The Foundation of Clinical Chemistry in the United States

In this century of astounding scientific progress and brilliant research, recognition must be given to the patient labors of the early pioneers of science, many of whom laid the foundation for the discoveries that have proved to be of inestimable value to the welfare of mankind. The history of our past, whether in science or art, is always worthy of study and contemplation (1).

In this presentation, I am submitting merely an overview of a few of the immortals and institutions that have contributed to the development of clinical chemistry in the US and in which I have entertained an interest. A complete and detailed accounting of the myriad of chemists and physicians who have contributed to the development of clinical chemistry would require a lifetime undertaking of a professional historian. The Organizing Committee for the 1993 National Convention of the American Association for Clinical Chemistry, chaired by Peter Wilding, prepared an excellent videotape and script of the history and activities of the AACC from its inception in 1948 until the present. The present review will include items only up until the AACC became firmly established; hence, there will be no overlap with the historical items in that account.

Just where the story of the development of clinical chemistry in the US begins is nebulous and somewhat puzzling. However, the story might start by paying homage to the great scientific institutions in Germany during the 19th century, where most of our pioneers in the fields of chemistry and medicine received their training. In Browne's review of chemistry in America from 1876 to 1926 (2), he stated: "In reviewing American contributions to physiological chemistry, the part that Germany has played in educating American scientists stands out strongly. It is a question whether we, in the United States, are not really living in the reflected glory of another country which has been exported hither."

In particular, the contributions of two outstanding European scientists should be recognized, Liebig of Germany and Bang of Norway, for their influence in establishing clinical chemistry as a discipline.

Justus von Liebig (1803–1873), after his appointment as Professor of Chemistry at Giessen in 1826, is credited with having established the first clinical laboratory in the modern sense that was open to serious students and research workers. This laboratory was epoch-making because, according to Welch, it was in Liebig's laboratory that the foundations of modern physiological chemistry were laid (3).

Ivar Christian Bang (1869–1918), the Norwegian scientist, was designated by Van Slyke as the "founder of modern clinical chemistry." Bang, the first to introduce micromethods for the analysis of blood, recognized the need for such methods for the furtherance of clinical science. A literal translation from the introduction of his 1913 papers is worthy of note (4):

... in some respects the blood is still a terra incognita. For determining blood constituents if one could provide methods which require no more blood than can be drawn from the tip of a finger, or the ear vein of a rabbit, it would become possible to explore an inconceivable number of the finer processes of the blood and the cells, with results which a priori are unpredictable.

Unfortunately, Ivar Bang died young, and his publications on blood ultramicro methods that came out just before World War I were in German and received only moderate attention. He measured blood samples gravimetrically on filter paper and titrated eluted volumes.1

During the latter part of the 18th and the early 19th century, chemistry, as a subject of study in a university, was considered merely a branch of medicine; the professor of medicine was frequently the holder of both chairs. William Cullen (1712–1790), Professor of Medicine and Chemistry of the Universities of Glasgow and Edinburgh, and his colleague, Joseph Black (1729–1799), were the teachers of Benjamin Rush (1745–1813). Rush (Fig. 1, left), upon his return to his native Philadelphia, joined the faculty of the Medical School of the University of Pennsylvania and became the first professor of chemistry in America. Rush's Syllabus of Chemistry was the first textbook written by an American and published in our country (1770) (5).

For establishing the scientific approach to medicine in the US, credit must be given to the pioneering influence of William H. Welch (Fig. 1, right). Welch became Professor of Pathology at the Johns Hopkins Medical School in 1893 and initiated the teaching of scientific methodology in the study of medicine. Welch had received his training in experimental medicine under Cohnheim in Leipzig and continued his early researches at Hopkins. Under Welch's influence, it gradually became recognized that, for the pursuit of science, laboratories with adequate facilities were essential for the furtherance of clinical chemistry.

Clinical science laboratories became established in

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1 Quantitative analysis of blood by more practical means was achieved by Folin (with Denis and others), as demonstrated in his 20 publications in 1912. It is not chauvinistic to say that America led the way in creating modern quantitative blood chemistry and its early clinical applications. Folin employed microliter volumes of blood and volumetric-colorimetric apparatus with specifications that could be readily adopted by others for clinical use.

