

Evolution of the William Pepper Laboratory

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The William Pepper Laboratory of Clinical Medicine of the University of Pennsylvania, which celebrated its centennial on December 4, 1995, appears to be the oldest clinical laboratory in the US. Its founder and his successors have been committed to ensuring that research and teaching are considered as important as the service role of the clinical laboratory. We highlight here some of the major accomplishments and events affecting the evolution of the laboratory.

Established in 1894, the William Pepper Laboratory of Clinical Medicine opened in 1895 as a fully equipped facility for performing routine laboratory work as well as research. The third Director of the William Pepper Laboratory, Herbert Fox, after investigating the Loomis Laboratory in New York City determined that it "was not in any sense a part of the medical clinic of Bellevue Hospital" [1]. The Pepper Laboratory, then, can claim to be the first clinical laboratory in the US to be associated directly with a medical clinic. In 1994–95, the University of Pennsylvania celebrated the centennial of the Pepper Laboratory by holding a symposium, "The Clinical Laboratory in the Future of Medicine"; establishing endowed William Pepper Laboratory fellowships; publishing a history of the William Pepper Laboratory of Clinical Medicine; and erecting a permanent exhibit illustrating that history.

Background

The University of Pennsylvania Medical School evolved from the Department of Medicine, which had been created in 1765. John Morgan and William Shippen Jr. were the first professors—Morgan as Professor of the Theory and Practice of Physic, Shippen as Professor of Anatomy and Surgery. Thomas Bond, chief physician at Pennsylvania Hospital, the oldest hospital in the country, soon joined the department. Benjamin Rush, the first American professor of chemistry, was also an early member of the department.

In 1872, the University of Pennsylvania moved from its original site in the center of Philadelphia to its current site in West Philadelphia. Upon completion of this move, William Pepper Jr., a member of the Department of Medicine, proposed building a University Hospital at the new site; he sought money from others and contributed personally to the construction of the facility. The first building opened in 1874. As chairman of the Hospital's building committee and in recognition of the value of laboratory support for patient care, he designed two laboratory rooms, each $\sim 10 \times 12$ ft. ($\sim 3.3 \times 4$ m), to be built around the base of the Hospital's amphitheater. Beyond the occasional blood count and slightly more frequent urinalysis, laboratory examinations in these rooms were limited. The rooms were first used by Horace Hare, who had been sent to Leipzig, Germany, for training in chemical methods to apply for clinical research. On his return to the University of Pennsylvania in 1875, Hare "entered at once with enthusiasm upon important chemical researches in connection with cases of disease in the hospital wards" [2]. Regrettably, Hare contracted tuberculosis shortly after his return and died 2 years later. In 1881, George Dock, another graduate of the University of Pennsylvania who also had gone to Leipzig for training, refurbished the two laboratory rooms. Ten years later, Dock became Chief of Medicine and Pathology at the University of Michigan and in 1896 established a teaching laboratory for clinical pathology there.

In 1881, at age 37, William Pepper Jr., Professor in the Department of Medicine since 1876, was elected Provost of the University, a position he held until 1894. At that time, the Provost was the chief educational officer and influenced the curriculum throughout the University. Pepper had already been active in developing a 3-year course in medicine with a systematic and compulsory curriculum. During Pepper's 13 years as Provost, the 3-year medical course was extended to 4 years, and the University of Pennsylvania expanded to include the Wharton School of Finance and Commerce, the Veterinary Department (later Veterinary School), the University Library, the School of Nursing, and the Wistar Institute of Anatomy and Biology.

In the early 1880s, Provost Pepper conceived the idea of creating an Institute of Hygiene. He raised funds to

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construct a building for it and recruited John S. Billings, then Director of Johns Hopkins Hospital and an eminent hygienist, to become the Institute's first director. At the time of his recruitment, Billings was working on the *Index Catalog*, a listing of all the materials received by the Library of the Surgeon General of the US Army. In 1879, he had started a companion work, the *Index Medicus* of medical literature. In 1956, the Library of the Surgeon General of the Army became the National Library of Medicine, 80 years after Billings had proposed this title for it.

