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History

Clinical Chemistry Since 1800: Growth and Development

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The 19th and 20th centuries witnessed the growth and development of clinical chemistry. Many of the individuals and the significance of their contributions are not very well known, especially to new members of the profession. This survey should help familiarize them with the names and significance of the contributions of physicians and chemists such as Fourcroy, Berzelius, Liebig, Prout, Bright, and Rees. Folin and Van Slyke are better known, and it was their work near the end of the second decade of the 20th century that brought the clinical chemist out of the annex of the mortuary and into close relationship with the patient at the bedside. However, the impact on clinical chemistry and the practice of medicine by the 1910 exposé written by Abraham Flexner is not as well known as it deserves to be, nor is the impetus that World War I gave to the spread of laboratory medicine generally known.

In the closing decades of the 20th century, automated devices produced an overabundance, and an overuse and misuse, of testing to the detriment of careful history taking and bedside examination of the patient. This is attributable in part to a fascination with machine-produced data. There was also an increased awareness of the value of chemical methods of diagnosis and the need to bring clinician and clinical chemist into a closer partnership. Clinical chemists were urged to develop services into dynamic descriptions of the diagnostic values of laboratory results and to identify medical relevance in interpreting significance for the clinician.

The modern understanding of disease began with the work of Giovanni Battista Morgagni (1682–1771), who introduced the anatomic concept of the organ as the seat of disease. For the first time a detailed analysis of postmortem findings was correlated with clinical symptoms and case histories. Disease processes were explained in terms of localized pathologic anatomy, rather than as attributable to an imbalance of the humors diffused throughout the system.

By the early 1800s, the anatomic approach that replaced the centuries-old interest in the body fluids—the centerpiece of humoral theories—had become too dominating and exclusive, and there was a renewed interest in examination of body fluids. Chemical analysis was seen as a refined type of dissection. The chemical revolution, directed by the work of Antoine Laurent Lavoisier (1743–1794), set down the foundation of modern chemistry with its new language of analysis. It was now possible to begin to understand chemical changes in nature as well as those produced artificially. However, despite improvements in analytical techniques, the complexities of animal chemistry made progress difficult. One branch of animal chemistry in which reliable results could be obtained was the analysis of urine and its deposits, using the methods of inorganic chemistry developed in assays of ores.

Animal Chemistry and Vitalism

Antoine François de Fourcroy (1755–1809) *(1)*, a chemist and nonpracticing physician who was interested in the application of chemistry to medicine, devised what probably was the first plan for establishing clinical laboratories in hospitals. It came as part of the reforms in the wake of the French Revolution. He proposed that a chemical laboratory be located near the wards, where chemical analysis of urine and other excretions of the sick could be carried out. Fourcroy believed that such investigations represented a new means of studying diseases *(2)*. However, practical implementation was destined to fail at this early stage because adequate chemical methods were not yet available. In any event, there were initial successes with the analysis and classification of hundreds of urinary calculi by Fourcroy and his assistant Nicholas Louis Vauquelin (1763–1829) *(3)*.

Jöns Jakob Berzelius (1779–1848) gave up medical practice to concentrate on scientific research and became the leading chemist in Europe during the first half of the 19th century. With no adequate Swedish textbook of chemical subjects, he published *Föreläsningar i Djurkemien* [(Lectures in Animal Chemistry), 2 volumes, 1806 and

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1808], which was based on the chemical knowledge of that time for animal tissues and fluids and included a protocol for examination of body fluids. Although never translated into English, the book, the first of its kind, directed the interest of physiologists and chemists to the chemical composition and processes taking place in the animal body. Berzelius defined organic chemistry as the part of physiology that describes the composition and chemical processes of living bodies. It was widely believed that these activities occurred only in living organisms. Most chemists of that time thought that a special "vital force", operating only within organized living things, was required to synthesize organic substances and convert inorganic material into organic compounds. As a result, only organic compounds were identified or associated with living forces. It was inconceivable to these vitalists that bodily functions could be explained by chemistry. They believed that the composition and workings of the body required a study of the vital functions.

However, there was growing opposition to vitalism along with a trend to explain vital phenomena in terms of physicochemical processes. This change was brought about mainly by Liebig's *Animal Chemistry.* This book was important for the development of clinical chemistry because it introduced a quantitative method of observation into physiological chemistry.

The work of Justus Liebig (1803–1873) was one of the forces making chemistry almost a German monopoly in the 19th century, as his school of chemistry was attracting students from all over the world. In *Animal Chemistry (4)*, Liebig treated physiologic processes as chemical reactions subject to the laws of chemistry and physics. The book was significant for the development of clinical chemistry because it introduced a quantitative method of observation into physiological chemistry.

However, Liebig's speculative excesses went far beyond the available experimental evidence. In his critique of *Animal Chemistry* in 1843, Berzelius wrote: "This easy kind of physiological chemistry is created at the writing desk, and is the more dangerous, the more genius goes into its execution, because most readers will not be able to distinguish what is true from mere possibilities and probabilities" *(5).* Although he had never performed an experiment on living animals, Liebig provided one of the first comprehensive pictures of chemical exchanges of the vital processes. *Animal Chemistry* had the most significant single impact on the future course of physiologic thought and investigation because of the discussion and new research by others that he helped to stimulate.

Chemical Analysis of Body Fluids

Applications of chemistry to medicine at the beginning of the 19th century were directed to the understanding of disease rather than to its relief. Vitalists denied chemistry a role in physiology. However, William Prout (1785–1850) *(6)*, himself a vitalist, was an early and consistent advocate of the benefits to be derived from the application of chemistry to physiology in the treatment of disease. He also favored the study of physics and chemistry by medical students. Henry Bence Jones credited him with being first to make the true connection between chemistry and medical practice *(7)*.

