at its center and denoted it “bedside medicine” (1976). Disease was here defined by the symptoms experienced by the patient and the diagnosis depended equally on the patient’s account of their physical and emotional state and on the doctor’s observations. This meant that diagnoses, to a certain extent, were designed on a case-by-case basis, and the patient, the epiphon of a whole body, was the clinical and pathological unit (Duden, 1991, provides striking examples of diagnoses from an 18th century doctor).

Turning to the bodily material, the anatomical investigations of the period likewise dealt with whole bodies in anatomical theatres such as the Danish Theatrum anatomico (1645), later Theatrum anatomico-chirurgicum, (1736), where dissections were performed for research and teaching (Koch, 1988). It is also the whole dissected body that is presented in drawings and models, where the overall integrity of the body is maintained as layers are gradually peeled away to reveal the insides, and where the coherence is highlighted by showing connectors such as sinews and vessels clearly. Indeed anatomists of the period showed particular interest in tracing the liquid connections inside the body such as the tear canals, vascular and lymphatic systems as well as the nervous system. Nicolaus Steno (1638–1686), for instance, investigated tear canals and lymph nodes in the ear, and when he dissected, he often boiled the body parts to make it easier to separate them into their

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4 Scale has also played a role in other fields. Historians have used it in a different sense to differentiate scopes of history such as micro- or macrosistory or local, national or global history (e.g. Manning, 2003). Geographers unsurprisingly use it for geographical scales on maps, but have furthermore theorized extensively on the concept of scale and applied it to social organization (e.g. Gregory et al., 2009). And philosophers of biology and physics have been interested in the relationships between different levels of scale and whether or not there is a hierarchy between them (e.g. Hendry, 2021; Thalos, 2013).
natural layers (Bastholm, 1968). In Honoré Fragonard’s (1732–1799) work, the layers are themselves fixed as his macerated, flayed bodies reveal their insides while maintaining the outline of the whole body (Rheinberger, 2010, p. 236). 5

Although practitioners themselves often contrasted humoral theory and dissection-based anatomical mapping, the two approaches overlapped in their concern with fluids and connections in the body. This is also manifested in the earliest preserved human specimens. Here, fluid connections were revealed by the celebrated method of the period – injections of coloured wax or mercury into vessels of the body – which highlighted, for instance, the intricate vascular networks in the placenta or the filigree of veins and arteries in the face (see Fig. 2). One of the earliest makers and collectors of specimens, the Dutch anatomist Frederik Ruysch (1638–1731), was particularly famed for his injection technique. With enormous skill, he prepared a child’s face to look alive with fresh rosy cheeks by injecting colour into the tiny vessels in the skin (Knoeff, 2015).

![Fig. 2. Head injected with wax to display blood vessels. The head has maintained facial characteristics such as eye lashes that relates it to a whole body (photo: Medical Museion and Morten Skovgaard).](image)

5 Particularly in the anatomical tradition models and atlases played important roles in mediating anatomical knowledge (see e.g. Alberti, 2011; Berkowitz, 2011; Hallam, 2016; Maerker, 2011). Both models and displays are, however, downplayed in this account which focuses on generating and applying medical knowledge rather than teaching or displaying it.
from another person. Diseases thus physically and conceptually became independent entities whose reality was conceived beyond their existence in the patients suffering from the diseases (Rosenberg, 2002). The fact that the specimens came to embody diseases also meant that the understanding of diseases in the 19th century was defined by the state of the disease at death.

When the specimen was separated from the body, it was inserted into another context. It became part of the landscape of pathology mapped out by the collection. Here it was placed in the vicinity of other diseases in the same organ or system, such as the brain or the nervous system, or next to similar diseases in other organs, such as inflammations or infections. In categorizing specimens, the pathological collections produced a form of natural history of diseases and as natural history collections divided specimens of plants and animals into categories, so the pathological collection treated diseases as species with their own reality and organization. Related ways of organizing diseases had started earlier, and eg Carl von Linné, who is mainly famous for his botanical taxonomies, created a categorization system for diseases (Linné, 1765). His system was mainly based on symptoms, but as the pathological collections became more and more based on lesions in the course of the 19th century. Registries of causes of death were also based on autopsies of the deceased. Thus both with regard to disease categories and medical practice, the final diagnosis was ascertained at death (see also 3.1).