Billings supervised the design and construction of the Laboratory of Hygiene, which opened in February 1892. During this time, Billings was also Director of the Hospital of the University of Pennsylvania. One of the early recruits to the Laboratory of Hygiene was D.H. Bergey, who had a major interest in bacterial taxonomy. *Bergey's Manual*, now in its ninth edition, is still the reference text for bacterial classification.

The Concept and Opening of a Clinical Laboratory

In 1891, Provost Pepper first discussed funding for the support of a Department of Pathology. He viewed the activities of the department as being "an essential part of the work of the medical school" and stated that he hoped "eventually to secure a laboratory of Pathology similar to that of Hygiene with an endowment that will provide the income of the Professor of Pathology and the needed assistance" [3]. When Pepper wrote of a "laboratory of Pathology," we interpret this as meaning clinical pathology, then in its infancy throughout the world. Besides being an internist, Pepper was also an anatomic and clinical pathologist. Before coming to the University of Pennsylvania, he had been pathologist at Pennsylvania Hospital, where he also had been highly productive in research. Among his accomplishments was the first description of the bone marrow in pernicious anemia.

In 1893, the Pennsylvania state legislature's appropriation for the University Hospital stipulated that the \$80 000 set aside for facilities be matched privately. \$25 000 of the total raised was to be used to construct a laboratory of clinical medicine. William Pepper personally contributed \$50 000 and raised another \$30 000 from friends and colleagues. Half of Pepper's personal contribution was used to endow a fund from which the interest was to help defray operating expenses. Provost Pepper named the laboratory in honor of his father, who from 1860 to 1864 had been Professor of the Theory and Practice of Medicine, and stated "that the purpose of said laboratory shall be to promote the interests of the patients in said University Hospital by the prosecution of minute clinical studies and original researches, and to advance the interests of science by the publication of such work" [4]. Pepper also stipulated that only graduates of the University of Pennsylvania, or of other approved medical schools with standards comparable with those of the University of Pennsylvania, could be taught within the

Pepper Laboratory. In his proposal to establish the Laboratory, Pepper placed it under the control of the Department of Medicine, where it remained until 1968.

Given Billings' success in establishing the Laboratory of Hygiene, it was only natural that Pepper would turn to him to design and construct the William Pepper Laboratory of Clinical Medicine. The four-story brick building was completed in 1895. On the first floor were laboratories for microscopic, chemical, and bacteriological investigations. The second floor contained a laboratory for anthropometry and the Director's office. The third floor had a laboratory for postgraduate students, and the fourth floor housed a library, a conference room, and another laboratory. The design of the building was unique in that corridors on the first three floors connected to nursing units in the Gibson Pavilion of the University Hospital. In October 1894, William Pepper Jr. was appointed the first Director of the laboratory that bore his father's name.

At the opening of the William Pepper Laboratory (December 4, 1895), Billings spoke in his capacity as Director of the University Hospital. He referred to William Pepper Jr. as "this far-seeing, bold-planning man of silver tongue and open hand who will be remembered as the founder of the first distinctive laboratory for research in clinical medicine in this country as long as there are sickness and death among the children of men" [5]. The plenary speaker at the opening of the Laboratory was William H. Welch, Professor of Pathology at Johns Hopkins University. Welch, who had organized the first experimental pathology laboratory in the US, sought to integrate all laboratory sciences for the benefit of humanity. In his address, recently reprinted [6], Welch traced the development of laboratories from the 3rd century BC to the late 19th century. He called for a greater commitment to research and pointed out that, whereas the daily practice of a physician affects the individual, research affects mankind. Welch also alluded to an important role for the new laboratory in teaching: "A hospital, and especially one connected with a medical school, should serve not only for the treatment of patients, but also for the promotion of knowledge. Where this second function is prominent, there also is the first most efficiently and intelligently carried out." He noted that the Laboratory was "intended especially for investigation and the training of advanced students" [6].

Even though the William Pepper Laboratory was associated with the University Hospital, Welch asserted his view that its staff should not just perform applied research but also "concern themselves with many problems which apparently have no immediate and direct bearing upon practical medicine." This was an early statement of the need to integrate basic and applied science into a clinical environment. Welch also felt compelled to state: "... but costly as may seem the support of a good laboratory, the amount of money expended would seem to us ridiculously insignificant if we could estimate the

benefits to mankind derived from the work which has been done in them."

