

Philadelphia: cradle of American pathology

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Received: 9 September 2010 / Accepted: 23 September 2010 / Published online: 6 November 2010
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Keywords Philadelphia · American Pathology · Pathology

The city of Philadelphia led the political, commercial, educational, and cultural development of the American nation. As the new nation began, Philadelphia was the largest English-speaking city in the world next to London and both the center of the government and the center of commerce. Not as widely recognized is Philadelphia's contribution to transforming America's stature from nineteenth century European apprentice to that of twentieth century worldwide leader in experimental scientific medical research and practice.

Nursery of American medicine

The nation's first medical community developed in Philadelphia. The first recognized hospital in the colonies, the Blockley Almshouse, opened in Philadelphia in 1742. The goal of the Almshouse was to provide medical care for the indigent. Benjamin Franklin (1706–1770) and Thomas Bond subsequently opened Pennsylvania Hospital in 1751 to improve on Blockley's services (Fig. 1). Medical leaders also recognized the need for formal medical education. John Bard, John Morgan, and William Shippen, Jr. established the first medical school in the colonies by persuading the trustees of the College, Academy, and

Charitable School of Philadelphia (as the University of Pennsylvania was known at that time) to create a department of medicine. In 1779 a new board of trustees named the College the University of the State of Pennsylvania and organized a medical faculty modeled on the University of Edinburgh Medical School.

Franklin felt there was a need to support forums that could investigate, discuss, and develop ideas and issues of importance. He established the American Philosophical Society in 1743 to pursue equally "all philosophical Experiments that let Light into the Nature of Things, tend to increase the Power of Man over Matter, and multiply the Conveniences or Pleasures of Life" [1]. It was in this spirit that in 1787 the medical community established The College of Physicians of Philadelphia, the nation's oldest professional medical organization. The College held regular meetings and formal discussions about provocative topics of importance to medicine and published its "Transactions" as the documentation of findings.

By the end of the eighteenth century, graduates and professors of Philadelphia medical schools began leaving Philadelphia to start new medical schools in universities throughout the new nation. In 1791, David Hosack began teaching medical courses at Columbia University. Nathaniel Potter and John Shaw, also Pennsylvania medical school graduates, founded the medical school at the University of Maryland in 1807. George McClellan graduated from the University of Pennsylvania in 1819 and founded a new medical college in Philadelphia, Jefferson Medical College. Thomas Hunt started the Medical College of Louisiana in 1834. David Brainard, Jefferson graduate, established Rush Medical College of Chicago in 1834 [2]. During these years, the Philadelphia community continued to serve as the national center and forum for medical education, practice,

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Fig. 1 Dr. Henry Fisher, Pathologist, examines a specimen in the pathology lab of Pennsylvania Hospital, c. 1890s. (Courtesy of Pennsylvania Hospital historic collections, Philadelphia)

publication, and the exchange and discussion of the nature of disease and its treatment.

Philadelphia's role as cradle of modern pathology in America

Philadelphia's success in nurturing the development of the discipline of pathology can be attributed to those who worked, both individually and in concert, to find and apply scientific advances to medical practice throughout the nineteenth century. These developments required ongoing communication, both verbal and written, between scientists and professors.

Postmortem examinations contribute to the differentiation of diseases

From its founding, lectures at the Pennsylvania Hospital by University of Pennsylvania medical school professors included postmortem examinations and demonstrations for medical students (Fig. 2). One of these professors, an anatomist named Samuel Jackson, assisted Nathaniel Chapman, who founded the American Medical Association, as professor of the Institutes of Medicine at the School of Medicine of the University of Pennsylvania in 1832. In his text, "The Principles of Medicine Founded on the Structure and Functions of the Animal Organism" (1832), Jackson used dissections and the study of pathological anatomy as a means to determine the cause and course of diseases. William Wood Gerhard (1809–1872), who operated his own medical school in Philadelphia, joined a group of



Fig. 2 The Pennsylvania Hospital Surgical Amphitheater, which was the first of its kind in the Philadelphia area, was in use as an operating room from 1804 to 1868. Seating around the room provided a place for medical students to observe and learn, as well as a place for paying spectators to be entertained. (Courtesy of Pennsylvania Hospital historic collections, Philadelphia)

American medical doctors, including Alfred Stillé and Caspar Pennock of Philadelphia to take a private course from Pierre Charles Alexandre Louis in Paris in 1831.