Collections grew steadily in the course of the 19th century allowing more fine-grained differentiation and they reached their maximum size in the early 20th century with the advent of formalin – a cheap and efficient liquid of preservation. At that time, the space allocated at the University of Copenhagen to the anatomical-pathological collections doubled. The pathological collections embodied settled knowledge and were used for teaching and reference. This usage is seen in the an image from surgical teaching at the Frederik's hospital in Copenhagen in the late 19th century, where specimens are brought into the hospital setting and are lined up alongside the patient to show what might be found inside. The collections went from categorizing lesions found in the clinic to materializing fixed and agreed pathological categories that could be applied in the clinic. The epistemic flow had turned.

Summing up, medicine at the organ level identified disease with the lesions found in organs and body parts, and the final diagnosis took place post-mortem. When the organ with the lesion was excised, prepared and displayed, it was organized and categorized in still larger pathological collections differentiating still more forms of disease.

2.3. Tissue, cells and microscope slides

The use of microscopes and the preparation of tissue on slides extended understanding of disease to a new level of the scale at the end of the 19th century. Histology and histopathology, the investigation of disease in cells and tissue, had begun already in the early 19th century, but gained momentum from the middle of the century with calls to move beyond observing the gross lesion in the organ. The microscope allowed investigation of “elementary parts” or “elementary components” of the lesions (Hannover, 1843, pp. 2–3, and Williams, 1843, p. 424, quoted from Reiser, 1978, p. 77), and with such language its early proponents made claims to a foundational nature for the cellular level. Moreover, microscopy offered, according to Danish doctor and microscopist Adolph Hannover, a finer differentiation between diseases than macroscopic lesions could distinguish (1843).6 Cells thus became an acknowledged part of describing disease, as was illustrated (literally) by adding images of diseased cells to pathological atlases, which previously featured just lesions in organs (e.g. Lebert, 1857–1861; described in Loison, 2016, pp. 279–285). A systematic basis for the study of disease at the cellular level came with the German doctor and pathologist Rudolph Virchow's Cellular Pathology (Virchow, 1858), where he advocated that disease could be understood as disturbances in the body's cellular structures. This new focus did not, however, make Virchow's enormous collection of specimens of organs obsolete. The gross pathological collections still formed the backbone of received medical knowledge, but it was advanced, extended and differentiated by investigations at the cellular level.

Not until the very end of the 19th century did histopathology gain real clinical importance, but then, for certain diseases, particularly cancer, it became the primary way of understanding disease. And over the course of the 20th century, slides took over from gross specimens as the predominant specimen for representing pathology. Vast collections of slides were amassed alongside the gross pathological collections, and the many shelf meters of boxes with slides demonstrate the ongoing importance of physical specimens – only smaller ones. As was the case with gross lesions outlined above (2.2), histopathologists correlated their observations with clinical information and new sub-diagnoses were categorized, differentiated and understood on the basis of slides (Löwy, 2013, p. 312) (Fig. 4). Pathologists maintained the terminology of lesions, but by the 20th century the term referred mainly to histological lesions.

The shift from understanding disease at organ level to detecting it at cellular level in practice is vividly traced in Ilana Löwy's account of changes in the evaluation of breast cancer in the early 20th century (2010). In the late 19th century, it was the surgeon who made the call regarding the degree of malignancy of a tumour using sight, touch and texture to the knife, while the role of the pathologist was to ascertain the cause of death at autopsy. In the early 20th century, however, pathologists began to investigate tissue during or straight after operations to decide whether or not to operate further. Malignancy of cancers thus went from being judged by surgeons on the basis of the gross lesion in

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6 Hannover’s What is Cancer? (1843) was submitted for a chair in pathology, but failed to secure him the position. Microscopic pathology was perhaps not mainstream enough for a chair.
the organ, to being judged by pathologists at the cellular level. Pathologists thus diagnosed not just the dead, but also the living. Biopsies – a term coined in 1879 – significantly means “sights of life” and they became a mainstay for understanding and diagnosing disease in the 20th century.

It required specialized material and technical work to investigate tissue as it needed to be fixed, thinly sliced and stained to be visible and revealing. An incredible palette of stains and staining techniques helped pick out structures that characterized and differentiated disease at the cellular level. The central importance of technique was also emphasized by the detailed descriptions of techniques in articles and treatises describing new finds in cellular pathology. These techniques, however, did not just render the disease visible, they simultaneously fixed a particular scale as primary for understanding disease.

Summing up, the use of the microscope slowly relocated the site of disease to the cellular level, and pathological collections shifted from gross specimens to slides although the collections existed side by side for almost a century. As the 20th century progressed, both understanding of disease and clinical practice relied increasingly on investigations at the cellular level, and the smallness of the samples taken meant that more patients could be compared and a conclusive diagnosis based on bodily material could be reached while the patient was alive.