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our country at the end of the last century. Their birthplace was in Philadelphia. The first laboratory was the William Pepper Laboratory of Clinical Medicine at the University of Pennsylvania, established in 1895; the second, the Ayer Laboratory of the Pennsylvania Hospital, was established in 1896 (Fig. 2). Medical laboratories soon became established in other cities, such as at the Rockefeller Institute in New York in 1903. The pros and cons for creating clinical laboratories were vigorously debated in 1900. In dispelling the objections that laboratories were too expensive, Camac blandly advised in an article in the Journal of the American Medical Association (6) that "$300 will fully equip" a hospital laboratory and that "the maintenance of the laboratory can well be accomplished on $50 a year."

Medical research laboratories in our country, such as the Pepper and Ayer Laboratories, were originally affiliated with the Departments of Medicine in their respective institutions.3 However, in the course of time, many of the scientific contributions from these laboratories emanated through the pathologists' study of biopsy and autopsy tissues. As a consequence, with the advent of the services of bacteriology, serology, and eventually chemistry, these disciplines became affiliated with anatomic pathology and subtly became grouped under the term "clinical pathology." The founding of the American Society of Clinical Pathologists occurred during the period of gradual emergence of clinical pathology as a specialty. The year 1922 is regarded as the birthdate of the Society.

The development of clinical chemistry as a specialty in the US was exceptionally slow. However, during the second and third decades of this century, clinical chemistry finally sprang to life, and, as a neophyte, I was privileged to participate in its development. This was the period when chemical descriptions of the body fluids in terms of mass and composition in health and disease were under investigation. Quantitative measurements of biological products were limited to gravimetric, titrimetric, colorimetric, and gasometric procedures. Specific items that are taken for granted today were more or less a blank wall during the first two decades. Knowledge of the metabolism of fats, proteins, and carbohydrates was meagre. Unknown were the roles of vitamins and hormones; the compositions and modes of action of enzymes; the transports of CO₂ and O₂; and the control of salt, water, and acid-base balance, etc.

The names of outstanding biological chemists of that period are recorded in Browne's review (2); however, unlisted were many other distinguished clinical scientists who made important contributions to our knowledge of clinical chemistry. Brief sketches are presented in this overview of just a few of the clinical chemists who were of special interest to me during my early career.

Early Clinical Chemists in the US

John Marshall (1855–1925) (Fig. 3) was probably the first clinical chemist-toxicologist in our country. His undergraduate studies in chemistry were undertaken under Breidenbaugh,4 Professor of Chemistry and Nat-

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3 In my opinion, "clinical science" is preferable.
4 Edward Swoyer Breidenbaugh (1849–1926) was also the teacher of Edgar Fales Smith (1854–1928), Professor of Chemistry and Provost of the University of Pennsylvania; William J. Gies (1872–1956), Professor of Biological Chemistry at Yale University and founder of the Columbia University Dental School; Charles W. A. Stine (1883–1948), Vice President, E. I. du Pont de Nemours Co.; and many others. Breidenbaugh was also my teacher (1919).
ural Sciences, at Gettysburg College (known at that time as Pennsylvania College). After graduating from Pennsylvania College and the Medical School of University of Pennsylvania, Marshall continued postgraduate studies in chemistry in Gottingen, Germany, under Wohler and in Tubingen under Hufner. Returning to Philadelphia in 1882, Marshall became a professor and dean at the University of Pennsylvania and began a long career from 1882 to 1925, teaching medical students and undertaking medical research in problems involving pure foods and the toxicity of drugs, alcohol, and snake venoms. His books, Chemical Analysis of the Urine (1881) (7) and Medicus’ Qualitative Analysis (8), translated from the German (10th edition in 1912), were widely used in our country and abroad.

One of the scientists in the early decades of this century who had a profound influence on the advancement of chemistry into the medical disciplines in the US was Graham Lusk (1866–1932) (9) (Fig. 3). He had undertaken postgraduate studies in Munich for 3 years—2 years spent in the research laboratory of Carl von Voit working on carbohydrate metabolism in diabetes and a third year (1891) with Baeyer in Munich (1). Upon returning to the US, he became active as a professor of physiology at Cornell University and in 1912 became the scientific director of the Russell Sage Institute. Lusk helped to organize the American Society of Biological Chemists and the Society of Experimental Biology and Medicine. He may be regarded as one of the pioneers in the field of clinical chemistry in the US.

During the first two decades of this century, the subject of biological chemistry attracted the attention of an increasing number of investigators interested in the composition of excreta obtained from patients with various diseases. Prominent among these investigators was H. G. Wells (1875–1943), Professor of Pathology at the University of Chicago (not the novelist) (Fig. 3). His book Chemical Pathology (10) was first published in 1907, with a fifth edition in 1925. In the first edition he stated: “Pathologists have come to feel that the opportunities for this requirement of knowledge by means of morphological studies have become reduced to a minimum, while the fields of pathological physiology and chemistry lie still almost unexplored.” Wells’ book was a noteworthy contribution to our knowledge of the chemistry of disease in the early years of this century.