Prout's *An Inquiry Into the Nature and Treatment of Diabetes, Calculus, and Other Affections of The Urinary Organs* (1825) included a list of *Tests, Apparatus, &c. required in making Experiments on the Urine.* "These with one or two small test tubes, and small stoppered phials, containing solutions of pure ammonia, potash, and nitric acid, can be readily packed into a small portable case, or pocket book, and will be sufficient, by the aid of a common taper or candle, to perform all the experiments on the urine, and urinary productions, that are commonly necessary in a practical point of view" *(8)*. Barely 1 year later, Richard Bright's studies of renal disease would add a spoon to this portable laboratory, for revealing the presence of albumin in heated urine.

Citing the lack of progress in animal chemistry, Prout's remedy was for physiologists to become chemists *(9)*. "Chemistry, however, in the hands of the physiologist, who knows how to avail himself of its means, will, doubtless, prove one of the most powerful instruments he can possess; . . . " *(10)*.

In 1827, Richard Bright clearly established the overall correlation of edema, albumin in the urine, and diseased kidneys observed after death when he described and illustrated the renal disease (chronic nephritis) that still bears his name. Having no particular knowledge of chemistry himself, Bright left the urinalysis to John Bostock (1773–1846), an Edinburgh MD graduate who succeeded Alexander Marcet (1770–1822) as lecturer in chemistry at Guy's Hospital Medical School *(11)*.

Bostock suggested that the presence of albumin in the urine may not necessarily be an indication of disease because "an albuminous state of the urine is produced by such a variety of circumstances, and many of them of so trifling a nature, as to render it almost a constant occurrence. In a great majority of cases it may be detected in the urine of persons in apparent health, by means of the appropriate tests" *(12)*. Nevertheless, this is where chemistry, with the first really useful diagnostic laboratory test, made its first great impact on clinical medicine. It was the starting point of modern clinical pathology. However, in the middle of the 19th century, despite the correlations found by Richard Bright, most medical men still regarded illness as an essentially general phenomenon and did not think it necessary to look for an association between symptoms in the living and structural pathology in the dead.

Although the utility of chemistry in medicine was gradually gaining recognition, the medical profession in general was still indifferent and even hostile to the idea that investigative work in animal chemistry could lead to improved methods of diagnosis, prevention, and cure of diseases. The widespread vitalistic view that body pro-

cesses could never be understood was supported by the theology of the time.

Thomas Hodgkin (1798–1866), pathologist and colleague of Bright at Guy's Hospital, believed that chemical studies were relevant to clinical medicine, and he challenged the tradition of vitalism taught by many clinicians. Inasmuch as exchanges are continually occurring between the solid parts and the blood, "it is in the blood that we must look for many important modifications in connection with disease". According to Hodgkin, disease will one day be explained in terms of "molecular movements", more chemical than mechanical, "by which our bodies . . . are continually changing the elements of which they are composed" *(13)*. But where chemistry is unable to explain physiologic phenomena, it is because "science has not yet arrived at the height of its perfection" *(14)*.

In an age when the description of disease was often a mere catalog of symptoms, there were a few medical men who appreciated the usefulness of chemistry in the explanation and treatment of disease. Although investigations in the chemistry of disease were being carried out in the 1820s and 1830s by Bright, Bostock, Rees, Prout, Bence Jones, and Marcet, its application in routine diagnosis was not very widespread.

On the Analysis of the Blood And Urine, in Health and Disease. With Directions for the Analysis of Urinary Calculi (1836), by George Owen Rees (1813–1889), was one of the earliest books in English on animal chemistry. Written as a manual for the medical practitioner in response to "The increased desire for a more intimate acquaintance with animal chemistry, which has lately been evinced by the medical profession, . . . ", Rees hoped it would stimulate study of animal analysis as applied to disease and would direct "attention to a subject which, in all probability, is no less rich in discovery, than it is neglected and uninvestigated by the great body of the medical profession. . . . Since chemists are not physicians, we shall scarcely benefit by their art, except by making the physician a chemist" *(15)*.

Diagnostic Signs

The discoveries of new substances in the healthy and diseased body had spawned a wave of interest in clinical chemistry as a recognizable identity in the late 1830s and 1840s. There followed a systematic search for pathologic changes in the chemical composition of body fluids to guide medical diagnosis and control therapy. A key location of research was Würzburg, where Johann Joseph Scherer (1814–1869) was the first to use the term "clinical chemical laboratory" (klinisch-chemischen Laboratorium) in the foreword of his monograph *Chemische und Mikroskopische Untersuchungen zur Pathologie* (1843).

During this mid-century period, tests were developed for many constituents in urine as volumetric (titrimetric) methods replaced the laborious gravimetric techniques. Characteristic reactions were reported for protein, bile acids, sugar, and urea. Proteinuria and glycosuria, as well as glucose and bile pigments in blood, became known as "diagnostic signs". The anticipation of finding other signs heightened interest in applications of chemistry to medical problems. However, although there were many isolated pieces of chemical information about blood and urine analysis in health and disease, they did not fit together. Investigators did not realize how little they knew about basic physiology and pathology when they rushed in to attack the most difficult problems in pathology. The analytical chemistry of urine had outdistanced them and would remain so for the rest of the 19th century. Hence, the concept of a "chemical sign" was premature.

Writing to his teacher Justus Liebig in 1849, Max Josef von Pettenkofer (1818–1901) said: "The reagent-case now holds the same position as the crocodile and basilisc used to in the stalls of those itinerant Aesculapian quacks. We must have it, but we can get no use out of it" *(16)*.

The burst of interest and activity in the simple chemical examinations of blood and, particularly, urine ended about 1860 because it failed to produce any significant benefits for the clinician. The majority of practitioners lost interest in chemical analysis of biological fluids *(17)*. In addition, limitations in the knowledge of chemistry and dependable methodology in the middle of the 19th century did not allow for rapid further development.