2.4. Blood samples, biomarkers and biobanks

In the 20th and 21st centuries, medical attention turned again to smaller parts of the body – this time biochemical, molecular and microbiological markers. Interest in the molecular level was in evidence already in the 20th century with molecular analysis of vitamins, blood products and hormones (de Chadarevian & Kamminga, 1998). Molecules were also made relevant for understanding pathology, and scientists expressed the connections between the molecular level and organs and tissues by for, instance, denoting haemoglobin a “molecular lung” and pathological changes “molecular lesions” (Strasser & Fantini, 1998). Meanwhile chemical and bacteriological analysis allowed extensive diagnostics on the basis of blood samples, and in the 1930’s and 1940’s collecting at this level took off. The Danish centre for disease control (Statsen Serum Institut, SSI), for instance, built up reference collections for typing salmonella and pneumococcae (SSI, 2021).

The importance of the molecular approach to understanding life and disease increased further after the discovery of the structure of DNA in 1953 and reached a culmination with The Human Genome Project (HGP) at the turn of the millennium (Fox Keller, 2000; Reardon, 2017). Three years before its completion in 2003, President Clinton expressed the vision of the project clearly. He proclaimed that “(...) today we are learning the language in which God created life” and further stated that “in coming years, doctors increasingly will be able to cure diseases like Alzheimer’s, Parkinson’s, diabetes and cancer by attacking their genetic roots” (Clinton, 2000). The idea of genes as the “roots” from which disease springs formulates yet another promise of a fundamental or elementary understanding of disease. Molecular biology and biochemistry of blood samples were the new level of interest.

In the course of the 20th century, blood samples thus became the specimen of choice for detecting disease and the number of samples taken increased rapidly (Bynum et al., 2006, pp. 467–468). Blood samples are today omnipresent in the clinic, where taking a blood samples is one of the first steps in investigating an ailment, and vast numbers of samples are collected and categorized in labs and biobanks. These collections show, despite the fact that genomic medicine is often described in terms of code, information or data, that physical specimens are central to the work of mapping disease (Radin, 2017; Strasser, 2019, ch. 2; Bangham, 2020). This is apparent also from the pivotal role of older collections in the development of genetic medicine as collections originally created for diagnostic purposes are frequently repurposed for genomic investigations. In Denmark, for instance, one of the most precious collections is the PKU biobank of blood samples systematically taken from newborns from 1982 and onwards to test for a number of rare metabolic disorders. These blots of blood on filter paper make it possible, from a 3.2 mm cut-out, to perform a genome-wide analysis. And drawing on health data, the results from genetic analysis can be correlated with disease history to investigate the early development of diseases (Nørgaard-Pedersen & Hougaard, 2007). Another Danish collection that proved valuable to genetic medicine is the epidemiological Copenhagen City Heart Study from 1976, which examined a random sample of Copenhageners for long term causes of cardiovascular disease. The study collected in the first instance blood samples in order to measure cholesterol and glucose levels, but the stored samples later made it possible to investigate also molecular markers for breast cancer (Bauer, 2008). Access to samples from diagnostic collections thus turned out to be central for understanding disease at the molecular level. Collection efforts were therefore soon launched aimed specifically at molecular markers and culminated in the establishment of large national biobanks from around 2010. These institutions store vast numbers of samples aiming to match disease histories with biological parameters for large or even countrywide cohorts (Frank, 2000) (Fig. 5).

Matching disease history with molecular markers detected in samples forms a continuation of earlier practices of correlating disease and bodily signs. With biochemical changes or genetic variations carrying a particular risk denoted “molecular lesions” (Lowy, 2013, p. 4) and the samples “liquid biopsies” (Alix-Panabieres, 2020), medical science moved down the scale into what has been called an “era of molecular pathology” (Keating & Cambrosio, 2003, p. 331). And in this era, diseases can be

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7 Although this account focuses on physical specimens, it does not seek to downplay the central importance of records and information in pathological collections or biobanks (Close-Koenig, 2015; Lesnelli, 2016; Strasser, 2019).
detected before they result in symptoms and even before they break out; they are understood instead as heightened risks.