When an epidemic disease with characteristics of typhoid fever broke out in Philadelphia in 1836, Gerhard and Pennock used the approaches they had learned from Louis to distinguish between typhus and typhoid fever to prevent the spread of the contagious typhus. Gerhard went on to publish an article in the *American Journal of the Medical Sciences* in 1836 which became one of the earliest and most significant published distinctions between the two diseases and he is credited with the first accurate study of tuberculosis meningitis [3]. His book on *Diseases of the Chest* ran through four editions.

In Philadelphia, Gerhard's pupil, Alfred Stillé, collaborated with the Bostonian, George Shattuck, Jr. at Harvard to categorize the distinctions among the numerous highly contagious "fevers." Stillé continued to differentiate typhus and typhoid fever and taught in the School of Medicine. In addition to this research, he contributed to the organization of the American Medical Association in 1847, later served as its president, published "Elements of Pathology" in 1848 and contributed a monograph of Cerebrospinal Meningitis and Cholera.

Horner develops pathological anatomy

William Edmonds Horner (1793–1853) (Fig. 3) had studied at Caspar Wistar's museum before being appointed Dean of



Fig. 3 William Edmonds Horner, images from Historical Medicine of the National Library of Medicine

the University of Pennsylvania medical faculty in 1822. His “Treatise on Pathological Anatomy,” published in 1829, was considered to be a compendium of pathology, guide to post-mortem examinations, and America’s first pathology text [4]. He continued as curator of the Anatomical Museum of the University of Pennsylvania, which had been established in 1809 by Caspar Wistar. Horner traveled to France early in his career where he worked with Bichat, Louis, and Andral and revisited Europe in 1848 with Joseph Leidy, where they met with leading scientists in England, France, Austria, and Germany.

Leidy pioneers natural and medical sciences

Seldom recognized are the contributions made by Joseph Leidy (1823–1891) (Fig. 4) to the Philadelphia medical and scientific community. From 1844 when he graduated from the University of Pennsylvania medical school, Leidy introduced the utility and versatility of the microscope to examine a wide range of subjects, including fossils, gems, parasites, and forensic medicine and human tissues. When presented with a dinner of terrapin at the Biological Club, instead of eating the creatures, he dissected them and discovered three new intestinal parasites. “Never give Leidy anything that is edible and worth

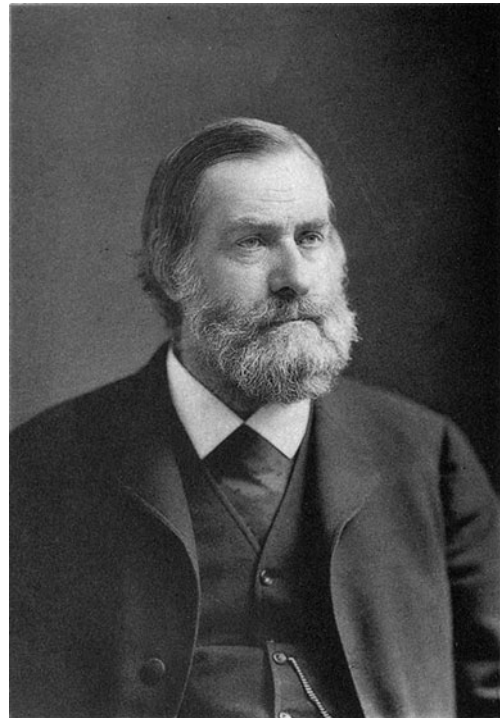


Fig. 4 Joseph Leidy

dissecting,” S. Weir Mitchell observed, “We all know where it will go” [5].

Leidy’s examination of parasite cysts in cooked ham led him to advocate the thorough cooking of meat to prevent infection by harmful parasites. He found houseflies to be carriers of disease and worked to eliminate their presence in hospitals.