The revival of clinical chemistry in Germany and Austria came sometime after 1860. The clinicians became chemists and began using chemistry for their experimental research. The preferred term was "pathological chemistry". The subject was covered in medical school courses as "chemical-microscopical examinations". Similar developments followed in England and the United States—with a lag time of ~20 years *(2, 17)*. However, in England it was mainly the microscope and bacteriologic examinations, not chemistry, that led to the setting-up of clinical laboratories.

A New Optimism

Berzelius had presented a protocol for examination of body fluids in 1806, but by 1840 he expressed his reservations in *Lehrbuch der Chemie*, saying: "There was a long way to go before chemical examination could differentiate between normal and diseased blood beyond the variations occurring in healthy individuals" *(18)*. But optimistic views were also being expressed. Alfred Becquerel (1814–1862) hoped to show that chemical changes in the urine could help establish diagnosis and monitor the course of the illness *(19)*. Gabriel Andral (1797–1876), in a lecture to the medical faculty in Paris, predicted that chemical analysis of body fluids altered by disease would play an increasingly important role in the investigation of pathogenesis *(20)*.

In his memoirs, Charles J.B. Williams, the first President of the Pathological Society of London, told of a house call early in his career and the favorable impression he had made by his "habit of bringing . . . not only a stethoscope, but also test-tubes and a few chemical reagents for

the examination of the state of the secretions, &c". Writing in 1884, he added that this practice was a matter of course in later years, but it was not so 40 years earlier *(21)*. Even as late as the 1860s, physicians were cautioned not to be ostentatious with their scientific examination of the urine because "abuse of his knowledge in this respect will stamp him in the eyes of his colleagues and of the public as a charlatan" *(22)*.

In 1848, Alfred B. Garrod (1819–1907), assistant physician at University College Hospital in London, described the application of chemistry to pathology and therapeutics as being of the greatest importance to the medical practitioner. "How very imperfect our knowledge must be, both of the healthy and diseased condition of the body, if we do not call in the aid of chemistry to elucidate its phenomena" *(23)*.

In the fourth edition of *A Guide to the Qualitative and Quantitative Analysis of the Urine, Designed Especially for the Use of Medical Men* (1863), Carl Neubauer and Julius Vogel assured the reader that analysis of urine at the patient's bedside was no longer a lengthy and difficult procedure. Aided by the microscope, positive conclusions concerning changes in the body could be made *(22)*. "Most of the quantitative analyses of the urine . . . have . . . been so simplified, that any properly educated physician may readily undertake them". If the physician did not have the time to run the analysis himself, "a chemist may always be found ready, for a moderate consideration, to undertake the simplified analysis; and, if necessary, any intelligent attendant, or servant, provided he be careful, may, as I know from experience, be taught enough for the purpose in a very short time" *(22)*.

Chemistry in Medical Education

In 1850, Henry Bence Jones (1813–1873) of St. George's Hospital stressed the practical diagnostic value of chemistry. "By such examination, both in serious diseases and in slight disorders, I believe that as much or even more useful evidence will be obtained regarding complaints of the stomach, the kidneys, and the system than has been acquired respecting diseases of the lungs and heart by the stethoscope" *(24)*. His selection as President of the Chemical Section of the British Association for the Advancement of Science, the first for a practicing physician, indicated the high regard in which he was held as a chemist and was evidence of the relationship that existed between chemistry and medicine. He appealed to the Chemical Section for greater attention to chemistry in the training of doctors. "Whatever sets forth the union of chemistry and medicine tends to promote not only the good of science but also the welfare of mankind". Citing the discovery of Richard Bright that chemistry is necessary for understanding the nature of disease, he stressed that "every medical man [must] become a chemist if he wishes to have any clear idea of the action of air, food, and medicine, . . . " *(25)*.

Bence Jones also urged revision of the medical school curriculum to include a first-rate instruction in English so that it could explain the nature of the disease and course of therapy in the most idiomatic and unmistakable English. Medical men would be much better served if they spent some time in acquiring knowledge about chemistry and physics instead of learning some Latin and less Greek. He contrasted "the present state of medical education with that reasonable knowledge, which . . . ought to be possessed by those who attempt to understand and to regulate an apparatus that works only whilst oxygen is going into it and carbonic acid is coming out of it" *(25)*. Opposition to these chemical ideas came from those who still believed that the chemistry of life was governed by a vital force. Most physiologists were vitalists, as were many of the leading animal chemists, including Liebig.

A leading critic of the role of chemistry in medical education was Armand Trousseau (1801–1867), a prominent clinician and convinced vitalist. He did not believe that chemical studies were relevant to clinical medicine. He advised those entering medicine not to lose time "in acquiring too extensive a knowledge of chemistry". Although not "wholly useless", he said, this is an accessory study and "too unimportant to be pursued at the sacrifice of physiology, clinical instruction, and therapeutics, . . . ". He condemned the exaggeration of the importance of accessory studies, their pretentiousness, and their "being mixed up with our art in an inappropriate and impertinent manner". He pleaded for "a little less science, and a little more art!" *(26)*.

Trousseau was critical of the vanity of the chemists, who believed that they could explain the laws of life and of therapeutics because they knew the nature of some of the reactions that take place in the living body. The laws of living matter "for the present remain autonomous, special, unexplained, inexplicable, . . . ". He agreed with the majority of physiologists and physicians who believed that "the acts of organic life, and . . . those of animal life, are subject to laws which . . . ought to be regarded as essentially different from those which govern inorganic matter". In living organisms, chemistry is controlled by special powers, "because in it there are special results". Trousseau was willing to confess his "ignorance as a chemist, but only on condition that chemists admit their ignorance as physiologists and physicians" *(26)*.