Genomic medicine has been particularly successful in identifying molecular lesions for special cases of diseases where single variations can be correlated to specific disorders. Mapping more common diseases with no single marker, however, proved more demanding, and has had limited clinical impact (Nature Biotechnology Editorial, 2012). Still, so-called Genome-Wide-Association-Studies (GWAS) attempt to correlate variations across the genome with traits or diseases, and attract huge amounts of research activity with more than four hundred diseases and traits treated in publications by 2010 (Richardson & Stevens, 2015). Such studies also lie at the heart of the recent trend for personalized or precision medicine, with its aims to pinpoint risk and decide preventative measures or treatments on the basis of the individual patient’s genome and other biomarkers. Because personalized medicine needs to differentiate very small groups, even down to individuals, it requires a very fine-grained taxonomy as well as data from large cohorts to correlate to clinical data. This work is ongoing today, and the recent head of the Copenhagen Hospital Biobank, Henrik Ullum, stated that some of the weak results have to do with the analyses being too coarse and numbers of samples too limited (Ullum, 2019). So genomic medicine continues to move towards still more fine-grained taxonomies based on still larger numbers of samples.

Summing up, investigating molecular and genomic biomarkers in blood samples, meant that diseases could be associated with genetic variants or outlying values of biomarkers. Blood samples are now collected in labs and biobanks in still greater numbers to correlate gene profiles and disease histories with an aim to produce fine-grained categories differentiating very small groups and with the possibility of determining the risk of disease rather than detecting disease itself.

3. More scales: timing of diagnosis, cohorts, categories and technologies

The history sketched above, shows how medical attention and collection efforts moved down a bodily scale. And how specimens of decreasing size were excised or sampled to detect and understand disease at new levels. But size isn’t everything. More scales of equal significance for understanding disease emerge out of the history of specimens.

3.1. Earlier diagnoses: from grave to cradle

Since specimens are used to define disease as well as ascertain diagnoses, there is a time component to the understanding of disease furnished by the specimens. The question “when was the specimen made?” fixes the point in the development of the disease, at which it is understood. This can be just after death, as was the case with lesions in organs, or very early, before a person has symptoms or even before a patient is born, as can be done with blood samples. As we shall see, the timing of diagnosis – and of the making of the specimen – follows its own scale. A temporal scale that is inverse to the size-scale of the diagnostic specimens or samples.

Starting with the organ specimens, these represent the determination of disease at the autopsy table – the cause of death. At the same time, these specimens, excised at death, defined and categorized the disease. The understanding of disease was thus intertwined with the cause of death. Doctors of course offered symptom-based diagnoses to patients while they were still alive, but it was understood that these were preliminary and that the final confirmation of the diagnosis took place at the autopsy table. When René Laennec (1781–1826) published his invention of the stethoscope and subsequent investigations that correlated sounds from the chest with lesions uncovered at autopsy, he was criticized by clinicians for being too obsessed with the pathological detail after death rather than with treating the patients (Duffin, 1998, ch. 9). But in order to categorize diseases in the living, he needed to diagnose them at death. In fact a Swedish professor indicated that, in some quarters, it was tantamount to unprofessionalism to even attempt to diagnose before death, when he stated that “the new method of auscultation had transformed medicine into an art of divination aiming to predict what would be found at the autopsy” (Gottfredsen, 1973, quoting Israel Hwasser (1790–1860)). This close association between defining disease and determining causes of death is also apparent in the history of the world’s main diagnostic manual – the International Classification of Disease (ICD) – which developed on the basis of manuals categorizing causes of death for statistical purposes (Moriyama, Loy, & Robb-Smith, 2011).

Investigating cellular structures and microorganisms on slides slowly altered the timing of diagnosis. At first the investigations of tissue simply complemented findings at the organ level and located signs of disease at several levels at once. But at the turn of the century, doctors and pathologists took samples from living patients, and biopsies became a standard diagnostic technique of the 20th century. Diagnosis on the basis of tissue could now be carried out while the patient was sick, but alive. Also this development is reflected in the international diagnostic manual, which from 1948 (ICD-6) included diagnostic codes for diseases in addition to causes of death (World Health Organization, 1948).

Last, analyses of biomarkers in blood samples became the go-to choice in the 20th and 21st centuries and these analyses enabled doctors and biomedical researchers to detect disease as “pre-disease” before the patient feels sick or has developed signs of disease (Aronowitz, 2009). Patients are now routinely screened and diagnosed for diseases pre-symptomatically, and the vision is that genetic testing can offer risk profiles that can reveal predispositions and possible prevention measures from birth or even before. This 21st century vision of
the future of medicine, personalized medicine, is often described with the four P’s: Predictive, Preventative, Personalized and Participative, emphasizing the hope of both predicting and preventing disease.

So while the specimens, on which diagnosis is based, decreased in scale, the time between the diagnosis and death increased. From the patient being diagnosed with a cause of death at the autopsy table, to being offered a risk profile on the basis of a blood sample even before birth.