Leidy may even have been the first to use the microscope in forensic medicine when he examined blood on the shirt of an accused murderer. He demonstrated that, since the red blood cells were not nucleated, the blood was definitely not that of a chicken as claimed but, instead, that of a human.

He published the *Elementary Treatise on Human Anatomy* in 1861, the standard medical school textbook widely used by generations of students and practitioners. With this publication, Leidy was the preeminent human anatomist in the United States. He is also known as the father of American vertebrate paleontology by having connected the relationships among fossil skeletons, evolution, and Darwin’s theory of natural selection for which he is known as the father of American vertebrate paleontology. Leidy became the first chair of the Department of Biology at the University of Pennsylvania and, in 1882, served as Dean of the University of Pennsylvania Medical School. His 800 published articles provided the groundwork for much scientific investigation throughout the country [6].

Advances in surgery contribute to the development of surgical pathology

Advances in surgical practices contributed to the emergence of surgical pathology. Samuel D. Gross (1805–1884) (Fig. 5), a 1827 graduate from Jefferson Medical College, published the *Elements of Pathological Anatomy* in 1839. It remained the most comprehensive American pathology text of its kind for over 40 years. After teaching in Kentucky, Ohio, and New York, Gross became professor of Surgery at Jefferson Medical College. His two volume work, *A System of Surgery: Pathological, Diagnostic, Therapeutic, and Operative* went through six editions. As a member of the Royal Medical Society of Vienna and the Royal Medico-Surgical Society of London, he presided over the 1876 International Medical Congress in Philadelphia. Although not formally trained in pathology, he made critical innovations to surgical techniques and publicized elaborate reflections about the diseases he encountered surgically. Gross advocated for more attention to the study of pathology, noting “It is certainly an anomaly in the history of our profession that a science (pathology) which admits of such extensive application as the present, and which may be regarded as constituting the very foundation of the grand edifice of medicine should be so neglected as a branch of elementary study in the United States” [7].

Samuel Gross shared with David Hayes Agnew (1818–1892) his approaches and insights to making continuous improvements in surgical practice. Agnew led surgical practice and instruction at the University of Pennsylvania



Fig. 5 Samuel Gross and the Gross clinic

Medical School and gained the reputation as one of America’s leading surgeons. After James Garfield was shot in 1881, Agnew was the chief consultant during the months of illness before Garfield’s death.

As was the case in many European medical centers, the Philadelphia Hospital, Blockley Hospital, Pennsylvania Hospital, and the College of Physicians of Pennsylvania each developed its own extensive museum that served as foundation for the study of pathology.

Improvements in surgical practice contributed to the quality of anatomic pathology and forensic pathology. Moreton Stillé, graduate of University of Pennsylvania and brother of Alfred and Charles Stillé, was well recognized as an expert in legal aspects of medicine. With Francis Wharton, he published *Treatise on Medical Jurisprudence* in 1855 which included precise instructions on post-mortem examination.

Pepper leads university reorganization and modernization

Efforts were also beginning to reform and change the nature of upper level education. As Charles Eliot was introducing major reforms at Harvard, Charles Janeway Stillé, Alfred Stillé’s brother, took steps to modernize and expand the University when he became Provost in 1868. Stillé successfully increased funding to guarantee the university’s growth and financial stability and convinced the trustees and faculty to support improvements in scientific education. The campus moved and expanded to include the University Hospital and a new scientific department.

William Pepper, Jr. (1843–1898) (Fig. 6) assumed the office of Provost of the University of Pennsylvania in 1881 and provided both the visionary and practical leadership to make sweeping changes to increase the quality of University and Medical School educational instruction, research, and publications.

Pepper had served as Medical School professor and curator of the hospital museum. This title was synonymous with being the pathologist and director of the hospital’s laboratory [2, p. 124]. His contributions to medicine included descriptions of perforative appendicitis and peritonitis, malarial parasites, the role of bone marrow in pernicious anemia, the treatment of tuberculosis, and numerous publications, including the *Textbook of the Theory and Practice of Medicine*.

