Without Pathology, medical education is futile.

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The study of pathology, including detailed examinations of bodies, dissections and inquires into specific maladies and diseases, dates back to antiquity. For as long as humans have roamed the Earth there have been people caring for the sick, the injured and the elderly. Palaeopathological investigations have unearthed a wealth information on prehistoric individuals with gross abnormalities, and numerous descriptions exist of conditions that continue to plague us now- hernias, tumours, ulcers and infections[1]. Modern medicine, however, often overlooks basic pathology in its rush to administer the latest treatment regime or implement cutting edge technology. Even more discouraging, many medical students have limited understanding of the nature of pathology; failing to see a huge discipline divided into subsections that interconnect biological research and medical practise. It is alarming that both students and doctors alike are failing to recognise pathology as a driving force behind medical advancement; it forms the scientific foundation of medicine, without which no understanding of disease would remain[2]. Life-altering targeted therapy would not exist. But even more basic – biopsies, resections, blood tests, sputum cultures – all would be rendered useless if it were not for our understanding of pathology. Not only does medical education become futile without this fundamental foundation, medicine in itself is ultimately impossible. How can one be expected to diagnose, treat and prevent disease, if they do not understand the disease in the first place?

Pathology links all medical fields. It informs immunology, parasitology, oncology, haematology. It bridges the gap between medical research and new treatment. It helps to solve crime, stage cancer, identify causative agents in infection and direct clinical treatment. In order to be an expert in any given field of medicine, one must first understand healthy tissue and anatomy and then grasp the four components of disease: cause, pathogenesis, morphologic changes, and the resulting consequences i.e. the clinical manifestations. If there is no basic understanding of disease as one progresses through their medical education, the information that one accumulates over the years has no true depth. This genomic era of medicine was born on a basis of understanding, and we will not advance with young doctors who can list off anticoagulant medication but cannot describe the coagulation factors that they inhibit. Treatment will change vastly as time progresses, but only if young intelligent individuals are given the tools to make those changes happen.

Pathology throughout the ages

Understanding anatomy and preventing disease has been at the core of medicine throughout civilizations. The ancient Egyptians believed that spells would help the sick, and they carried amulets to ward off disease. They removed and examined important organs before mummification, and strongly believed that the heart would be balanced by Osiris against the white feather of Ma'at to determine who was worthy of an afterlife[3]. Magic and medicine were deeply intertwined, and the Egyptians kept written records of the ailments and successful treatments- be it medicinal or incantation driven. The earliest known medical book is the Ebers Papyrus, which was written in 1550 BC. Disorders including depression and dementia are covered in this comprehensive manuscript, along with issues such as contraception, diabetes mellites, parasites, dentistry and surgical treatment of abscesses and tumours[4].