Follow the Money

In 1878, there were no clinical laboratories in London, not even in the teaching hospitals, and few of the largest hospitals provided any facilities for what later became known as "clinical pathology". In *The Microscope in Medicine*, Lionel Smith Beale (1828–1906) wanted laboratories and microscope rooms to be established at the major hospitals, for research and teaching. Opposition to microscopic inquiries was voiced by some of the senior and most influential members of the medical profession. Medical research was held in low regard because it had little if any money-earning value *(27)*.

Beale believed that there was only one hospital in London with efficient means for conducting scientific inquiries into the nature of disease, but not one that would allow as little as £300 for this kind of work. He urged rich establishments such as Guy's, St. Thomas's, and St. Bartholomew's to take the lead. "One would think that £1,000 of their large incomes might be spent very advantageously in scientific work, but I fear it will be difficult indeed to convince the authorities who have command of the purse". The persons most suitable to engage in medical research, said Beale, were the young physicians and surgeons attached to the medical schools and hospitals. As inducement, Beale suggested providing them with a place in which to work, "and an income just sufficient to provide the necessaries of existence—say, £100 a year". Would this not be time better spent by a talented physician and surgeon than for him to devote "fifteen or twenty years to seeing out-patients?" *(27)*. Could Beale not see ahead to the effect such spartan living for so extended a period would have on the quality of the medical research that he wanted to encourage?

The great hospitals in the country were established as charities for the relief of the sick poor, and it was considered inappropriate to spend these funds on laboratories or research workers. It took until the end of the century before the governors of the charity teaching hospitals realized that such laboratories were of the greatest service to the sick poor.

Generation Gap

The rapid growth of modern science prompted a practicing physician and essayist, John Brown of Edinburgh, to write in 1882: "Let us by all means avail ourselves of the unmatched advantages of modern science, and of the discoveries which every day is multiplying with a rapidity which confounds; let us convey into, and carry in our heads as much as we safely can, of new knowledge from Chemistry, Statistics, the Microscope, the Stethoscope, and all new helps and methods; . . . ".

"Chemistry and Physiology have become, to all men above forty, impossible sciences; they dare not meddle with them; and they keep back from giving to the profession their own personal experience in matters of practice, from the feeling that much of their science is out of date; and the consequence is, that, even in matters of practice, the young men are in possession of the field" *(28)*.

Progress in America

In the United States, as of 1870, the average medical student or average practitioner had barely a nodding acquaintance with chemistry and could not use a microscope. Clinical pathology was nothing more than simple examination of the urine *(29)*.

The earliest beginnings of the clinical laboratory in America took place in Boston in 1847, when the trustees of the Massachusetts General Hospital, recognizing the powerful aid that the science of medicine "has received from the study of organic chemistry and the knowledge and use of the microscope", authorized the purchase of a microscope at a cost not to exceed $50. In 1851 they established the position of "Chemist-Microscopist", whose duties included assisting at autopsies, and in 1855 they separated the position of chemist from that of microscopist, for whom a "Pathological Cabinet" was provided. A small laboratory was built in 1874, but it soon became inadequate, and a new "Clinico-Pathological Laboratory" was opened in 1896, on the 50th anniversary of the first public demonstration of ether during surgery. Shortly thereafter, a chemical laboratory was provided and a chemist appointed *(30)*.

The Philadelphia General Hospital created the position of microscopist in 1866, and in 1885–1886, a small two-story building was erected for a morgue and laboratory for clinical microscopy and bacteriology. The Hospital of the University of Pennsylvania, the nation's first university-owned hospital, opened the William Pepper Laboratory of Clinical Medicine on December 4, 1895. This was the first laboratory of its kind in the United States amply equipped for both routine work and research and provided with its own four-story brick building.

To cope with the growing number of chemical tests, the physician in private practice, rather than do the tests himself or hire an assistant, would usually enlist the help of chemists or physicians skilled in chemistry. This demand led to the establishment of private laboratory services. As early as 1883, a Philadelphia physician, Judson Daland, advertised his willingness to make *thorough chemical and microscopical urinary examinations* . . . in the most careful manner, and to furnish promptly a written report of the results. A moderate fee will be charged" *(31)*.

Biochemical analyses were making inroads in the curricula of medical education. The instructional program of the Department of Medicine at Johns Hopkins Medical School (opened in 1893) emphasized that particular attention would be paid "to Clinical Microscopy in the study of the urine, sputum, and blood" in the third year. "The students will learn the use of the instruments of precision employed in clinical research—the Stethoscope, Microscope, Ophthalmoscope, etc.—by daily routine manipulations" *(32)*. Speaking about the clinical and ward laboratory, William Osler (1849–1919), physician-in-chief at Johns Hopkins from 1889 to 1905, said: "They are to the physician just as the knife and scalpel are to the surgeon" *(33)*.

At Harvard University, the catalog entry for physiological chemistry (1896–1897) stated that "instruction in physiological chemistry is given by lectures, recitations and exercises in the laboratory where each student will be taught the chemistry of the carbohydrates, proteids and fats, the chemistry of digestion, the chemistry and microscopy of the urine and the tests for the important poisons".

Technical progress in the 1880s and 1890s was rapidly having an effect on practice in America. In 1897, a

prominent figure in medicine wrote: "The microscopical and chemical examinations of the secretions and excretions and of the blood have become our daily duty. . . . The time is indeed at hand in which, without the ready access to a laboratory manned by experts in all these lines, or the association with a trained laboratory assistant, no physician can do his patients, himself, or his science justice" *(34)*.