Along with Horatio C. Wood, he organized the University of Pennsylvania with its various graduate schools and programs with sequenced courses and extensive curricula. A fourth year was added to the medical school curriculum. His efforts resulted in a remarkable number of American firsts for the University of Pennsylvania Medical College;



Fig. 6 William Pepper, Jr.

the first teaching hospital affiliated with a university medical school (1874), the first nurse's training school (1887), and the first laboratory of clinical medicine (1894) [8]. Pathology was designated to be a department in 1877 and James Tyson appointed as chair.

William Osler invigorates the Philadelphia community

During this period of reform and transformation, the trustees of the University of Pennsylvania medical school appointed William Osler (1849–1919) (Fig. 7) to follow Pepper as professor of clinical medicine in 1884. In its first 120 years, the medical school had appointed only one faculty member who was not a Pennsylvanian or an alumnus. Most professors were both. “Inbreeding of a faculty could hardly go farther,” the official history notes [9]. “Quality had not necessarily suffered. Philadelphia arguably remained America’s leading medical center” [10].

At the time, Osler was professor of the Institutes of Medicine at McGill University and pathologist at Montreal General Hospital. He had studied with leading British, German, and Austrian physicians and researchers, including Virchow. Osler attended the Seventh International Medical Congress in 1881 and was elected fellow in the Royal College of Physicians of London. Pepper’s vacant chair presented trustees of the Pennsylvania Medical School with the opportunity to invigorate the medical school faculty.

He did not disappoint. Osler immediately set up a small clinical laboratory under the hospital amphitheater and there he is said to have produced an atmosphere so encouraging and helpful that young fellows trooped to his

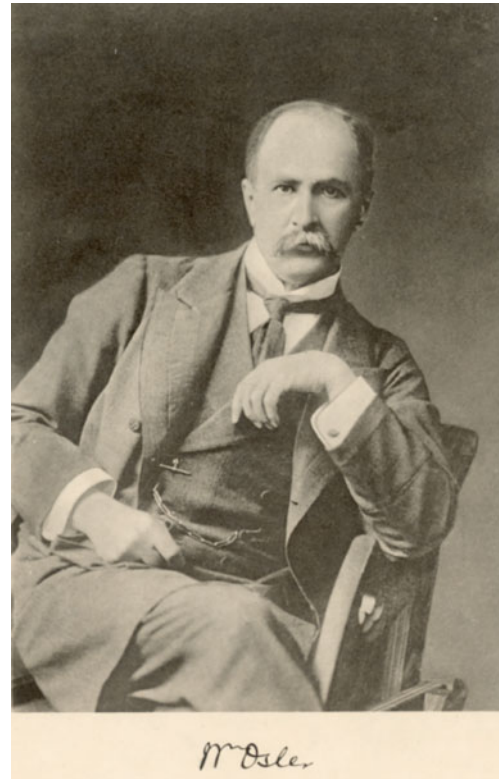


Fig. 7 William Osler. (Courtesy of the University of Pennsylvania Archives)

side [11]. This was a new experience to the senior students who had previously been fed more graceful generalizations and personal anecdotes than scientific study.

“In Philadelphia Osler was the doctor’s pathologist” [2, p.160]. He immediately joined dining clubs in the University community, including the Pathological Society, Club of 19, whose members had positions of influence in the medical school, and the Biological Club, led by Joseph Leidy and S. Weir Mitchell (1829–1914). Mitchell was a neurologist and future president of the American Association of Physicians. Osler shared observations on blood platelets, the malaria parasite, cardiovascular lesions, especially aneurysms within these various groups.

What was remarkable about Osler’s experience in Philadelphia was his success at bringing together a community of scientists and physicians to share, discuss, and refine their understandings of medical science and practice. He had Sunday dinners at the home of Samuel D. Gross where he met with the “Jefferson men,” as he referred to the staff at the Jefferson College of Medicine. While he delighted in the company of high performing, inquisitive colleagues, he had little patience for staff whose practices were outdated. Concerned that the American Medical Association and related societies were rewarding such practices, he, James Tyson, and William Pepper, Jr., along with a number of prominent physicians, most of whom were pathologists, organized the

Association of American Physicians in 1885 to encourage the pursuit of medical knowledge through experimentation and the application of basic and clinical science to clinical medicine.