Walter R. Bloor (1877–1966) (Fig. 3) became one of the early clinical chemists in America. The first of Folin’s outstanding graduate students at Harvard (1911), he also served with Folin as an assistant professor of biochemistry from 1914 to 1918. He founded the Department of Biochemistry and Pharmacology at the University of Rochester, NY. I recall visiting him in 1924 and 1925 when the medical buildings at Rochester were still under construction. At that time he suggested that I join his department and continue my researches on cholesterol. I had published a paper in 1925 [with Weidman (11)], reviewing the nine or more cholesterol methods that had appeared in the literature. It was our conclusion that values for cholesterol recorded with the different methods were so inconsistent that no reliable range of normal values could be established. I visited Bloor again in 1947 when his laboratory had expanded to provide facilities for 25 research workers and 72 medical students. Bloor’s principal research programs were concerned with cholesterol, lipids and fatty acid metabolism, enzymes, and the metabolism of adrenal steroid hormones.

Stanley R. Benedict (1884–1936), of Cornell University (Fig. 4), was an important early contributor to the field of clinical chemistry. He devised and greatly improved a number of methods for the study of body fluids, including uric acid, creatine, and creatinine, total sulfur, and sugar. His name became well known as the originator of Benedict’s solution (12), a reagent used to test for the presence of glucose in urine. It is said that Benedict was best known for his ability as a critic (13).

The two giants in the field of clinical chemistry in the US during the second and third decades of this century were Otto Folin (1867–1934) and Donald D. Van Slyke (1883–1971) (Fig. 4).

Meites’ recent excellent biography, Otto Folin, America’s First Clinical Biochemist (14), presents a thorough accounting of Folin’s remarkable achievements in the furtherance of clinical science in our country. For many of us, our first experience in the clinical laboratory was the preparation of a Folin–Wu protein-free filtrate of
blood, which produced a water-clear solution for the colorimetric analyses of glucose, creatine, creatinine, and uric acid with the use of the Duboscq visual colorimeter. Although colorimetry measurements are well known to be based on Beer's Law, it is of note that no publication of August Beer has ever been found that bears any reference to this law (15).

The second giant in clinical chemistry in this century was Donald D. Van Slyke at the Rockefeller Institute. He was able to meet challenging problems in clinical science by combining a thorough knowledge of chemistry with an extraordinary ability to devise efficient apparatus for the analytical methods that he designed. His apparatus for measuring amino acids became a useful instrument in the study of protein metabolism. The chemical techniques for the analysis of blood gases were developed with the use of Van Slyke's manometric and volumetric apparatuses. Van Slyke's gasometric methods involved the vacuum-extraction of liberated gases from blood serum and body fluids and measurement of these gases either volumnetrically or manometrically after selective gas absorption by added reagents. Many of the present-day advances in clinical chemistry in that era emanated from the Rockefeller Institute and Hospital under the leadership of Van Slyke. Outstanding workers in Van Slyke's laboratory with whom I became directly associated both scientifically and socially included A. Baird Hastings (1895–1987), Harvard; William C. Stadie (1896–1959), University of Pennsylvania; John P. Peters (1889–1955), Yale; Glen Cullen (1890–1940), University of Cincinnati; and J. Harold Austin (1883–1952), University of Pennsylvania. All of these men became heads of departments in Eastern medical schools, and all of them contributed to the advancement of clinical chemistry. Peters collaborated with Van Slyke to produce the classic two-volume work, Quantitative Clinical Chemistry (16), in 1931. This masterful contribution became a standard reference for the next quarter of the century.

After the publication of Peters and Van Slyke's treatise in 1931, workers in the fields of medicine and clinical science expressed the need for ascertaining and determining values and characteristics that constitute the so-called "norm." Although the need was clearly recognized, practically no attempt had ever been made to select and assemble such pertinent data into a comprehensive unit. At the urging of publishers and associates, Frederic Boerner and I were persuaded to engage in this undertaking. The book, Normal Values in Clinical Medicine (17), was not published until 1949, owing to Dr. Boerner's early demise and the intervening years of World War II.

When I undertook the organization and supervision of the chemistry divisions of both the Pepper and Ayer Laboratories in the late 1920s, 10 to 20 analyses were undertaken per day in each laboratory. Twenty years later, the number of analyses had increased to between 75 and 125 per day in each laboratory. Not only was there a spectacular increase in the amount of routine analyses, but the variety had increased correspondingly. Of great importance to modern blood chemistry analysis was the development of suitable syringes for blood drawing and the US industrial development of instrumentation.