3.2. Bigger cohorts and narrower categories

The cohorts of patients mapped to understand disease and develop the diagnostic categories also increased inversely to the size of the body parts investigated. As the specimens became smaller, less demanding to store and less invasive to obtain, more cases could be compared, and subdivisions of categories made more refined.

While doctors in 17th and 18th centuries investigated a small number of private patients, and anatomists based their understanding of the body on a limited number of corpses, the 19th century hospital setting allowed comparisons of larger groups of patients across wards or even hospitals. At the same time the pathological collections outgrew single collectors and became institutionalised mappings of pathologies rather than embodiments of the knowledge of individual doctors.

Likewise, the numbers of patients investigated and compared expanded with collections of tissue slides. Being more storage-friendly, collections could hold more slides, and hospitals and diagnostic departments kept vast archives of microscopic slides for reference. The main university hospital in Copenhagen, for instance, still keeps all its parts kept vast archives of microscopic slides for reference. The collections could hold more slides, and hospitals and diagnostic departments kept vast archives of microscopic slides for reference.

The instruments are, however, not just larger and more complex. The technology employed to access the smaller specimens is also increasing in amount and complexity. Put simply, the smaller the specimens, the larger the technologies required to render their structure and composition accessible: from scalpel and formalin, over microtomes, stains and microscopes, to genomic sequencing centres.

3.3. Larger technologies, distances and intersections

The table moves from a focus on the unit for physical investigation of disease. The different scales can all be connected through the historical scale of specimens outlined above (section 2) that tracked the decreasing size of the body parts under scrutiny. The specimens connect the time when diseases can detected or diagnosed, the number of patients investigated to understand and categorize disease, the number of categories differentiated, and the extension of the technology involved. These interrelated scales may be summed up in Table 1 below inspired by Jewson's tables, which also schematized long-term developments in medicine (1967, p. 228).

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2) A historical understanding of the developments in diagnostics leading from the post-mortems that ascertain the cause of death to current interests in diagnosing or prognosing pre-disease and risk.

Considering the expansion in cohorts offers:

3) An account that places the explosion of diagnostic categories in a historical context and shows how the increased precision or differentiation of the categories – with personalized medicine aiming for the single individual – is based on larger and larger cohorts.

And last, the development in technological systems that make the body accessible at a given level gives rise to:

4) A history of the technological investigation of the body where increasingly large instrumentation is applied and the integration of the technology and the bodily material deepens.

While such scales might seem a crude instrument for writing history, they allow several complex developments to be tied together through the specimens. Several central elements of medical knowledge and practice are materially embodied in the specimens: understanding of disease (what is excised and collected), diagnostic practice (when is the bodily material extracted), cohorts and categories of disease (how many specimens are collected and how many categories are they classified into) and investigative technology (how are specimens prepared to yield knowledge). At the same time, the specimens tie together histories of museums, hospitals, labs and biobanks highlighting how bodily material and knowledge flows back and forth between them.

### 4. Implications for historiography and history of medicine

In addition to connecting different aspects of understanding disease-describing, detecting and differentiating disease-, the scale of specimens also carves out a particular historiography of medicine. It allows for a history that is periodized, but which at the same time connects across periods and captures the pace of development of medical knowledge (4.1). It also provides a historical epistemology of medicine anchored in specimens (4.2). The specimens simultaneously highlight the materiality of medicine – a materiality that does not disappear in today’s biomedicine (4.3). And last, it opens new lines of sight in the history of medicine both from past to present and from present to past (4.4).

#### 4.1. Periods and connections

The history of medicine is often told as punctuated by discontinuities or even revolutions such as the rise of hospital medicine in the Paris School (Ackerknecht, 1967; La Berge & Hannaway, 2016); the laboratory revolution of the late 19th century (Cunningham & Williams, 1992); or the molecular or genetic revolution situated variously in the 1930’s, 1950’s or at the verge of the postgenomic era (Kay, 1993; de Chadarevian, 2002; Fox Keller, 2000). The history of medicine has also been told as a sequence of