Osler both contributed to, and grew from, his Philadelphia experiences by practicing, instructing, writing about, and sharing insights as part of that community. The stimulating and provocative experiences in Philadelphia foreshadowed more significant contributions to medical and pathology practice at Johns Hopkins University. Osler left behind a group of colleagues at the University of Pennsylvania who were able to implement reforms that raised the quality of instruction with respect to medical practice and produced investigative research of the highest quality.

The new pathology emerges as Hopkins' cornerstone

Baltimore millionaire Johns Hopkins donated his fortune to create the most scientifically progressive of universities and hospitals. When Hopkins died in 1873 he left US \$3.5 million to finance America's premier hospital, and Daniel Colt Gilman and John Shaw Billings (1838–1913) convinced the trustees to make pathology the cornerstone of Johns Hopkins Medical Institutions [12]. William H. Welch (1850–1934) was designated to direct the department of pathology and its laboratory in 1884 based upon recommendations of Julius Cohnheim in Germany and his own work at New York's Bellevue pathological laboratory. Welch tapped three physicians who had contributed significantly to the Philadelphia community to support and develop the new medical center. By 1888 Billings and Welch had recruited William Osler as physician-in-chief of the hospital and professor of the Theory and Practice of Medicine. Osler chose Howard A. Kelly, University of Pennsylvania graduate, physician, and surgeon from the Kensington neighborhood in Philadelphia, to organize the gynecological service at the Hospital. Kelly, along with Welch, was instrumental in founding the first experimental pathology laboratory at Hopkins and in the United States devoted to the study of specimens removed during surgery. Welch named William Halsted, his former colleague at Bellvue as professor of surgery. Halsted, in turn, selected another Osler assistant and Pennsylvania graduate, Joseph Colt Bloodgood, as his primary first assistant. Bloodgood graduated from the University of Pennsylvania Medical School and had worked with Osler there. Welch, Halsted, and Bloodgood established and developed the surgical pathology laboratory at Hopkins. Bloodgood made significant contributions to the development of surgical pathology as he and Thomas Cullen developed procedures for biopsy and frozen sections for intraoperative diagnoses.

Osler, Kelly, and Bloodgood replicated and extended on practices from Philadelphia, including regular cross-disciplinary meetings, publications, discussions, and reviews of ongoing practices and findings. "The Pathological Department at Hopkins was to revolutionize not only the teaching of pathology in this country, but in large measure that of every branch of medicine as well. From then on pathology was an independent science in America, but it was a science that made use of all other biological and medical sciences as well" [2, p.147].

Philadelphia plays key role as pathology takes full stage

By the time Johns Hopkins graduated its first class of medical students, pathology had won its place there and at the University of Pennsylvania, Jefferson Medical College, Harvard, and Columbia. The University of Pennsylvania had supplied Hopkins with three outstanding professors to create the University with the new pathology as its cornerstone. In turn, Pennsylvania pathologists now valued and selected Hopkins' leaders and graduates of the Hopkins medical and pathology program as prime candidates for teaching and leadership positions at the University of Pennsylvania.

Pepper launches first clinical research lab associated with medical clinic and hospital

William Pepper had invited John Shaw Billings to create, design, construct, and staff a Laboratory of Hygiene in 1892. Billings had served as curator of the Army Medical Museum for 10 years and Gilman's personal advisor as he planned and developed Johns Hopkins. Although he only stayed a year, Billings was able to staff the laboratory with researchers who pioneered frontiers in bacterial research such as D.H. Bergey whose work, *Bergey's Manual*, currently in its ninth edition as the reference text for bacterial classification. When Billings left the directorship, Pepper decided that it should be a robust clinical laboratory whose staff would perform applied research but with this critical distinction they would also "concern themselves with many problems which apparently have no immediate and direct bearing upon practical medicine" [13]. He became its first director, having both secured outside funding and made a US \$50,000 personal contribution to finance its development.