By the turn of the century, increasing numbers of physicians were relying on laboratory tests. However, these "diagnostic" procedures provided essentially qualitative (yes/no) results. Writing in 1900, Camac said that the time had now come to bring the practical application of the knowledge and methods developed in the clinical research laboratories to the bedside in the hospital or to the ward clinical laboratory. Objections were raised by some authorities that such laboratories were scientific luxuries because they required space, were expensive, and imposed on the busy schedule of the interns. Concern over the appropriation of apparatus by members of the intern staff could be dealt with by the hospital's examining board, in ascertaining more correctly the character of applicants for the position of internship. Camac also recommended that clinical tests be a full-time assignment for one or more of the ward's interns, for bacteriology, clinical microscopy, and chemistry *(35)*.

Clinical Pathology

George Dock described his experiences in clinical pathology in the 1880s and 1890s when, during the 17 years that he was head of medicine at University Hospital in Ann Arbor, his office was the clinical laboratory *(36)*.

In 1890, clinical pathology was defined as the examination of urine, blood, sputum, and the bile, but London hospitals did not always provide adequate facilities for this kind of work. The arrangements for clinical research were, as a rule, far inferior to those afforded for postmortem investigations. In Continental hospitals, on the other hand, clinical laboratories were attached to the principal wards, a necessary arrangement if the work was to be properly done *(37)*.

The term "clinical pathology" seems to have come into use in the 1880s, although the subject is much older than this date suggests. In 1886, Julius Dreschfeld, professor of pathology in Manchester, wrote in the *British Medical Journal*: "But even apart from *post mortem* examinations, there is a bed-side or clinical pathology in which English physicians have taken a leading share; as, for instance, the study of the altered arterial tension in certain diseases" *(38)*. He clearly gives the term a wider meaning than we have today, for he includes the study of blood pressure in patients. Although this may be the earliest use of the term, "clinical" was used here in the context of active practice or clinical work.

Clinical Chemistry (1883), by C.H. Ralfe of London Hospital, was the first book in English to carry the title "Clinical Chemistry". In the preface, Ralfe states: "In spite of the disparagements of such eminent clinical teachers as Graves and Trousseau, chemistry has become more and more important to the physician as a means of elucidating many pathological conditions, or of determining the character of the morbid changes effected in tissues or secretions. Indeed, it is becoming more and more evident that we must eventually look to Chemistry for information with regard to the primary alterations that occur in fluids and tissues, and which are the first step in every disease".

In America, Charles W. Purdy could claim "through uranalysis alone can an almost daily increasing number of diseases be determined, their intensity be gauged, and their progress toward recovery, or their tendency toward a fatal termination be predicted" *(39)*. His book, *Practical Uranalysis and Urinary Diagnosis. A Manual for the Use of Physicians, Surgeons, and Students*, was adopted as a text in more than 60 medical colleges in the United States. A fourth edition was published in 1898.

A Rush to Publish

In 1902, the assistant resident physician in charge of the clinical laboratory at Johns Hopkins Hospital wrote: "Clinical laboratories are growing in favor and influence; publishers have produced a superabundance of textbooks which purport to 'make clinical chemistry easy'; medical journals accept at sight articles on almost any chemical subject, some of scientific value, some of practical value, some of no value". Every practitioner received a free course in chemistry through the mails and was swamped with pamphlets detailing some recent chemical achievement. The whole practical medical world was studying chemistry. Publication in clinical chemistry was becoming the goal of the scientific practitioner *(40)*. The preoccupation with publication was seen as a hindrance to progress.

Clinging to the Past

In 1907, a Boston physician addressing the Congress of American Physicians and Surgeons said that "the oldest and simplest methods are still the best", and added: "In nine out of ten cases, as I see them in private practice, I make no examination of the blood other than that afforded by direct inspection of the color of the blood when soaked into a slip of paper". Nor did he "regard it as essential, or even of any considerable importance, that every patient suffering from diseases of the heart, lungs or stomach should be examined by the X-ray" *(41)*.

This minimal approach was still being advocated as late as 1928, when a physician described 12 routine chemical blood tests in common use and the indications for the ordinary clinical patient. "The average physician in general practice will not see more than ten or a dozen cases a year in which a chemical analysis of the blood will be of any value to him in diagnosis or treatment" *(42)*. Why so dismissive an attitude toward chemical analysis at this late date? The reluctance to accept quantification stemmed from a dislike of submitting insights, cumula-

tive wisdom, and experience to numerical testing. Physicians prided themselves on their intuitive skills in making a diagnosis by the use of their senses alone. Such feeling usually appears within any discipline when it is first threatened, as this one was, by quantification *(43)*. Not all doctors adjust to change and continue to treat patients according to the authoritative judgments of past knowledge.

A Fresh New Look

In 1908, Otto Folin proposed that American hospitals employ clinical chemists to advance their ability to differentiate between the physiologic and the pathologic. He cautioned that although hospitals should become involved in biochemical research, clinicians could neither do nor direct chemical work. Systematic biochemical research required the "ingenuity, resourcefulness and critical judgment of the trained chemist" *(44)*.

These views were complemented and reinforced by Abraham Flexner (1866–1959) in his celebrated 1910 exposé of the serious deficiencies and disgraceful practices of the American (and Canadian) medical school systems. He made specific recommendations for correcting the deficiencies. Concerning the laboratories connected with the university hospital, he wrote: "To suffice for clinical investigation the laboratory staff must be so extended as to place, at the immediate service of the clinician, the experimental pathologist, experimental physiologist, and clinical chemist in position to bring all the resources of their several departments to bear on the solution of concrete clinical problems. Of these branches, experimental pathology and physiology have already won recognition; the next step in progress seems to lie in the field of clinical chemistry, thus far quite undeveloped in America" *(45)*. Flexner's emphasis on the use of laboratory sciences in the training of medical students and in the teaching of specialties contributed to the favorable environment for the rapid growth of clinical chemistry. The Report urged that universities take over control of medical training so that laboratories could be provided and properly equipped and staffed for the first 2 years of the curriculum.

