A Guide to the History of Clinical Chemistry
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BACKGROUND: This review was written as part of the celebration of the International Year of Chemistry 2011.

CONTENT: In this review we provide a chronicle of the history of clinical chemistry, with a focus on North America. We outline major methodological advances and trace the development of professional societies and journals dedicated to clinical chemistry. This review also serves as a guide to reference materials for those interested in the history of clinical chemistry. The various resources available, in sound recordings, videos, moving images, image and document archives, museums, and websites dedicated to diagnostic company timelines, are surveyed.

SUMMARY: These resources provide a map of how the medical subspecialty of clinical chemistry arrived at its present state. This information will undoubtedly help visionaries to determine in which direction clinical chemistry will move in the future.

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The International Year of Chemistry 2011, designated by the United Nations General Assembly, has the goal of increasing public awareness of chemistry in meeting world needs, increasing the interest of young people in chemistry, generating enthusiasm for the creative future of chemistry, and celebrating the 100th anniversary of Madam Curie’s Nobel Prize. Clinical chemistry most certainly must be featured in such an initiative because it plays a key role in the diagnosis and treatment of the sick and in the maintenance of health through preventative medicine. Clinical chemistry also has a direct link to the contributions of Marie Curie through the development of the technique of RIA (which led to Roslyn Yalow’s Nobel Prize). This technique has revolutionized endocrinology and has led to remarkable contributions to other subspecialties (such as toxicology and cardiology).

Chronicle of the History of Clinical Chemistry

This discipline, which could originally be practiced in small laboratories in which relatively few manual tests were performed, now requires highly automated and integrated laboratories that perform millions of tests each year (Fig. 1). There is a body of literature, albeit not extensive, in which the history of clinical chemistry is chronicled. Table 1 lists the most significant general reviews of the field, most of which chronicle the development of clinical chemistry from its beginnings in antiquity (1–11).

Johannes Büttner has contributed several articles and books based on research of the roots of clinical chemistry, with a primary focus on clinical chemistry in Germany (3–6). These texts include History of Clinical Chemistry (5), edited by Büttner, which explores the origins of clinical chemistry. The most ambitious publication on the history of clinical chemistry is a book by Louis Rosenfeld, Four Centuries of Clinical
Chemistry (9), which describes the development of knowledge of analytical chemistry and biochemistry and the emergence of clinical chemistry. Contributions beginning in the 16th century and leading to more recent times are covered. Specific assays that formed the cornerstone of the clinical chemistry laboratory in the 1960s are described, such as glucose, urea, creatinine, electrolytes, cholesterol, some basic enzymes, total protein, and albumin/globulin. Of course, the contributions and impact of Donald Dexter Van Slyke, Stanley Benedict, and Otto Folin are prominently featured, as is the introduction of analysis by color comparison and the Duboscq colorimeter, invented by Jules Duboscq in 1870. Rosenfeld’s extensive publication was preceded in 1973 by an article by Wendell Caraway, a practicing clinical chemist in Michigan who graced the clinical chemistry scene in the post–World War II era. Caraway was the president of AACC from 1965 to 1966 and was
a pioneer in chronicling the history of clinical chemistry. His landmark papers (1, 2) are concise and present a fascinating exploration of the origins of the field.

Major technological milestones that have contributed to the present day clinical chemistry laboratory are listed in Table 2 (2, 12–23). The analytical balance has been known since antiquity because the accurate weighing of gold and other precious materials was vitally important in ancient civilizations and contributed to the development of trade and accumulation of wealth. Spectrophotometry, a development that dates back more than a century, has, in all of its forms, certainly contributed the most to the process of performing basic measurements in the routine clinical chemistry laboratory. Previously known as colorimetry, this method was used for most of the early clinical chemistry assays such as urea, creatinine, uric acid, glucose, total protein, and albumin. Chemical reactions be-

| Scientific Development of Clinical Chemistry to 1948 | 1979 | Caraway (1) |
| Major Developments in Clinical Chemistry Instrumentation | 1981 | Caraway (2) |
| Emergence of Clinical Chemistry in the 19th Century: Presuppositions and Consequences | 1982 | Hickel (3) |
| From Medicinal Chemistry to Biochemistry: The Making of a Biomedical Discipline | 1982 | Kohler (4) |
| History of Clinical Chemistry | 1983 | Büttner (5) |
| Roots of Clinical Chemistry | 1987 | Büttner and Habrich (6) |
| Clinical Chemistry as Scientific Discipline: Historical Perspectives | 1994 | Büttner (7) |
| Laboratory Instrumentation in Clinical Biochemistry: A Historical Perspective | 1997 | Olukoga et al. (8) |
| Four Centuries of Clinical Chemistry | 1999 | Rosenfeld (9) |
| A Golden Age of Clinical Chemistry | 2000 | Rosenfeld (10) |
| Clinical Chemistry since 1800: Growth and Development | 2002 | Rosenfeld (11) |