Early Development of the Laboratory

William Pepper Jr. continued as Director of the Laboratory through 1897. During this period, Charles Leonard, one of the first associates in the laboratory, assembled an x-ray apparatus on the top floor of the Laboratory and, beginning in 1895, with his colleagues Arthur Goodspeed, Professor of Physics, and J. William White, Professor of Surgery, published roentgenographs only 2 months after Roentgen had announced his discovery of x-rays. The paper by the Philadelphia authors begins, "The Roentgen method is, of course, in its infancy. It has, however, already reached a degree of usefulness that makes it obvious that the necessary apparatus will be an essential part of the surgical outfit of all hospitals" [7]. Leonard went on to become the University Hospital's first radiologist and later founded the Department of Radiology.

A debilitating illness led Pepper to resign in January 1898; 6 months later, he died in California. The respect his colleagues felt for him was well stated by his friend Sir William Osler. "There are two great types of leaders; one, the great reformer, the dreamer of dreams—with aspirations completely in the van of his generation—lives often in wrath and disputations, passes through fiery ordeals, is misunderstood, and too often despised and rejected by his generation. The other, a very different type, is the leader who sees ahead of his generation, but has the sense to walk and work in it. While not such a potent element in progress, he lives a happier life, and is more likely to see the fulfillment of his plans. Of this latter type, the late Professor of Medicine at the University of Pennsylvania was a notable example—the most notable profession of this country has offered to the world" [8]. Pepper was succeeded as Director by Alfred Stengel, who had been acting director since 1896.

In the early days of the Pepper Laboratory, all of the scientific investigation was carried out by the associates—who were unpaid because of a lack of endowment of the Laboratory. It is unclear how they were selected. After completing medical training in this country, most seem to have undertaken further training in Europe and then selected the Pepper Laboratory in which to continue their studies. One of the first associates was William Spiller, whose research was concerned with the pathology of the nervous system. In 1903, he was appointed Professor of Neuropathology. He eventually established a separate Division of Neuropathology in the Medical School. In this Division, working in the Pepper Laboratory, M.P. Ravenel and D.J. McCarthy made the first microscopic diagnosis of rabies in the US [9]. Ravenel also isolated, and first described, a bovine tubercle bacillus from a human [10].

Caspar Miller, David Edsall, George Woodward, and Alonzo Taylor were also among the first associates. Together, they formed a Section of Physiological Chemistry within the Pepper Laboratory. Of the group, Edsall is the

best known. Between 1897 and 1910, he published 70 papers related to his interest in digestive diseases and body fluids. A clinician as well as a clinical chemist, Edsall was one of the founders of the Society for Experimental Biology and Medicine and of the American Society for Clinical Investigation. He also cofounded the *Archives of Internal Medicine*. Edsall was appointed to the American Medical Association's Council on Pharmacy and Chemistry, and in 1910 his highly critical report on the state of the pharmaceutical industry had as much impact on the industry as Abraham Flexner's report had on the training of physicians [11]. Although he was actively recruited by other medical schools, Edsall elected to stay at the University of Pennsylvania, having been made Professor and Chairman of the Department of Medicine. However, after frustration at being unable to obtain adequate research space and funding, he left the Department for 1 year to go to Washington University in St. Louis and then moved permanently to Harvard University, where he was appointed Jackson Professor of Clinical Medicine. He remained at Harvard until his retirement in 1935; for 12 years he had been one of the most innovative and popular deans of Harvard Medical School.

Stengel, Pepper's successor, had first been appointed to the Department of Pathology in the University of Pennsylvania, serving as assistant to William Pepper Jr. When his primary appointment shifted to the Pepper Laboratory in 1896, he retained a strong interest in anatomic pathology. In 1898 he published his *Textbook of Pathology*, in which he correlated anatomic and physiological changes in patients with their clinical status. Stengel's tenure as Director of the Pepper Laboratory ended in 1911, when he became Professor of Medicine. He later became Vice-President of Medical Affairs at the University of Pennsylvania.