Before 1920, comparatively few data were available pertaining to changes in the composition of body fluids during the course of various diseases. This was due mainly to the lack of appropriate methods then available. Most of the analytical methods required relatively large amounts of the fluids. In the score of years that followed, analytical methods were developed that required only 1 or 2 mL of body fluids. This led to a profusion of publications on serum electrolytes during health and disease, the colligative properties of body fluids, conductivity, blood volume, acid–base equilibrium, etc.

One of the first books on methodology for clinical chemistry was published by Victor C. Myers (1883–1948) (Fig. 4) in 1921, entitled Practical Clinical Analysis of Blood (18). Myers's book contained procedures for the analysis of only seven components of blood: nonprotein (urea) nitrogen, uric acid, creatinine, sugar, carbon dioxide, cholesterol, and chlorides. Incidentally, Myers became renowned for developing the blood sugar method used by Banting and Best in the discovery of insulin (19).

The number of procedures that became available for the analysis of body fluids increased remarkably during the ensuing years. For example, the procedure book I published in 1945, Methods in Clinical Chemistry (20), contained >50 quantitative methods for measuring the components of body fluids. Levinson and MacFate in 1937 published an outstanding textbook, Clinical Lab-
An historian in clinical science cannot help but be amazed at the explosive burst of scientific activity in the field of clinical chemistry that emanated from clinical laboratories at the middle of this century. The historian will be especially impressed with the progress of clinical chemistry as evidenced by the astonishing increase in the number of medical publications involving chemistry. By 1949, the field of clinical chemistry had begun to exert a dominant role in laboratory medicine. However, let it be noted that clinical chemistry’s place in the field of medicine was not truly established until accurate, useful quantitative analyses of the body fluids, tissues, and excreta became available. It was not uncommon practice for physicians in the first half of this century to obtain a sample of blood from a patient, divide it into two parts, send the blood to two different laboratories, and obtain widely divergent results. Once confidence in the accuracy of the results of chemical analyses became established, clinicians began to correlate the changes in the body’s chemical components with disease states.

Mid-Twentieth Century Developments

Three major noteworthy activities in the middle of this century led to the furtherance and the salutary advancement of clinical chemistry in the US:

1. The creation of the American Association of Clinical Chemists (1948), now the American Association for Clinical Chemistry, Inc.
2. The inauguration of a nationwide proficiency testing service for clinical chemistry (1949).
3. The establishment of comprehensive seminar workshops in clinical chemistry in 1954 in an effort to improve the accuracy and reliability of measurements undertaken for the care and treatment of human beings.

American Association for Clinical Chemistry. The American Association of Clinical Chemists was formed principally through the efforts of the clinical chemists in New York City under the leadership of Max M. Friedman. The first official meeting of the Association was held in New York on December 15, 1948. I recall meeting with Friedman early in 1948 to discuss the qualifications for membership and the future course of the proposed organization. There were many proponents for limiting membership to persons holding doctorate degrees and others who favored membership for all persons working in clinical chemistry laboratories. It was finally agreed that membership levels should be based on the educational requirements of the American Chemical Society but would include only those chemists working in the medical area. At the meeting of the new organization held in Atlantic City in September 1949, it was decided to publish a newsletter entitled The Clinical Chemist. After several years, the Association started a monthly journal, Clinical Chemistry (1955). This journal underwent a continual expansion, from 28 articles in the first year to sometimes almost double that number per month at the present time. Clinical Chemistry is now recognized as one of the leading scientific journals in our country.

Proficiency testing in clinical chemistry. In 1946, the Committee of Laboratories of the Medical Society of Pennsylvania undertook a survey to check the accuracy of chemical measurements on common components of blood made in hospital laboratories throughout the state. The results of the Pennsylvania survey indicated an appalling inaccuracy in the measurements of the components (22). This led to two national surveys under the auspices of the College of American Pathologists. The results of these three surveys, all of which emanated from my laboratory, were even more appalling in their unfavorable findings. As a result of these early surveys, clinical chemists and directors of clinical laboratories became deeply concerned with the inaccurate results of analyses being reported from their laboratories. It became unthinkable that the faulty laboratory practices should continue. These leaders recognized that, to maintain high standards of chemical analysis, it was essential to keep the accuracy of measurements under constant surveillance. This led to the inauguration of a monthly proficiency testing service, which was conducted by our laboratory without interruption for 36 years (23–26).