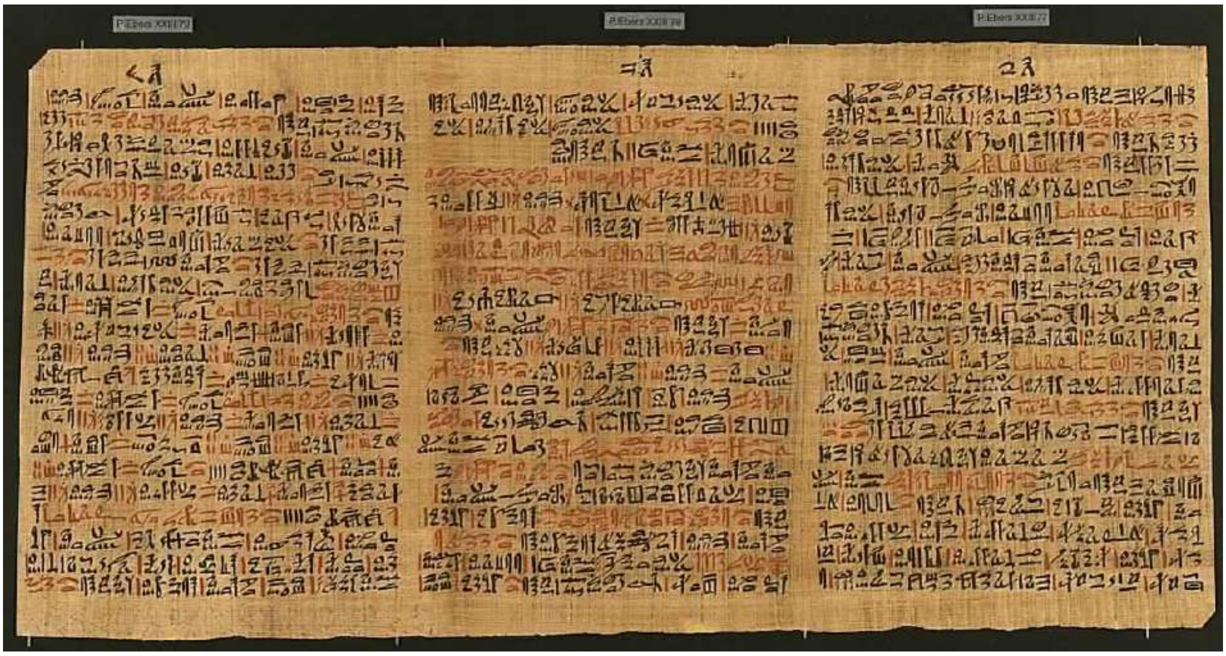

Figure 1. The Ebers Papyrus. Photo: Hanf Museum Berlin [ref 4]

Soon people wanted to know why a person died- what exactly had gone wrong. The first recorded autopsies were carried out around 300 BC by doctors in Alexandria, who were allegedly supplied with criminals to vivisect to further their anatomical understanding[5]. In 44 BC, Julius Caesar was the subject of an official autopsy after his murder by rival senators, the physician's report noting the second wound received by Caesar was the fatal one[6]. In 131-201AD, the Greek doctor Galen of Pergamon correlated patient symptoms and complaints with findings on autopsy[7]. As pathological understanding developed from Hippocrates's four humors to Andreas Vesalius's book 'The fabric of the human body', medicine and medical education too evolved (figure 2).