War and the New Technicians

On the eve of World War I, judging from P.N. Panton's popular text of *Clinical Pathology* (1913), blood chemistry in England was in a very elementary state. The tests were based on qualitative visual observation of color changes or precipitate formation. The author admitted that little information of any clinical value could be obtained from such methods because no purely chemical examination of the blood had, at that time, any wide application in clinical medicine *(46)*.

Faced with reductions in medical staff because of America's entry into World War I, hospitals found that it was possible "to get much work done by securing at a comparatively small salary the services of a well trained laboratory helper who is not a physician, ... Women are now fitting themselves for these positions in rapidly increasing numbers" *(47)*.

Medicine is the only winner in wartime. The contributions of military experience to civilian medical practice, surgery, and nursing are milestones of history. But the impetus that World War I gave to the spread of laboratory medicine is less generally recognized. Early in 1918, the American Army laboratories overseas, as well as competent personnel to staff them, were few, and equipment was makeshift. Worse yet, the usefulness of the pathologists was limited by the indifference of many medical officers who were unaccustomed to the consultant services of laboratory doctors in civilian practice. Laboratory personnel were not infrequently assigned to "more important" storeroom or mess hall duties. In most base hospitals, simple urine and sputum examinations were something to fill the time when things were slow *(48)*.

Following the war, there was rapid development in the number of clinical laboratories, leading to an additional shortage of medically trained men. Despite the training of many technicians by the Army during the war and the laboratory courses offered by several medical schools, the demand for reliable, well-trained technicians greatly exceeded their availability *(49)*. Citing the Army's example, R.B.H. Gradwohl (1877–1959) proposed the establishment of schools for the proper training of laboratory technicians and for the organization of a laboratory examining board to pass on their qualifications for employment. "Technicians have come to stay" and so that "a better class of women be urged to enter this field", women's clubs should be informed of this new career opportunity "so that the best possible raw material may be selected and utilized in the upbuilding of this highly technical branch of medical specialism". Gradwohl also suggested the formation of some kind of national association by the technicians themselves to bring about recognition by the medical profession *(50, 51)*.

De facto recognition of the role of trained technicians was not long in coming, as a word of caution was sounded in 1918. "To have ward laboratories where the interns make the examinations at their sweet pleasure is to invite slovenliness, inefficiency, and inaccuracy in all the routine examinations". Interns should do laboratory work for assigned periods "under the guidance and with the assistance of the trained workers, . . ." *(52)*.

No sooner were clinical laboratories on the hospital landscape than the naysayers felt obliged to voice their criticism. In 1919, from an unexpected source, the director of laboratories at New York City's Bellevue Hospital, came strong words of reproach for those who "overemphasize the importance of laboratory procedures. This tendency, which is becoming more pronounced each year, appeals strongly to those faddists among whom any test which suggests an easy approach to the solution of any problem, or which promises a division or evasion of responsibility, is assured of a kindly reception. Whether

Fig. 1. Otto Folin.
(National Library of Medicine, Bethesda, MD).

Fig. 2. Donald D. Van Slyke.
(National Library of Medicine, Bethesda, MD).

its credentials are written in the language of science or in that of pseudoscience appears to make little difference. It panders to laziness, which is man's most easily accessible weakness" *(53)*.

Location Is Everything

The laboratory was not always accorded the respect its importance deserves. The following comments, made in 1918, are typical of the long-held popular misconception of "the laboratory" *(52)*: "Usually after the hospital has been completely erected, certain space, unsuitable for any other purpose, is assigned to the laboratory. It is thus that we find this department frequently located in basements, in out of the way nooks and corners, in outhouses or roof structures built as an afterthought. The laboratory is gloomy, the ventilation unsuitable, and the general conditions such as to make the scientist working there cognizant of a spirit of depression in his assistants and help".

"It must be definitely understood that the twentieth century hospital must have a laboratory—not a makeshift, two by four, 'urine room,' not a gloomy, unventilated, poorly cleaned cranny, but well-constructed, properly lighted, scientifically equipped quarters. A hospital has been defined as a hotel with an operating room and laboratory attached. It is just as improper to have an inadequate laboratory as a dark and dirty operating room".

After 1950, and aided by generous government funds that fueled the boom in hospital construction in the United States, building plans provided for adequate space and equipment needs of service and research laboratories.

Clinical Chemistry Takes the Stage

With the start of the 20th century, clinical chemistry emerged into its own space on the mosaic of medical practice. The pattern of its future growth and development took shape during the first two decades of the new century, the United States leading the way with the decisive breakthrough. Until then, the United States had played no role in the growth or development of clinical chemistry. Afterward, the nation quickly achieved leadership, which it never relinquished.

Two names dominated this period: Otto Knut Folin (1867–1934) (Fig. 1) and Donald Dexter Van Slyke (1883–1971) (Fig. 2). Their systematic explorations on blood and urine set the style and shaped the parameters for clinical chemistry for the remainder of the century as they developed practical and clinically applicable methods of analysis. On the basis of a new approach to methodology—analysis of small volumes of biological fluids—they determined reference intervals, correlated variations with pathologic conditions, and elucidated metabolic pathways in health and disease. Neither Folin nor Van Slyke held medical degrees, yet their research and teaching of