While Director of the Pepper Laboratory, Stengel continued to treat patients. William Stanton, an assistant instructor in the Pepper Laboratory who worked with Stengel, devised a practical sphygmomanometer that could not only be taken to the patient's bedside but could also measure both systolic and diastolic blood pressures—a previously difficult technical problem. In 1910, Stengel brought the first electrocardiograph to Philadelphia and installed it in the Pepper Laboratory.

Herbert Fox succeeded Alfred Stengel as Director of the William Pepper Laboratory in 1911. Even though the Laboratory continued under the Department of Medicine, it was now directed by a trained anatomic pathologist. Fox's training had largely been as an animal pathologist, and he had been Director of the Laboratory of Comparative Pathology at the Philadelphia Zoological Society before his appointment as Director of the Pepper Laboratory. Fox's research interest was animal models of human disease. One of his most important studies was a collaboration with C.Y. White on tuberculin tests in monkeys; together, they demonstrated the practical value of the tuberculin test in the diagnosis of tuberculosis.

Organizational Changes

In 1914, under an agreement between the University of Pennsylvania and the University Hospital, the work of the William Pepper Laboratory was greatly expanded, to include responsibility for all chemical, serological, bacteriological, and electrocardiographic studies on patients.

Until 1917, there was minimal national oversight of hospitals and clinical laboratories. At this time, the American College of Surgeons proposed certain minimum standards and granted approval to hospitals that provided chemical, bacteriological, serological, and pathological services under competent medical supervision. In 1926, the College went further, amending its prior minimum standard for the clinical laboratory by proposing that the clinical laboratory be under the direction of a medical doctor especially trained in clinical pathology [12].

In 1928, the activities of the William Pepper Laboratory were grouped into Divisions. Division chiefs were appointed for bacteriology, cardiology, chemistry, pathology, and clinical microscopy. A separate section of surgical pathology was established in the Department of Surgery. Neuropathology was jointly managed by the Departments of Neurology and Pathology.

Despite the Laboratory's assumption of more service work, its staff continued to perform research. Leon Jonas developed a national reputation for his clinical research on diabetes mellitus and acidosis. John Cooke Hurst and Charles Francis Long used the glucose tolerance test as an aid for the diagnosis of pregnancy. Charles Wolferth did much of the early research on the use of quinidine to control atrial fibrillation. During this period, the William Pepper Laboratory remained an autonomous unit in the Department of Medicine, where William Pepper Jr. had placed it administratively. Moreover, nomination of the Director of the Laboratory remained the prerogative of the Professor of Medicine, although the actual appointment was made by the Trustees of the University. The University of Pennsylvania, rather than the University Hospital, was responsible for any monetary deficits from the Laboratory's operation.

For many years, the William Pepper Laboratory had been the focus of medical research within the University, but under Herbert Fox its service responsibilities increased as well. Even though Fox himself had little time for research, in 1930 an effort was made to shift more of the clinical laboratory testing responsibility to the hospital and thereby free more of the faculty's time for research.

Fox held important views about the role of the pathologist vis-à-vis that of a clinician. He opined "a pathologist is as much a chief and consultant as any other member of the staff and, consequently, equivalent to any staff chief. The pathologist should be subordinate in no way to the managerial director or the board of directors other than would be the case with a surgeon, a podiatrist, and the like. His duties, if they have to be outlined, are professional matters at the discretion of the staff, and any

member of the staff should be willing to cooperate to the extent that he should be advised and influenced by the staff in hospital matters." Fox also introduced the concept of the laboratory-based physician as a "practitioner of laboratory medicine" rather than a clinical pathologist, because the laboratory physician's responsibilities extended beyond preparing for a clinical decision and involved the applying of some of those decisions [13].

A New Physical Facility

In 1928, the original William Pepper Laboratory building was demolished and a new building, the Martin Maloney building, was erected on its site. The Pepper Laboratory occupied two floors of this facility built for research. The Laboratory staff hoped that the better space and equipment that came with the new building would allow them to devote more time to research. However, the service workload also increased, and little planning went into the organization and management of the clinical laboratory services. Indeed, writing in 1957, Dale Coman, Chairman of the Department of Pathology, stated that "the present organization of the laboratories of pathology in the University Hospital occurred by whimsical evolutionary stages rather than by thoughtful design" [14].