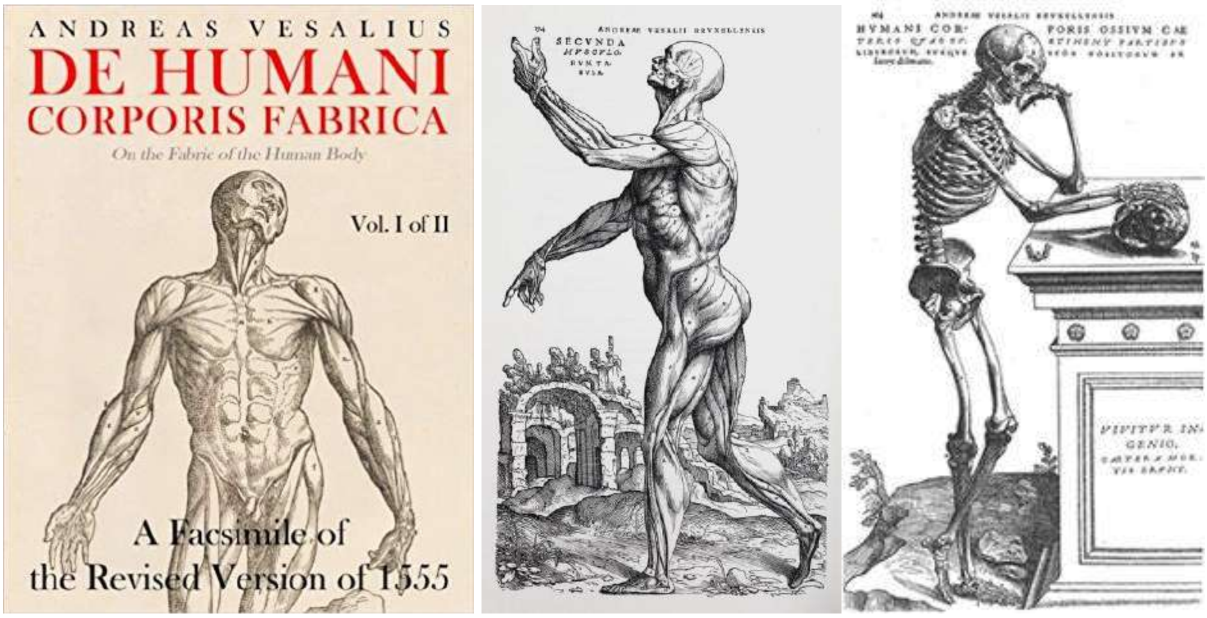

Figure 2. De humani corporis fabrica (Of the Structure of the Human Body),1555. Andreas Vesalius Photo: Met museum art collection, New York.

The sick often went to temples and places of worship in seek of healing. The Romans constructed valetudinaria for the care of sick slaves, gladiators, and soldiers in 100BC[8]. Hospitals, as we know them, eventually began to emerge. Although it is unclear when the first hospital was built, many believe it was built in 369CE, founded by St Basil of Caesarea. This 300-bed hospital cared for the seriously ill and disabled, victims of the plague and had isolation units for those with leprosy[9]. About 500AD The Academy of Gundishapur was founded. This is understood to be the first teaching hospital on record, where students were supervised by senior physicians and expected to practise on patients as part of their education, required to work in the hospital and integrate into the faculty as a whole. As in modern times, these students were expected to pass exams in order to practice as accredited Gondeshapur physicians (as recorded in an Arabic text, the Tārīkh al-ḥukamā)[10].