The Proficiency Test Service enabled each participating laboratory to obtain an unbiased and critical assessment of its proficiency in relation to that of >2500 clinical laboratories throughout the US. The service was, in essence, a self-auditing discipline that was in continuous operation until 1985 (36 years), when it was incorporated into the Check Sample Program of the American Society of Clinical Pathologists.

Seminars in clinical chemistry. Experience in giving certifying examinations for the American Board of Pathology established that the directors and residents in hospital laboratories were not being trained in the fundamental procedures of analytical chemistry—e.g., weighing of chemicals, calibration of pipets and burets, preparation of standard solutions. The effort to correct these deficiencies in clinical chemistry led to the formation of an informal subgroup of ~30 members of the American Society of Clinical Pathologists (ASCP). Initially this group was known as the Friends of Clinical Chemistry. Because ASCP did not accept PhD scientists into full membership, the Friends of Clinical Chemistry in 1949 formed a separate organization known as the Clinical Science Club, which included both MD and PhD members. This club later became incorporated as the Association of Clinical Scientists.

Our group of dedicated clinical scientists resolved to correct the deficiencies in the training of students entering the field of clinical chemistry and to further high

The College of American Pathologists was founded in 1946, and I served as a member of the Founding Board of Governors. Among the first projects inaugurated by the College were two national surveys on the accuracy of chemical components of blood in clinical laboratories, which I conducted. The results were so overwhelmingly discrepant that the Board of Governors, by official action, requested that they not be published.
professional standards of performance. As a starter for this resolve, we decided to schedule a seminar workshop (Fig. 5) on hemoglobinometry in conjunction with the International Congress of Clinical Pathology in Washington, DC, on September 6–11, 1954. There were no precedents to guide us, as all plans for the workshop had to evolve de novo. The topic of hemoglobinometry (27, 28) was selected because hemoglobin was the most frequently analyzed component of blood, and national surveys had revealed marked discrepancies in the results of hemoglobin measurements both in our country and abroad (29). I was chosen to be the director of the workshop, with Capt. Vernon Martens, director of laboratories at the Naval Medical Hospital, as my assistant.

The Naval Medical School in Bethesda graciously invited us to use the student laboratory facilities for our scheduled workshop on September 8, 1954. Owing to the limitation of space, only 120 directors of clinical laboratories could be accepted for the workshop, although many more had applied. There were no registration or tuition fees. Instrument manufacturers and laboratory supply companies were exceptionally helpful in providing the instrumentation and supplies required for the registrants and the additional 30 instructors. The Naval Medical Center generously cooperated by printing a manual (30) detailing the methodologies for the workshop analytes. Later, a condensed version was made more widely available (31).

Two 3-h laboratory sessions were held. The workshop exercises covered preparation of reagents, measurement of iron, preparation of an iron calibration curve, analysis for iron in whole blood, measurement of oxyhemoglobin in blood, and calibration of pipets. (Unless certified by the US Bureau of Standards, the calibration markings of commercial volumetric glassware could not be relied on.) At the conclusion of the laboratory exercises, there was enthusiastic, unanimous agreement that the workshop format was a superb and effective method for continuing education in clinical chemistry. With the cooperation of the US State Department and the Navy, an invitation was accepted to present the Hemoglobin Workshop at the Royal Army Medical College in London in 1957 (Fig. 6). More invitations led to similar workshops in Brussels, Belgium, and San Juan, Puerto Rico.

As a result of the enthusiastic response from participants, workshops in clinical chemistry have continued on as an annual activity of the Association of Clinical Scientists ever since. The 44th seminar workshop of the Association of Clinical Scientists, held in Toledo (November 4–7, 1993), was on Advances in the Laboratory Diagnosis of Cancer.

During the lifetime of every organization, occasions occur in which it seems appropriate to pause for a moment to reflect upon its origins and early history, to review its purpose, and to test its basic principles against the backdrop of modern society. One can hope that this relatively brief overview will have served its mission.
Special credit and appreciation are given to the Library of the College of Physicians of Philadelphia for photographic prints from the Sturgis and other historical collections.

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Frederick William Sunderman is a great living pioneer of clinical laboratory sciences. He participated in and witnessed the birth of modern quantitative clinical chemistry, largely an American innovation. He helped develop and promote the College of American Pathologists and the American Society of Clinical Pathologists and founded the Association of Clinical Scientists. He has edited key clinical pathology-related journals while serving as an educator in that field. He has published more than 30 books and laboratory manuals and more than 300 scientific articles. Wherever he has worked