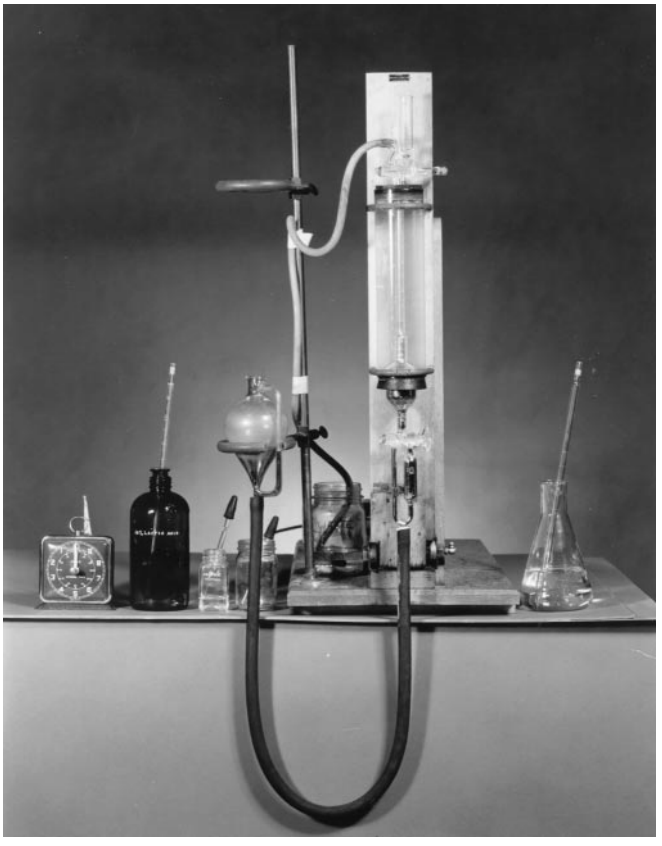

Fig. 3. Van Slyke volumetric carbon dioxide gas analysis apparatus.

biochemistry and clinical chemistry demonstrated that chemists could make great contributions to advances in medical diagnosis and the treatment of disease.

The growth of medicine and its dependence on clinical chemistry derives from the development, in 1917, of Van Slyke's volumetric gas measuring apparatus (Fig. 3) for determining carbon dioxide concentration, the first instrument designed specifically for the clinical chemistry laboratory, and shortly after that, the development by Folin and Wu of a protein-free filtrate method for determining blood sugar. These developments made the chemist immediately useful and necessary for the clinician. Now chemical analyses could keep up with the patient's changing clinical condition. Occurring about the time of the discovery of insulin, these advances brought the chemist from an annex of the mortuary into close relationship with the wards. For this reason the modern name, clinical chemistry, is a more valid description than the older term, chemical pathology *(54)*.

The development of modern clinical chemistry depended on the introduction of colorimetric methods of analysis that were at the same time simple and accurate. Folin's use of the Duboscq-type colorimeter (Fig. 4) for color comparison in the quantitative analysis of creatinine in urine in 1904 ushered in the modern era of clinical chemistry. It gave great impetus to the development of additional colorimetric methods for quantitative analysis of other nonprotein nitrogen compounds in urine and later in blood. Laboratories in England were still dominated by the classical analysts who would recognize only volumetric and gravimetric procedures. Prior to 1918, colorimetric methods were regarded with the greatest suspicion by analytical chemists, and anyone who advocated them was regarded as being irresponsible, if not slightly immoral *(55)*.

There were problems with colorimetric analysis. In the United States in 1922, Behre and Benedict warned against hasty determination on the basis of a single, nonspecific color reaction of "substances whose existence in the tissues or fluids analyzed has never been proved. . . . The modern color reactions are very attractive playthings, but the facility with which they can be employed should not lead to neglect of the more fundamental work of seeking definitely to prove exactly what these color reactions may signify". They concluded: "Our finding that creatinine does not exist in blood in detectable quantities need not, of course, raise any question as to the value of the determination of the chromogenic substance for clinical or other purposes" *(56)*.

Donald Van Slyke did not believe that the chromogenic substance could all be attributable to creatinine. "It is regrettable only that this unknown substance or mixture of substances continues to be called 'creatinine' in laboratory reports, and probably to be considered as creatinine by most physicians to whom such reports are rendered" *(57)*.

The controversy over the actual existence of creatinine

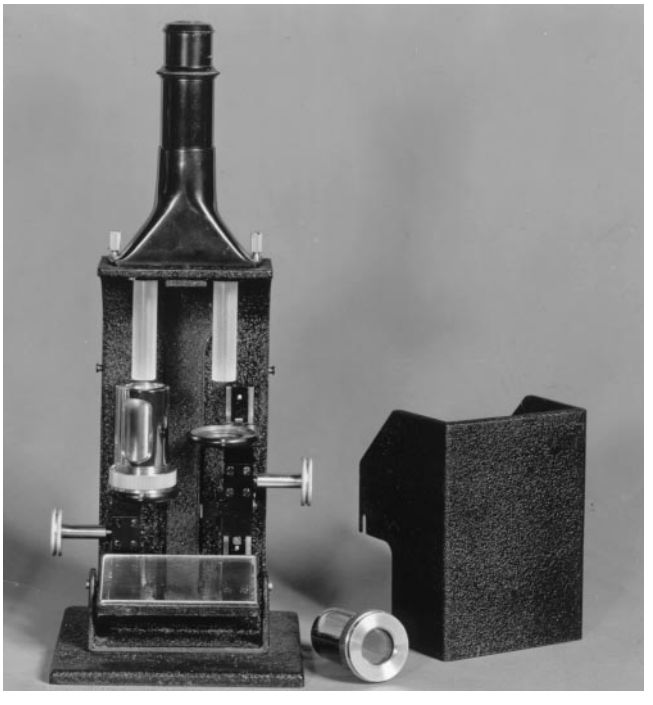

Fig. 4. Duboscq-type visual colorimeter (front view) by Bausch & Lomb, Rochester, NY (circa 1950).
Note light shield, fixed plungers, and glass bottom of sample cup.

in normal blood was decided in 1937 by the isolation of bacterial enzymes capable of decomposing creatinine. The difference in color produced by "creatinine" before and after enzymatic action represented the true creatinine.