| Table 2. Milestones in the application of instrumental techniques to clinical chemistry. |
|---|---|---|
| Instrument/technique | Developer | Year | Reference |
| Analytical balance for urinalysis | Bang IC | 1913 | Caraway (2) |
| Duboscq colorimeter for the measurement of creatinine in urine | Folin O | 1904 | Caraway (2) |
| Beckman DU spectrophotometer | Cary AH and Beckman AO | 1941 | Caraway (2) |
| Atomic spectroscopy | | | |
| Flame photometry | Hald P | 1947 | Hald (12) |
| Atomic absorption | Zettner A | 1964 | Zettner and Seligson (13) |
| Gasometric analysis | Haldane JS | 1912 | Caraway (2) |
| Electrochemical techniques | Hober R | 1900 | Caraway (2) |
| Proficiency testing | Sunderman FW Sr | 1945 | Sunderman (14) |
| Zone electrophoresis | Cremer HD and Tiselius A | 1950 | Cremer and Tiselius (15) |
| | Durrum EL | 1950 | Durrum (16) |
| RIA | Berson SA and Yalow RS | 1959 | Berson and Yalow (17) |
| Monoclonal antibodies | Schwaber J | 1973 | Schwaber and Cohen (18) |
| Automation | Skeggs LT | 1957 | Skeggs (19) |
| Computers | Sunderman FW Jr. et al. | 1968 | Sunderman (20), Sunderman et al. (21) |
| Point-of-care testing/dry reagent technology | Free AH et al. | 1957 | Free et al. (22) |
| PCR | Mullis K | 1983 | Mullis et al. (23) |
between the analyte and a reagent that possessed some degree of specificity were used with a final colorimetric measurement and calculated against a standard curve. Most reactions were relatively insensitive and required relatively high volumes of sample that would lead to protein precipitation. Hence, protein-free filtrates were usually required and resulted in time-consuming measurements. The introduction of enzymes as reagents and the use of measurement in the ultraviolet wavelength range led to increased sensitivity, decreased sample volume, and simpler analytical procedures. Urease, which converts urea to ammonium ion, was used as early as 1914 (24). The modern clinical chemistry laboratory now uses a wide variety of photometric techniques, including fluorescence, fluorescence polarization, nephelometry, chemiluminescence, phosphorescence, and electrochemiluminescence. It is with some hesitation that we include the technique of gasometry into this list of important breakthroughs in technology. Gasometric techniques were doomed to extinction from their first use because they were so cumbersome and fraught with mercury-related environmental problems; however, the use of such methods led to a basic understanding of blood gases and acid–base balance. There is no question that the invention of the continuous-flow autoanalyzer changed the character of clinical chemistry testing so that minutes rather than hours (or days) were needed to complete an analysis, and personnel were then free to develop emerging subspecialties such as toxicology, endocrinology, and later, molecular diagnostics. Other innovative approaches to automation were also introduced, including the centrifugal analyzer developed by Norman Anderson in 1968 (25). This instrument was the first clinical analyzer to incorporate a computer. The final autoanalyzer, the SMAC (Sequential Multiple Analyzer with Computer), introduced in 1974, also had a built-in computer. An instrument known as the Robot Chemist, which was introduced by the Research Specialties Company in 1959, used conventional cuvettes with automatic pipetting and mixing, but the mechanical complexity of the instrument made it impractical. One of us (J. Savory) worked with both the first autoanalyzer and the Robot Chemist and can attest to the above statement. Eventually automated pipetting was perfected and it is now the approach of choice for automation in clinical chemistry laboratories, thanks mainly to the introduction of the Beckman Astra in 1978. As early as 1949, Örjan Ouchterlony used antibodies as reagents for immunodiffusion methods (26), but the major breakthrough was with the application of RIA, which was developed by Solomon Berson and Rosalyn Yalow and for which Yalow was awarded the Nobel Prize. The introduction of this method made available for the first time highly specific and sensitive methods for measurement of a wide variety of hormones, proteins, and drugs. This technique replaced other bioassays for pregnancy, including follicle-stimulating hormone, and indirect hormone tests such as 17-ketosteroids. Many immunoassay techniques are used in clinical chemistry laboratories and are reviewed in Table 3 (27). Other than the invention of RIA, the most important development in immunoassay techniques was the ability to produce monoclonal antibodies, which have served as immensely important reagents with a large variety of applications. Controversy exists as to who first produced monoclonal antibodies in the laboratory, but this achievement is often ascribed to Jerrold Schwaber in 1978.