This was the first laboratory in the United States associated directly with a medical clinic and a university. George Dock, graduate of the University of Pennsylvania, had studied in the Leipzig Institute and Laboratory and collaborated closely with Pepper on its design. Alfred Stengel succeeded Pepper and

during his tenure as director, published the *Textbook of Pathology* which correlated anatomic and physiological changes in patients with their clinical status. Herbert Fox, the laboratory's third director in 1911, expanded its responsibility to include all chemical, serological, bacteriological, and electrocardiographic studies of hospital patients. The laboratory pioneered numerous breakthrough innovations, including molecular pathology testing on a routine basis and inspired even discoveries and innovations throughout the United States and the rest of the world.

Philadelphia leaders influence subsequent developments in pathology

As the nineteenth century ended, the Department of Pathology at the University of Pennsylvania was providing high caliber instruction as well as leading innovative clinical research. Simon Flexner was a protégé of William Welch at Hopkins. Flexner came to the department in 1899 and soon became chair. He isolated the dysentery *Bacillus* that causes a prevalent form of the disease, now known as the Flexner's bacillus. His skills in both the laboratory and in management were so well recognized that John D. Rockefeller, Jr. asked him to head his Rockefeller Institute for Medical Research in 1903. Flexner's younger brother, Abraham, a researcher at the Rockefeller Foundation, published the famous "Flexner Report" in 1910 which served to reform medical education in the United States. Hideyo Noguchi who had worked with Flexner at the University of Pennsylvania studying bacteriology and diseases of the blood joined him at the Rockefeller Institute. Noguchi went on to discover *Treponema pallidum*, the agent of syphilis.

The medical community in Philadelphia continued to progress and transform throughout the twentieth century. The Wistar Institute of Anatomy and Biology, which developed from the Wistar Anatomy Museum, has exerted a leading influence as a center for vaccine, cancer, and most recently generics and immunology research. In 1904, the first cancer hospital in the United States, the American Oncologic Hospital, opened in Philadelphia and later became the Fox Chase Center when it merged with the Institute for Cancer Research. Numerous significant discoveries have been made by and Nobel prizes awarded to Fox Chase scientists.

As the practice of pathology transformed, key professional associations emerged to support pathology and products or members of the Philadelphia community, such as Howard T. Karsner and R. M. Pearce, provided outstanding leadership for them. Karsner graduated from and served as demonstrator at the University of Pennsylvania, School of Medicine and resident physician at Phila-

delphia Hospital, taught at Harvard, and chaired and oversaw the development of the Institute of Pathology at Case Western Reserve School of Medicine. Dr. Karsner contributed directly to the organization and work of the American Association of Pathologists and Bacteriologists, the National Research Council, National Board of Pathology, the Armed Forces Institute of Pathology, and other associations related to pathology. R. M. Pearce chaired the Department of Research Medicine and Department of Pathology at the University Of Pennsylvania School of Medicine and became director of the Division of Medical Education of the Rockefeller Foundation and founded the American Society for Experimental Pathology.

The contributions of the Philadelphia medical community provided a cradle for pathology, helping it enter the twentieth century as the discipline that provided the foundation of medical science in America throughout the twentieth century. The field itself has expanded and transformed continuously as a result of the revolution begun by Virchow's *omnis cellula e cellula*, "every cell stems from another cell" [14]. Changes include distinction between bacterial and viral infections, malignant and non-malignant tumors, and the molecular structure of DNA. Notably, the discovery in 1960 of the first genetic abnormality associated with a human cancer, by David Hungerford of the Fox Chase Cancer Center and Peter Nowell (52 University of Pennsylvania School of Medicine) (Fig. 8) of the University of Pennsylvania, was recognized as the "Philadelphia Chromosome" in recognition of this medical community that nurtured the development of modern pathology in America.



Fig. 8 Peter Nowell. (Courtesy of Peter C. Nowell, MD)

Conflict of interest We declare that there is no conflict of interest.

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