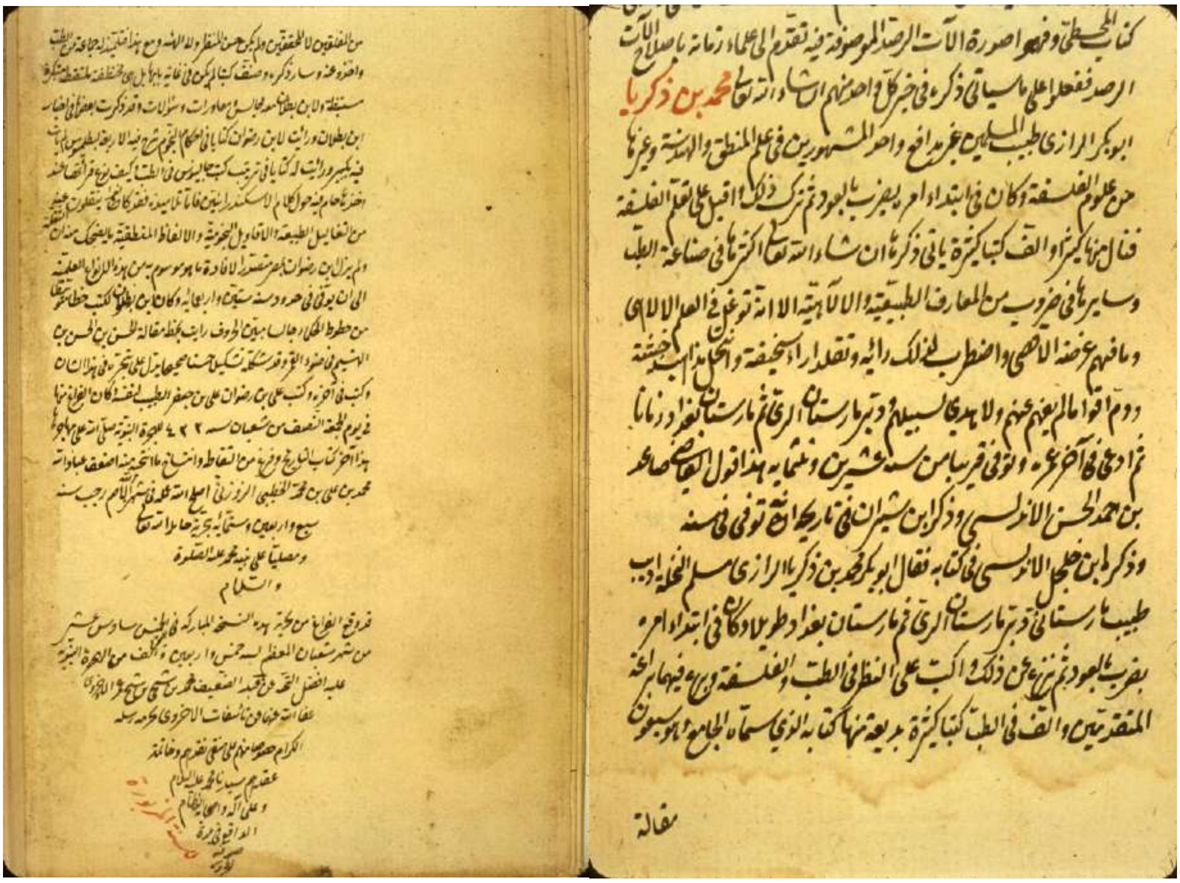

Figure 3. Islamic medical manuscripts Ta'rīkh-i ḥukamā', National library of medicine Bethesda, MD, USA 20894 [ref. 10]

It wasn't until the 9th century that medical schools were built, and medical education took a step away from the apprentice-like profession it had been throughout the ages. One of the first schools open was Schola Medica Salernitana at Salerno in southern Italy. Open to both women and men, the 'curriculum studiorum' consisted of 3-years of logic, 5-years of medicine and a year apprentice with an experienced physician. Every 5-years a human autopsy was planned, and students were expected to attend[11,12]. I can only speculate that 'logic' may have consisted of basic science and pathology, a foundation that enabled the understanding of disease that was expected during the subsequent 5-years of medicine. Interesting too how they included women. Salernitana is believed to be the only medical school in Europe, at that time, that unreservedly opened its doors to women. Trota De Salerno taught in the school and wrote texts, such as *'Practica secundum Trotam'* (Practical Medicine

According to Trota), covering topics from infertility and menstrual disorders to snakebites and cosmetics. Her fame spread as far as France and England during the 12th and 13th centuries but was largely forgotten until the re-emergence of her work in the 20th century. After a gradual decline, the school was shut in 1811 and it was not until the late 19th century before another woman was to be awarded a medical degree[13].

Evolution of pathology

Treatment of ailments has undoubtedly changed over the years. Unfortunately, we can't chant over our patients and wave them away with a magic amulet. Or we could, it would just really complicate a busy afternoon clinic. And possibly result in a report to the medical council. Possibly. But how much has pathology truly changed over the years? Has it changed at all? The underlining disease process, the fundamental cellular processes- how does that differ from ancient times?

Take Hippocrates, for example. He describes in florid detail the manifestations of what he coined peripneumonia and pneumonia:

'If the fever be acute, and if there be pains on either side, or in both, and if expiration be if cough be present, and the sputa expectorated be of a blond or livid colour, or likewise thin, frothy, and florid, or having any other character different from the common... When pneumonia is at its height, the case is beyond remedy if he is not purged, and it is bad if he has dyspnoea, and urine that is thin and acrid, and if sweats come out about the neck and head, for such sweats are bad, as proceeding from the suffocation, rales, and the violence of the disease which is obtaining the upper hand'

– Hippocrates [460 BC – 370 BC]

Such a description would still lead clinicians to place pneumonia high upon a differential list[14,15]. Repeated paroxysmal fevers, and other characteristic symptoms of malaria -often associated with epidemic occurrence – have been recorded by ancient writings of Greek, Chinese, Roman, Assyrian, Indian, Arabic, and European physicians up to the 19th century[16]. **Figure 4**. depicts photos of deformities and mutilations of the face as depicted in the Chimu Pottery of Peru. Cleft lips are obvious in photo A and B[17], and although these figures are from 900AD, they are not unlike 21st century presentations of facial abnormalities.

Figure 4. Deformities and mutilations of the face as depicted in the Chimu Pottery of Peru, Redcliffe N. Salaman.[ref.17]

The question thus arises; have we simply changed the way we look at disease? Could this somewhat account for modern medical schools no longer emphasising pathology in the curriculum, as they once did during the middle ages?