<table>
<thead>
<tr>
<th>Scales</th>
<th>Whole Body</th>
<th>Organ</th>
<th>Tissue/cells</th>
<th>Molecular</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Specimens</strong></td>
<td>Anatomized body emphasizing connections</td>
<td>Organs</td>
<td>Tissue slides</td>
<td>Blood samples</td>
</tr>
<tr>
<td><strong>Location of disease</strong></td>
<td>Imbalances in the whole body</td>
<td>Localized lesions / gross lesions</td>
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<tr>
<td><strong>Time of physical confirmation of diagnosis</strong></td>
<td>At death</td>
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<td><strong>Cohorts</strong></td>
<td>Individual patients</td>
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<tr>
<td><strong>Categories</strong></td>
<td>Symptom based nosologies</td>
<td>Categories of causes of death – 161 (1893)</td>
<td>Manual of diagnoses and causes of death extended to include diseases (ICD-6, 1948)</td>
<td>Diagnostic manual includes 55,000 diagnostic codes (ICD-11, 2018)</td>
</tr>
<tr>
<td><strong>Technologies</strong></td>
<td>Observation</td>
<td>Scalpels and techniques of preservation</td>
<td>Staining and microscopes</td>
<td>Laboratory analyses / sequencing</td>
</tr>
</tbody>
</table>

Table 1: Scales of investigating, categorizing and diagnosing disease.
periods of differing outlook, method and organization characterized as “medical cosmologies” by Jewson, “frames” by Rosenberg, or “ways of knowing” by Pickstone (Jewson, 1976; Pickstone, 2010; Rosenberg & Golden, 1992); or more concretely, periodized according to the dominant medical institution (bedside, library, hospital, community and labs) in Bynum (2008).

The principle of scale offers in the first instance just another alternative to such broad principles of periodizing in history of medicine. As noted in many of these studies, it is, however, important not to lose sight of the continuities between periods. And this is where the principle of scale is strong. It offers an organisational principle that both periodizes and connects. Specimens of organs, tissue and molecules distinguish periods, but they also materialize the bodily links across revolutions as they are preserved. In its focus on connections, my account most resembles Pickstone’s “ways of knowing”, where each way of knowing has its heyday, but does not disappear from the scientific horizon.

The specimens connect periods in several ways. First, by the simple fact that the levels are all connected in the body. Secondly, the practices of classifying disease and of correlating lesions in specimens to symptomatic disease (whether this breaks out before or after the specimen is taken) are in evidence across the scale – from organs to genes. Thirdly, the physical specimens from previous periods are stored and continue to be accessed despite new practices emerging. Each new level of interest adds not just a layer of understanding, but also physical collections of specimens. This cross-periodic connection of medical knowledge through collected material has also been noted by Mendelsohn, investigating the use of case histories in libraries. He argued that the continual use of old cases connected medical knowledge across revolutions making the breaks seem less significant (Mendelsohn, 2017, p. 89 and 94-95).

4.2. A historical epistemology of disease in the body

The principle of scale also connect the specific ways in which knowledge is generated through different specimens. As stated in the introduction, the present account centres on what Rheinberger describes as “the things around which the knowledge process unfolds”, i.e. on the objects of research processes or what Rheinberger denotes “epistemic things”. In his careful analysis of experiments in biomedicine, he shows how an epistemic thing is a product both of its nature and of the technical experimental set-ups that make it accessible. When investigated, the epistemic thing is reconfigured by the different material, conceptual and technical ways of making it manifest, and when it is investigated by new set-ups, it reveals still new aspects of itself (Rheinberger, 1997, 2010). After a period of research and new insights, the epistemic thing can become well-understood. At that point it can itself become part of a technological system used to investigate another epistemic thing.

Rheinberger’s analysis resonates with the processes in which specimens are shaped by concepts of disease and technologies of investigation, but they also themselves become technologies that shape ideas of disease, fixing how they can be viewed at particular levels of scale. In this process the specimens at a given level of scale are first objects of investigation and later become instruments for understanding disease.

When Rheinberger writes specifically about specimens himself, he, however, distinguishes them from “epistemic things”. They are, he argues, fixed in a particular materialisation – excised or stained in a particular way – and therefore cannot reveal themselves in new ways. But Rheinberger considers one type of specimen at a time – body parts, dried plants, slides and genetic material in electrophoresis gels – and he analyzes each method of preparing tissue separately with attention to its particularities. He does not present the different forms of specimens as a connected history of investigating disease in the body. So although he goes through specimens in roughly chronological fashion, they are not made to constitute a connected history and are not viewed as successive materialisations of the body.

If, however, we tie the different types of specimens together in a scalar history, we can see them as one epistemic history. New types of specimens, organs, slides, blood samples, may be seen as successive investigations of disease in the body each making new aspects of the diseased body manifest. So the history of medicine according to scale not only combines medical, material and cultural aspects of investigating the body, it also extends Rheinberger’s analysis to a longer time-frame. It extends it into a history of investigations that over centuries have materialized still new aspects of disease in the human body. The fact that specimens are usually investigated as part of collections or cohorts also allows for more epistemic flexibility than Rheinberger initially envisages for the preparations. By being reorganized, collections can materialize new understandings or categorizations of disease and thus manifest the diseased body anew.