Table 3. Histories of key techniques and technologies in clinical chemistry.

<table>
<thead>
<tr>
<th>Technique</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>Filter paper electrophoresis</td>
<td>Martin and Franglen (28)</td>
</tr>
<tr>
<td>Clinical enzymology</td>
<td>Büttner (29)</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>White (30)</td>
</tr>
<tr>
<td>Blood gas analysis</td>
<td>Severinghaus and Astrup (31),</td>
</tr>
<tr>
<td></td>
<td>Breathnach (32)</td>
</tr>
<tr>
<td>Dry chemistry (Eastman Kodak)</td>
<td>Kaiser (40)</td>
</tr>
<tr>
<td>Lipid and lipoprotein testing</td>
<td>Sunderman (41)</td>
</tr>
<tr>
<td>Enzyme immunoassay/ELISA</td>
<td>Simpson (42), Young et al (43)</td>
</tr>
<tr>
<td>Molecular (DNA/RNA) diagnostics</td>
<td>Meites (44)</td>
</tr>
<tr>
<td>Immunoassay</td>
<td>Wu (27)</td>
</tr>
</tbody>
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Histories have also been written of 2 important early US clinical chemistry laboratories, the William Pepper Laboratory of Clinical Medicine of the University of Pennsylvania (Fig. 2), (43) and the Children’s Hospital of Columbus, Ohio (44). In addition, the history of the journal Clinical Chemistry has been summarized by its long-time editor J. Stanton King (45).
One of the most fascinating aspects of the study of the history of clinical chemistry is the lives of those who founded the field. Otto Folin was one of the pillars of the field of clinical chemistry, and his life and work are captured in Samuel Meites’ biography of Folin (46). Biographies of other key figures include those of Henry Bence Jones (47) and Joachim Kohn (developer of cellulose acetate electrophoresis) (48).

The first professional organizations dedicated to clinical chemistry sprang up in the 1940s, beginning with the AACC in the US in 1948 (49). This was followed by the founding of national societies for clinical chemistry in many countries (e.g., the Association for Clinical Biochemistry in the UK in 1953) (50) and also an international body, initially known as the International Association of Clinical Biochemists (1952) that subsequently became the IFCC (International Federation of Clinical Chemistry) in 1953 (51).

**Museums of Clinical Chemistry**

The size and weight of some of the larger clinical chemistry analyzers has no doubt posed a barrier to their retention for exhibition in museum collections. Never-
theless, several museums have exhibits related to the history of clinical chemistry that contain analyzers of different types. The Chemical Heritage Foundation (CHF) (52) has a number of clinical chemistry analyzers on display, such as a Technicon AutoAnalyzer Sampler Unit, in their permanent exhibition in Philadelphia, “Making Modernity.” The AACC also has a small exhibit of historic instruments at its office in Washington, DC, which includes a Klett Photoelectric Colorimeter, a Folin-Wu Sugar Tube, a Technicon AutoAnalyzer System, and a Beckman Model DU Spectrophotometer (53). The Beckman Coulter Heritage Center and Caltech’s Science Museum’s Beckman Room Exhibit (54) feature exhibits relating to the work of Arnold O. Beckman and the analyzers produced by the Beckman company. In addition, several companies have virtual museums in the form of illustrated online interactive timelines and histories, e.g., Beckman Coulter (55), Ortho Clinical Diagnostics (56), Abbott Laboratories (57), Roche (58), Instrumentation Laboratory (59), and Olympus (60).

**Sound Recording, Video, Movie, Image, and Document Archives**

Various archives of surviving photographs, moving images and oral histories, and collections of artifacts and memorabilia, make it possible to trace the growth of clinical chemistry from its origins in small one-room laboratories with a few staff performing a very limited menu of manual tests to large modern laboratories with large staffs overseeing an extensive menu of highly automated tests.

The Science Museum in London, UK, has a website, Brought to Life, which explores the history of medicine. It includes images of early instrumentation (e.g., a urinometer from the 1800s), urine test kits (e.g., the Clearblue One Step Pregnancy test kit, England, 1988), and biographies of famous clinical chemists [e.g., Leonard Skeggs (1918–2002)] (61). Getty Images (62) also provides numerous images relating to home testing (e.g., pregnancy and diabetes testing).

The Wellcome Images: 2000 Years of Human Culture archive at the Wellcome Library, also located in London (63), contains numerous images relating to test strips (e.g., pregnancy tests, urine tests) and glucose meters. A detailed and illustrated history of pregnancy testing can be found on the NIH archive (64). This source contains images of test devices and early advertisements for over-the-counter pregnancy tests.