Compound microscopes are believed to be designed by Dutch spectacle makers Zaccharias Janssen and Hans Lipperhey. Nearly 100 years later Anton van Leeuwenhoek became the first to observe live cells (most likely bacteria), following Robert Hooke's description of cells in 1665. It is a man called Rudolf Virchow, however, who is recognised as the father of microscopic pathology. He viewed disease from a cellular level, eventually concluding '*omnis cellula e cellula'*; cells must develop from existing cells. Experimental pathologist Julius Cohnheim emerged, and pioneered the use of the frozen section procedure (still paramount in modern pathology)[18]. Other advancements occurred including the gram staining technique in 1884, developed by Danish bacteriologist Hans Christian Gram. The technique arose from Gram's innate understanding of the differing physical and chemical properties of bacterial cell walls[19].

The microscope revolutionised concepts of disease; conditions viewed at a cellular level enabled the development of histopathology and drove advances in techniques now utilised in modern practise. Tissue fixation, embedding techniques, microtomes, numerous biological stains, and greatly improved microscopes enabled the growth of experimental pathology. Entering the 20th century, research of the pathologist Karl Landsteiner provided the basis for modern blood typing (1901), ultimately leading to new fields of blood transfusion, and eventually tissue transplantation[1]. Pathology informatics emerged with the advent of computers, the Internet and digital imaging. It has unequivocally shaped the field into what it is today: a discipline centred around top-quality diagnostics, incredible imaging techniques and personalised medicine. Areas of genomic, molecular and data analytics are advancing at rapid paces in this digital decade, contributing greatly to new therapy development and more comprehensive pathological understanding[20].

Although it is overwhelmingly apparent that an understanding of pathology drives advancement in medical techniques, I wondered if fundamental disease process had stayed the same; had we just gained better insight with modern technology? Or had diseases adapted with us?

I struggle to believe that the pathogenesis of diseases has stayed static since antiquity. Look at microbial resistance. VRE, MRSA, CPE – names that strike fear into those in healthcare. Or at least they should. Do young doctors truly understand the dangers of the pathology underlying these conditions?

Perhaps if there was a greater emphasis on the pathogenesis of microbial resistance doctors at all stages would hesitate when prescribing broad-spectrum antibiotics. 1950 to 1960, the golden age of antibiotic discovery, resulted in nearly 50% of the drugs commonly used today. Although transferable resistance identified in Japan as early as the 1950s, many believed antimicrobial resistance would be a rare event[21]. In the 1940s it was advertised that penicillin could 'cure gonorrhea in less than 4 hours!' (figure 5). In modern times, resistance is at such a peak cephalosporins may be the last antibiotics left to treat it, and other STI's are developing resistance too[22].

Figure 5. This poster attached to a curbside mailbox offered advice to World War II servicemen: Penicillin cures gonorrhea in 4 hours. (Photo: © National Institutes of Health).

Microbes are not alone in their quest to adapt and resist our treatment. Cancer- first documented by in Ireland in the 8th century by Johann Kaspar Zeuss a (German historian and founder of Celtic philology[23])- has consistently been difficult to treat. It struck me initially that pathology held the ultimate key for finding that elusive 'cure for cancer'. Yet to understand the complexity of cancerogenesis one must first grasp the fundamental basis of apoptotic cell death and how the cell cycle regulates replication. There is no simple cure for cancer. The pathophysiology is too dynamic, the microenvironment too complex. Even with successful treatment, some cancers recur. Small cell lung cancer, for example, is an aggressive disease that responds remarkably well to initial chemotherapy and radiation. Significant tumour shrinkage is apparent in 80 to 100 % of patients, 50% of whom have a complete response (with no remaining evidence of cancer, be it on physical examination or visible on scans)[24]. Relapse then occurs in majority of patients within 1 to 2 years, with an overall survival rate at 5-years approximately 5-10%[25]. It would be unethical to let junior doctors discuss cancer, or any disease, if they do not truly understand them[26,27].