The scalar view thus offers a historical epistemology of pathology and, at the same time, it ties together an array of studies of epistemically significant objects: namely the organ preparation, the microscope slide and the blood sample. In doing so, it bridges a series of historical studies that lie at the foundation of this account, for instance Alberti (2011) who detailed how elaborate material processes of preservation and display made patients’ bodies into objects of knowledge in 19th century; Lowy (2010 and 2013) who showed how microscope slides defined new types of cancer in the early 20th century not just by revealing cell structures, but through the exact techniques that made them visible; and Strasser (2019) and Bangham (2020) who in different ways connected genetics to collections of specimens. While the processes of investigation are particular to the different levels and the contexts differ, the epistemic thing under investigation and classification, the diseased body, ties them together.

4.3. A material history

Tracing specimens at different levels of the body does not just tie together epistemically important objects in medicine, it also demonstrates the continued importance of collections in medicine. Collections were not only part of medical practice in the 18th and 19th centuries, when museums were an essential part of the scientific infrastructure. They continued to be so as medical science moved to the laboratory. They just became less visible as the specimens became smaller. So although medicine is not normally seen as a collection science and is not, for instance, included in Robert Kohler’s extensive list of collection sciences (Kohler, 2007), it should be regarded as such (Tybjerg, 2015). Medicine is – like the other disciplines characterized by Kohler as collection sciences – dependent on large quantities of physical material such as pathological collections, slide archives and biobanks, and it draws on the concomitant practices of categorizing and redefining the collections. The continued role of collections in laboratory science has also been demonstrated in the biological sciences, where Bruno Strasser has shown how museum collections, living collections and experiments feed into each other (Strasser, 2012 & 2019; see also Bangham, 2019; Peres, 2016; Curry, 2019). Collections operate both as a way of knowing when they map and categorize disease and as a reference for fixed knowledge to be taught.

The scale of specimens also emphasizes the importance of materiality in biomedicine. Modern biomedicine can seem bloodless and information-driven and has often been viewed as disembodied as well as distanced from the patients (Jewson, 1976; Reiser, 1978). Looking at biomedicine through its specimens and samples, however, challenges such a view and shows that bodily material has not disappeared from modern biomedicine (as also noted in de Chadarevian, 2018 and Pinel & Svendsen, 2021). Rather, the large numbers of small samples require a range of material practices such as storage at certain temperatures, repacking and cataloguing, and they are, due to their very materiality, a finite resource. So while a sense of disembodiment may be correct from the patient’s point of view, it is less apposite from the point of view of medical knowledge as the bodily material still lies at the foundation of
big-data-driven personalized medicine. Specimens provide access to the past and information not yet understood (Gere & Parry, 2006), and managing them cannot be reduced to questions of governing information that have dominated the biobank literature (eg. Gottweis & Petersen, 2008).

4.4. New lines between past and present

Last, the focus on specimens and the principle of scale changes some of the links drawn from past pathological collections to today's medicine by historians of medicine. Studies of anatomical and pathological collections in 18th and 19th century museums and universities have tended to look for practices that are similar in scale when looking for historical descendants. Both Alberti’s Morbid curiosities (2011) and Hallam’s Anatomy Museum (2016) contain final chapters that link the histories of anatomical collections to the extravagant shows of plastinated bodies created by the German anatomist Günther van Haagen (1995-). But while the van Haagen Body Worlds shows may indeed be seen as contemporary versions of the popular anatomical displays that horrified and fascinated Victorian publics, they capture to a much lesser degree how the specimen collections are used to link symptoms, diagnoses and lesions. These practices are now found in biobanks, which offer an alternative modern descendant of 19th century collections. Following the decreasing scale of medical interest rather than a type of specimens has highlighted a different historical connection.

Likewise attention to scale draws a new line when looking for antecedents to contemporary biomedical science. Scholars have linked new developments in personalized medicine back to bedside medicine with its concern for the particularities of the individual patient (Tutton, 2014). This connection reflects the hopes that personalized medicine might tailor preventative measures and treatments to each individual. Personalized medicine may, however, also be linked to the scalar development of greater cohorts providing more differentiated categories of pathology. It may be seen as the epitome of a reductionistic movement towards investigations of increasingly refined parts of the body and earlier detection of disease (Bynum, 2008, p. 119) rather than a new form of holism that considers the whole and individual body. Both prehistories are important and keeping both in mind helps explain tensions between denoting this approach respectively “personalized” or “precision” medicine.