In 1942, J. Harold Austin succeeded Fox as Director of the Pepper Laboratory. He held both undergraduate and MD degrees from the University of Pennsylvania and had worked with Donald D. Van Slyke on the problems of transport of gases by blood. F. William Sunderman organized the Clinical Chemistry Division within the William Pepper Laboratory and was its Director from 1936 to 1948. During this time, Sunderman also wrote a 222-page manual on *Methods in Clinical Chemistry*, and in 1949 edited with Friederich Boerner another book, *Normal Values in Clinical Medicine*. This book, whose publication was delayed by World War II, was the first attempt to compile the data constituting "norms" into a single comprehensive document. Sunderman was also the US pioneer in assessing the quality of performance of clinical laboratories through proficiency testing.

In 1950, Robert F. Norris, an associate in both Clinical Medicine and Pathology, was named to succeed Austin as Director of the William Pepper Laboratory. John G. Reinhold succeeded William Sunderman as Director of the Clinical Chemistry Division of the Pepper Laboratory. Reinhold was instrumental in starting the series *Standard Methods of Clinical Chemistry* and became the third president of the then American Association of Clinical Chemists [15]. Under Norris, the workload of the Laboratory continued to increase. A separate blood banking section was established under Harold Wurzel, and two important contributions to clinical microbiology were made: Edward Steers developed an inoculum-replicating apparatus for the routine testing of bacterial susceptibility to antibiotics, and Harry Morton devised what became known as the Morton cap, a stainless-steel culture tube

closure that made obsolete the use of cotton-wool plugs for the tubes.

In 1968, Howard Rawnsley was appointed to succeed Norris as Director of the William Pepper Laboratory. J. Henry Wilkinson was recruited from Britain to become Chief of the Clinical Chemistry Division but later left Philadelphia to become Professor of Chemical Pathology at Charing Cross Hospital of the University of London. Wilkinson was an internationally recognized clinical enzymologist and a founding member of the International Society of Clinical Enzymology. When Wilkinson left, Dean Arvan became Chief of Clinical Chemistry. With Rawnsley, Arvan organized the first system in Philadelphia for interpretive reporting and clinical consultation for protein analyses. Samuel Raymond developed polyacrylamide gel electrophoresis and introduced one of the first computerized systems for reporting inpatient and outpatient test results. Harold Wurzel became the Director of the Blood Bank, which had been in existence since at least the 1930s, and pioneered the use of automated equipment for blood grouping. He developed reference laboratory services for the American Association of Blood Banks. Wurzel also laid the foundations for a Coagulation Laboratory, which became preeminent in the Philadelphia area. Faculty members in the Pepper Laboratory collaborated with, and provided support for, the group of scientists at the Fox Chase Cancer Center headed by Baruch Blumberg, whose work ultimately led to the discovery of the Australia antigen and earned him a Nobel prize.

Department of Pathology and Laboratory Medicine

In 1967, when Peter Nowell became Chairman of the Department of Pathology, he began the difficult process of consolidating pathology services at the Medical Center. Surgical Pathology had been administratively in the Department of Surgery, Neuropathology in the Department of Neurology, and Laboratory Medicine in the Department of Medicine. Although titles of the staff of the Hospital pathology laboratories were held jointly between the clinical departments involved and the Hospital departments, there was little interaction among the groups of Hospital-based and Medical School pathologists. Then Nowell, whose own brilliant research led to the discovery of the Philadelphia chromosome, moved to strengthen the Department's commitment to immunology. Immunobiology research became well established, and those involved in it made up a separate entity within the Department of Pathology. Nowell recruited Nicholas Gonatas, whose clinical and research efforts are internationally recognized, to head Neuropathology. Nowell's reemphasis of the Department's commitment to research probably accounts for the 82 publications credited to the Department in 1973.