And so, pathology is dynamic. Everchanging. Undoubtedly, unashamedly and absolutely central to medical education.

Medical Education

Medical schools have changed throughout the years. The curriculum has moved from separating disciplines of anatomy, physiology, biochemistry and pharmacology, to looking at organ systems as a whole, and now it is centred around problem based learning[28] and simulated environments[29]. As students are driven towards clinical application there is a danger that pathology will become lost along the way, an afterthought as students compete against technological advancements and rapidly evolving fields of medicine. Medical schools are drifting away from basic science, laws of physics and concepts in chemistry and fundamental pathology is crumbling as a pillar of medical education. The emphasis is currently on treatment- what medications are needed to treat heart failure, what initial management is there for diabetic ketoacidosis, how would you stabilise a trauma patient. Very few students understand why. Why does paroxysmal nocturnal dyspnoea occur before orthopnoea? Why do noncaseating granulomas form with sarcoidosis, or bronze diabetes occur due to hemochromatosis?

An understanding of the molecular basis of disease led to the development of targeted therapies. Electron microscopy, immunohistochemistry, and molecular biology developed and have expanded an already vast speciality. Current leaders in pathology and medical education need to recognise that treatments will always evolve if the fundamental understanding of the disease is in place. Young enthusiastic doctors will not be able to recognise a niche for a future technology or an unmet need in a medical discipline if they do not have a basic, solid foundation of pathological understanding.

What is in store for pathology?

Pathology as we once knew it is no more. We've entered the era of technology, and digitalization, genomics and personalised medicine. It is not a complete shock, I hope, as pathologists currently play an integral part in the multidisciplinary team dealing with a patient's issues. Some are involved with onsite rapid diagnostics, others are supervising or taking biopsies, many no longer spend all day hidden, looking down a microscope. Han Van Krieken, former president of the European Society of Pathology (ESP), discussed 'The Changing Face of Pathology' in an interview with Michael Schubert for The Pathologist. He describes embracing this change, emphasized how it enriches the field of pathology and how care of patients can be optimised by sharing expert opinions with digital slides. He describes feeling poorly equipped to analyse a biopsy of an organ transplant patient. "I have no experience with transplant pathology at all," he confessed, "so I needed the help of a colleague. When I received the slide, I just sent a link to two colleagues, one in the north of the Netherlands and one in the west – and I had an expert opinion for the patient within an hour."[30]

Digital autopsies have been conducted since 1980, where Neuroradiology, University Hospital Mainz, Germany studied 105 specimens of human stillborn and live-birth infants, ranging in age from gestational week 13 to postnatal month 18 in great detail[31]. In recent years, 3D examinations of ancient mummified specimens have been conducted in Amsterdam and at the British Museum[32](see figure 6). Currently digital autopsy is being successfully used in many countries like Switzerland, The United States of America, The United Kingdom, Malaysia, and Japan. iGene is a UK company currently offering *'effective, efficient, respectful, appropriate, timely and professional Digital Autopsy service to the Office of Her Majesty's Coroner and bereaved families'*[33]. That is not to say traditional autopsies need to be forgotten, but digitalization offers a new perspective and unique possibilities.

Figure 6. A 3D model of Egyptian chantress Tamut's face (Photo: British Museum)

The Medical Futurist believes that not only should this change be embraced, it needs to be encouraged. Pathologists need to drive the change in education- before there is no interest in a career in pathology[34]. One study suggested by 2030 the number of active pathologists may drop by 30% compared to 2010 levels[35]. Not only should microscopes be digitalised, artificial intelligence in the field should be utilised, point-of-care testing maximised with digital technologies and tight collaborations should be formed with radiological disciplines.

Ultimately, we need to emphasise the clinicopathologic correlations- reiterating how better understanding of disease will create better clinicians in the future. We need to remind medical schools that pathology is the strongest foundation that they could build upon to equip young doctors to adapt at the same pace medicine is. Without pathology medical education is incomplete, it is unsafe, and it ultimately not worth pursuing.

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