The Wellcome Moving Image and Sound Collection (a collection of moving images on 20th-century healthcare and medicine) contains what may be the earliest movie of a hospital laboratory, shot around 1932 at the Royal Hospital Sheffield (Sheffield, UK) (65). It shows a clinical chemist performing a glucose test. This image provides a graphic illustration of the changes in laboratory safety standards between now and then: he is mouth-pipetting and not wearing gloves! (Fig. 3). Despite the long and concurrent histories of the clinical laboratory and movie/video cameras, there are relatively few other examples of movies or videos showing the content and workings of early clinical laboratories. Another notable example is the movie taken by Peter Wilding in 1966 at the clinical chemistry laboratory of the Los Angeles General Hospital, California (66). This archive also has video recordings of lectures on RIA by John Landon at the University of London in 1972.

In addition, the Nobel Prize website contains links to a video lecture (“RIA: Tool for Biomedical Investigation and Clinical Medicine”) presented by Rosalyn Yalow (1977 Nobel Prize in Physiology or Medicine) at the 1978 Nobel Laureate Meeting in Lindau, Austria (67). There are now available numerous grand rounds video archives and live audio and synchronized PowerPoint presentations of more recent lectures by famous clinical chemists, and these provide a historical record of the state of knowledge and thinking at a particular point in time.

Notably, the Smithsonian Institution Archives (Oral Histories in Medicine and the Health Sciences) has a number of oral and video histories of relevance to clinical chemistry, including histories of DNA sequencing and PCR (68).

A more extensive collection of interviews with prominent clinical chemists is to be found on the Oral Histories section of the CHF website (69). In addition the CHF website includes images of clinical analyzers such as the circa 1975 YSI (Yellow Springs Instrument) Blood Glucose Analyzer, Model 23A (70), and the Photovolt Hemoglobin and Glucose Meter (71).

The Images from the History of Medicine website provides access to images in the collections of the History of Medicine Division of the US National Library of Medicine (72). This collection contains images of clinical chemists (e.g., Donald S. Fredrickson), chemistry laboratories of various military and university hospitals (e.g., University of Virginia Hospital in 1929, the chemistry laboratory in the laboratory of pathology at St. Elizabeth’s Hospital Blackburn, UK, circa 1910), and posters for cholesterol testing and for the National Medical Laboratory Week. One of the latest image archive initiatives has been the AACC History Division Analyzer Archive. The objective of this project is to collect images of the full scope of clinical laboratory analyzers (including chemistry, immunoassay, hematology, and other areas) and associated automation equipment (73).
The advent of YouTube in 1985 has provided a source for numerous contemporary videos of clinical laboratories, commercial diagnostic tests, and the testing that is performed. These films will provide future historians with a wealth of historical data on clinical chemistry from the end of the second millennium onwards. A notable entry on YouTube is the introductory video for the 45th annual meeting of the AACC in New York, NY, in 1993, which documents the contribution of the Northeastern US to the development of clinical chemistry (74).

Whither Clinical Chemistry?

At the AACC National Meeting in 1984, one of us (J.S.) presented the National Lectureship Lecture, which was entitled “On Such a Full Sea Are We Now Afloat,” a quotation from Shakespeare’s Julius Caesar. The year, 1984, was a time of some despondency by clinical chemists because the exciting early times of method development in the hospital laboratory had been virtually taken over by commercial manufacturers of instruments and reagents. The purpose of the lecture was to point out the golden future of the field, with the introduction of molecular diagnostics, the applications of robotics, and the routine use of mass spectrometry in the clinical chemistry laboratory of the future. Now, some 27 years later, these predictions have come to pass.

As we conclude this present history we are cautiously offering our predictions for the next quarter century. We expect that as the cost of healthcare continues to spiral almost out of control, major developments in technology related to clinical chemistry will be made to reduce these costs. More point-of-care testing linked to telemedicine will be introduced to decrease the number of hospital visits for patients with chronic conditions and hence reduce overall healthcare costs. We will mimic the electronics industry and see more technology convergence and cost reduction for handheld devices. Emphasis will continue to be placed on more specific markers for disease and testing for a patient’s vulnerability to acquiring an illness. Cancer and heart disease will continue to be targeted, but there will be an intense initiative to develop early markers for neurodegenerative disorders. Despite a great deal of research into the pathogenesis of Alzheimer and Parkinson disease, little progress at the early detection and treatment has been made. This will change and we anticipate that the clinical chemistry laboratory will play an important role.
As members of the clinical chemistry fraternity we can take great pride in our heritage and look forward to the future with considerable optimism.

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

Authors’ Disclosures or Potential Conflicts of Interest: No authors declared any potential conflicts of interest.

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