The Duboscq-type visual colorimeter was the mainstay of the clinical chemistry laboratory for nearly half a century. In spite of inherent sources of error, this instrument was described in 1939 as "still the most versatile and useful instrument" for colorimetric chemical analysis *(58)*. Two years later, in a comprehensive review of chemical instrumentation, the same writer added: "The assumption that any photoelectric instrument must be more accurate and reliable than a visual instrument is wholly unwarranted. . . . However, the future does seem to lie in the direction of the photoelectric types, for there is no inherent limit in the attainable sensitivity and objectivity of the measurement" *(59)*.

By the early 1960s, all colorimetric methods had been adapted to the photometer and were in the process of being adapted to the new arrival in the chemistry laboratory—the AutoAnalyzer, a continuous-flow instrument that reacted specimen and reagents to produce a measurable color density recorded on a moving chart. After briefly working alongside the photoelectric colorimeter and the single-channel AutoAnalyzer, the Duboscq-type visual colorimeter passed into history.

Overuse and Misuse of Testing

Concern about insurance compensation and malpractice suits, blamed in part for the increase in the number of laboratory tests, is not a recent phenomenon. In the 1930s, some physicians felt pressured "by public opinion—the patient, his family, his friends—to utilize every laboratory test" even when physical examination readily revealed the diagnosis *(60)*. During the 1950s, physicians were criticized for ordering laboratory procedures for the record or for protection *(61)*. Data that did not fit the clinical picture were either ignored or repeated until they did conform *(62)*.

From the mid-1950s through the 1960s, the ever-expanding role of the laboratory in clinical diagnosis and patient care was evident on the wards, in the records, in the building plans, and not least of all, in the finance office of every hospital *(62)*. The capability of automated devices to produce more chemistry test results at a lower cost gave rise to the almost universal identification of routine or baseline tests, an ever-expanding category, and patterns of physician ordering of packages, panels, profiles, screens, and surveys or other groupings named according to the instrument and its output, instead of making specific single test requests. As expected, this increased the number of laboratory tests that were done. Diagnosis and follow-up that depended heavily on technology were equated with the practice of scientific medicine.

By 1932, the most common problem cited by doctors was the large number and unintelligent use of laboratory tests ordered in hospitals as a matter of course, without apparent relevance to the condition for which the patient was admitted or understanding of the test's meaning or limitations. Clinical application of blood chemistry determinations was especially abused *(63)*. This later perception of excessive laboratory testing occurred 25 years before the appearance of automated chemical analysis and its by-product, mass-produced laboratory data.

Physicians continually expressed their concern over the possible harm done to the practice of medicine and to medical education by overdependence on laboratory tests to the detriment of careful history taking and bedside examination of the patient. The routine ordering of many laboratory tests was labeled "excessive diagnostic inquisitiveness" and "nondiscriminating use of . . . laboratory tests" in the 1930s *(63)*; "professionally unwise and economically unsound" in the 1940s *(64)*; "shot-gun testing" in the 1950s *(65)*; "wasteful, unproductive and conducive to 'decerebrate medical practice' " in the 1960s *(66)*; and in the 1970s, an "unchecked drift into the technologically thorough, sometimes obsessively complete workup of our patients in our teaching hospitals", directed to all diagnostic possibilities. This was a call for technologic restraint and a patient-oriented approach to problems, rather than the problem-oriented approach to patients *(67)*. One physician in 1944 described the approach to patients as "a five-minute history followed by a five-day barrage of special tests in the hope that the diagnostic rabbit may suddenly emerge from the laboratory hat . . . " *(64)*.

Renewal of the Partnership

By 1963, the widening application of chemical techniques to the quantitative estimation of many different constituents, chiefly in blood and urine, had made the practice of medicine and surgery increasingly dependent on the support provided by clinical chemistry *(68)*. There was increased awareness by clinicians of the value of chemical methods of diagnosis and that this was attributable to greater emphasis on functional concepts of disease with less emphasis on morphology and taxonomy *(69)*.

Complaining in 1975 of the growing resemblance of chemical departments to "supermarkets", Poul Astrup said that chemists should "*develop this service from a static description of concentration of components*" into dynamic and interpretive descriptions of "*the diagnostic values of the results*", and the "*biological and medical relevance* in interpreting significance for the clinicians". He added that "the discipline will grow only if the clinical chemists *think of themselves as belonging primarily to the biological/medical sphere* and only secondarily to the technical/analytical sphere" *(70)*.

Forgetting the Patient

The lure and fascination of machine-produced data were an outgrowth from the 20th century's faith in science and technology, and there has been a price to pay. "First we

digitized them, then we punched them into cards, and now we have reduced them to a few spots of magnetism on a strip of tape" *(71)*. We were warned in 1982 about the danger of dehumanization as a threat to the work of the clinical laboratory. We were also urged to avoid a black box or pushbutton philosophy toward equipment *(72)*. This unwelcome dividend of the technical approach to modern medicine was nothing new. Nearly six decades earlier a clinician wrote: "Laboratory methods tend to make one forget the patient altogether in the nicety of the scientific" *(73)*.

The Complete Clinical Chemist

This survey of two centuries of change and development for clinical chemistry closes with a tribute to Ivar Christian Bang (1869–1918). In 1958, Van Slyke characterized him as "the complete clinical chemist. For clinical chemistry includes, not only the development of methods, but study of all the phenomena of the body's normal chemical processes, and of the alterations that they undergo in disease" *(74)*. There have been momentous advances in laboratory technology since these words were spoken, but they remain the essence of clinical chemistry.

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