5. Conclusion

Summing up, the principle of scale has excited a history of medicine from collections of human specimens used to generate medical knowledge. While closely related to classic histories of medicine moving from humoral theory through laboratory medicine to molecular biomedicine, it shifts perspective by structuring the account around specimens and scales (section 2). Both the specimens and the scale forge new historical connections.

To start with the specimens, these are – as has often been noted – in-between objects. They are at once parts of patients' bodies and objects of knowledge; they are structures of anatomy as well as manufactured artefacts; and they derive from the clinic, but are investigated in the laboratory. This makes them ideal objects for understanding medical knowledge, which exactly straddles these categories. The in-between nature of specimens allows for the history to not fall hard on either side of dichotomies between doctors and patients, culture and nature, clinic and laboratory, local and general. The specimens bridge them:

Organ specimens moved between the hospital and the Surgical Academy; biopsies between surgeons' operations and pathologists' labs; and blood samples between clinics, biobanks and research centres. While specimens have been viewed as creating distance between patient, doctor and scientist they may also seen to create a material connection between them (Hallam, 2017).

Viewing the well-known historical episodes through a set of scales also brought out broader conceptual patterns in how disease is defined, diagnosed, categorized and investigated (section 3). It revealed a set of interlinked scalar developments in the size of pathological unit, time of diagnosis, size of cohorts, number of disease categories and extension of technology. These developments are of course parts of medical, institutional and cultural history, but they can – as shown by Table 1 – also be condensed into a few simple questions: How large were the excited chunks of bodily material? When were they excited? And from how many patients and with which technologies? The connected scales thus produce a historical overview similar to that of Jewson's classic paper, but with the medical object of investigation at its centre and a different set of connections revealed.

Historiographically the account offers both a history of practices of preserving and studying specimens and a historical epistemology (section 4). Its concern with the material processes of generating knowledge out of specimens connects practices of preservation and investigation with concepts of disease. It follows Rheinberger's interest in the objects of research, but extends it over several centuries and links existing studies of the cultural and epistemic practices of investigating human material at the different steps of the scale: organs, slides, samples. The idea of the scale was itself materially fashioned by working with museum collections and it demonstrates how museums might contribute to history of medicine. Not just with histories of the local and particular (Lubar & Kingery, 1993; Ulrich et al., 2015), but with broader conceptual histories.

To conclude, one of the difficulties when I began to work with scale in the context of pathological collections was that the periods did not quite fit the standard periodizations in history of medicine. This turned into an insight, however, that the arduous process of accumulating material bodily specimens lags after the hectic pace of discovery. Like a landscape it changes slowly as ideas of disease are formed by collections and concrete practices of excising and investigating human material. The material inertia reveals a process where knowledge and specimens first moves from the clinic to map new categories, and then back again as reference and teaching collections for clinical categories. There is a time lapse between beginning to investigate a given level and using it for clinical diagnosis; time for the epistemic direction between clinic and collections to turn.

This insight adds a new perspective to the current situation in biomedicine. In the 21st century, it seems left at an impasse. In the middle of a vast expansion of samples transcribed into ever more genomes, the value of the effort has been doubted: Does the mapping of genomes help prevent or treat disease? And are the data generated at all meaningful (Reardon, 2017)? These doubts mirror criticisms that were historically launched at gross and cellular pathology when their categories and diagnoses did not translate into better treatment – for instance against Laennec that he was more interested in the pathologies predicted by the stethoscope than in treatment. However, taking the slowness of how medical knowledge develops into account, we may now see ourselves, not at a post-genomic tail-end, but rather in the thick of investigating disease at the genetic level. The biobank collections have not yet reversed the epistemic flow to become a resource for clinical decisions. They are still in the process of mapping the landscape. In the same way, the cellular level was collected and characterized by slides for years before slides, in the 1920's, became the reference for diagnostics (Close-Koenig, 2013, p. 343). A history based on the scale of specimens shows how medical knowledge develops slowly like the sedimentations of collected specimens that materialize its history. And it shows that each of the layers of the scale is essential for understanding medical knowledge and practice – there's no privileged scale, but there are deep

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8 Specimens are both anatomy and refined handiwork (see Alberti, 2011; Lowy, 2013; Rheinberger, 2010); both scientific objects and parts of persons from whose bodies they came (see Gere & Parry, 2006; Hallam, 2016; Hoeyer, 2010; Radin, 2017); and they cross over between the clinic and the laboratory (Close-Koenig, 2013; Lowy, 2010).
questions of how both layers in the body and the layers in the history of medicine are connected.

Declarations of competing interest

None.

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