In 1973, after a single term, Nowell resigned his chairmanship of the Department to become the first Director of the University of Pennsylvania Cancer Center. He was

succeeded by David T. Rowlands, Jr., an authority in developmental immunology. Rowlands, with experience as a hospital pathologist, moved to strengthen the links between the Medical School and the Hospital. He recruited Chester Zmijewski to expand tissue typing to include all aspects of HLA typing, antibody screening, and posttransplant monitoring. This led the Pepper Laboratory to become the preeminent laboratory in the Philadelphia area for such services. Burton Zweiman in the Division of Allergy and Clinical Immunology made available tests of connective tissue immunology through the Pepper Laboratory. Dean Arvan, with the assistance of Royden Rand, modernized the clinical chemistry laboratory, introducing a large Vickers analyzer that became the workhorse for much of the chemistry workload for many years.

In 1976, when Howard Rawnsley moved to Dartmouth, Pascal Viola became Director of the Pepper Laboratory. Moreover, in 1978, Rowlands resigned as chairman of the Department of Pathology, to be succeeded in an interim capacity by Arnold Rawson.

In 1980, the newly named Department of Pathology and Laboratory Medicine came into being, and Leonard Jarett was appointed its first chairman. He brought an administrative background in laboratory medicine from Washington University in St. Louis and international recognition as an investigator of insulin action. At the time of his appointment, the Department was understaffed, located in inadequate and outdated facilities, and financially in debt. Jarett initiated complete reorganization of the Department, delegating responsibility and authority to Division heads, thereby achieving a team approach to managing all aspects of the Department. His initial priorities included the acquisition of additional space and the upgrading of existing space for both research and service. The service aspects of the Department were organized into three divisions: Anatomic Pathology, Neuropathology, and Laboratory Medicine. A fourth, the Division of Immunobiology, was established without service but with major teaching and research responsibilities.

The Present

The Department of Pathology and Laboratory Medicine has expanded gradually, its faculty now comprising >60 members who present a broad range of skills in teaching, research, and service. Pathology is taught to medical students in their first 2 years. The major courses, for which the Department consistently receives high ratings, are complemented by a wide variety of electives whereby the students can be exposed to the workings of individual laboratories in the Department. A "year-out" program enables students to spend an entire year in one of the clinical divisions—6 months learning service skills and 6 months undertaking a research project. One 2-week elective course taught by the Division of Laboratory Medicine, with participation by many of the Division's faculty,

residents, and senior technologists, deals with the proper use of the clinical laboratory. Medical students have given this elective the highest ranking of all Medical School courses.

With the support of the faculty, the Chairman has developed residency training in the Department, which is oriented primarily to training faculty for academic medical centers in either anatomic pathology or laboratory medicine. Currently, >40 residents and fellows are participating in the program, an important feature of which is a minimum commitment of at least 1 year to research training. A new program is being developed to train residents for positions in hospitals related to the academic center via outreach programs.

The Department of Pathology and Laboratory Medicine is in the forefront of offering clinical laboratory services, with both regional and national outreach programs. It was one of the first university hospital laboratories to offer molecular pathology testing on a routine basis. At present, the Department is integrating regional hospital laboratories into a network while at the same time taking on work for ~400 primary care physicians.

The research mission of the Department continues to expand. Support from the National Institutes of Health ranks it second highest nationally of all Pathology Departments in the amount of money received and first in the number of grants obtained. The Department also receives considerable support from industry. Several faculty have obtained patents that have led to some start-up University-sponsored companies. Faculty members now produce ~300 research publications and several books each year.

Many of the faculty have achieved national and international prominence. Four individuals who are, or were, members of the faculty—John Reinhold, Royden Rand, Donald Young, and Peter Wilding—have been presidents of the American Association for Clinical Chemistry. Two of the Pepper Laboratory's trainees, David Seligson and George Bowers, have also served as AACC presidents.

This superficial account of the evolution of the William Pepper Laboratory sketches the ideals of its visionary

founder and some of the efforts involved in his successors' pursuit of the same ideals. In spite of today's healthcare climate, the current faculty has an excellent opportunity to continue William Pepper Jr.'s record of, and commitment to, excellence in teaching, research, and patient care. We are confident that in another 100 years our successors will still be reporting more firsts, as the Laboratory continues to evolve.

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