The Skeptical Chemist

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Clinical chemistry, the science in which chemical and biologic analysis of body fluids and tissues is used in the diagnosis and treatment of disease, is undergoing rapid change. Engineers and physicists have entered the field and have designed automated and mechanized equipment which, some people postulate, eventually may replace not only the technician, but also the clinical chemist. I feel, however, that there is more to clinical chemistry than the mere performance of laboratory tests. The clinical chemist must be, as the playwright wrote, a man for all seasons. He must be a capable administrator of his laboratory, able to solve the many personnel and instrumentation problems that face him daily. He must understand the fundamentals of biochemistry and immunochemistry, and keep abreast of all of the rapid changes in these burgeoning fields. He must be able not only to initiate new organic and inorganic analyses of biologic material, but also to recognize and appreciate the development of physical science and engineering, and perhaps most importantly, to discriminate between industrial science fiction and reality. Finally, during his training, and perhaps also as a result of strenuous personal effort, he must have obtained at least a smattering of ignorance in the art of clinical medicine so that he can provide the clinicians with the proper counseling for their myriad of pathologic-biochemical problems. Therefore, I hope that the modern clinical chemist will not pass into the limbo of medical and chemical history, dragging his pipets, burets, and AutoAnalyzers behind him. I hope he will not go quietly into the dark night, but instead, rage, rage against the monsters of mechanization and computer conformity. A review of the early history of clinical chemistry may help him arm against these modern horrors and help him gain an appreciation of the background of this hybrid science and of the many interesting individuals—scientists, physicians, priests, wizards, and charlatans—who have contributed to the development of the field.

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It is possible that the first clinical chemists were the Babylonians. It is true that they did not use body fluids for their diagnostic procedures, but apparently they did appreciate the fact that something other than physical evidence of disease could be utilized to make a clinical decision: In the days of the Hanging Gardens of Babylon, if a patient had a serious disease, he would visit a priest who would ask him to breathe into the nose of a sheep. The animal then would be slaughtered, and the liver removed and carefully inspected for evidence of disease; on the basis of the changes he observed in the liver, the priest would predict the outcome of the case and treat the patient (1). Obviously, the Babylonians were as unconcerned with biologic sampling and controls as some of us are nowadays. The Babylonians based this diagnostic art, which has been called Haruspex, on their theory that the liver was the center of the organs of the human body and that the whole of human physiology occurred there. Obviously, this is not too far from our modern concept that the hepatic cells are really the chemical factories of the animal organism.

Even during the time of Ikhnaton and Cleopatra, civilization was concerned with the now contemporary problems of the detection of pregnancy and the prepartum sexing of the fetus. In fact, early Egyptian priests developed a technic for diagnosis which apparently recognized that the urine of pregnant women contained a special material which was related in some way to her pregnancy (2). They would perform the following pregnancy test: urine was obtained from a woman suspected of being pregnant and the sample was used to water various cereal seeds planted in the ground. If the seeds germinated, it was believed that the woman was in fact pregnant; and if a specific seed germinated, such as an oat seed instead of a wheat seed, then it was thought that the fetus was a male. As far as the sexing technic was concerned, I assume the procedure worked at least 50% of the time.

Although the Greeks and the Romans were aware of the various metabolic diseases, including diabetes and gout, they made no cogent contributions to the field of clinical chemistry. The ancient Hindus and Chinese apparently had much more biochemical acumen than our Western ancestors, for they noted that there was a sweetness in the urine of patients with the syndrome of diabetes. For it is in the writing of a Hindu, Ayus Veda of Susruta, about 500 AD, that we find the first reference to mellita urina or "honey urine," representing accumulations of diabetic patients’ urine which were approached selectively by insects (3). Certain Chinese physicians also had noted this particular phenomenon (3), and it is interesting that it was not until 1674 that
Thomas Willis, in England, made a similar observation (3). It would appear that in this area, Hindu medicine was at least 1000 years ahead of Western medicine.

Perhaps the first systematic attempt to use body fluids for the diagnosis of disease was made by the medieval uroscopists who had their headquarters in the medical school of Salerno, Italy (4). Although we do not know when this ancient university was founded, there is an apocryphal tale that demonstrates its interesting, international character, for it is felt that the four original teachers at this Italian university were doctors of four different origins: a Greek, a Latin, a Saracen, and a Jew, each of whom lectured to his countrymen in his own tongue. The uroscopists, or as they have come to be known, the watercasters, felt that any unusual or abnormal pathologic change in the patient could be detected in the urine. They described 18 different colors of urine related to 18 different diseases. The pedantic urine analysts collected their samples in special containers, some of which were encrusted with diamonds. In fact, some of the most prominent physicians of that time often visually analyzed the urine before they would examine the patient. A Persian physician, Rhazes, who incidentally invented a hydrostatic method for measuring specific gravity, was quoted as saying: "When I began to practice medicine, I resolved to ask no questions when the urine was given me and I was much honored. Later when I made circumstantial inquiries, my reputation sank (5)." The Breslau Codex of Salerno, devotes about 40 tightly packed pages to instructions on the appraisal of the sediment, the odor, and the weight of urine (6). Johannes Actarius, the last of the Byzantine writers, wrote an elaborate treatise on urine in the 13th century (7). He was the first to use a graduated glass for examining urine, although the markings were based on qualitative, rather than quantitative, differentiation. Another eminent physician, a Jew, Isaac Judeas, suggested that the urine glass be divided into 4 equal parts, each corresponding to a region of the body (8). If the top layer of the liquid seemed turbid, there was trouble in the head to contend with, and so on down to the bottom of the glass and the bottom of the body. Before we leave these watercasters with their ancient urinary Auto-Analyzers and move forward in history a few centuries, I would like to quote from the eminent physician of that day, Arnold of Villanova, who, at the end of the 13th century, wrote the following: "If you don't find anything in the urine, but the patient insists on suffering of headache, tell him that it is an obstruction of the liver and just continue to speak of obstruction, a word he won't understand but one that
sounds very important. Either the headache or the patient will soon go away.”

The alchemist was the chemical analyst of his day in the 15th and 16th centuries, and though his basic purpose was to increase his worldly possessions by converting base metals, such as lead and nickel, into gold and silver, these often pseudoscientists laid the foundation of modern analytic chemistry by developing methods of distillation, sublimation, and fractionation in order to test for their precious metals. Many of the clinicians of their day took advantage of the alchemy and used it in their practice of medicine, especially for the preparation of drugs. Perhaps the most interesting of all of these was the father of modern pharmacology, Theophrastus Bombastus von Hohenheim, better known to us as Paracelsus, who lived from 1493 to 1541. He provided rather complete descriptions of respiration and digestion, almost modern in their connotations, and he also developed certain technics for quantitating urinalysis (9).

It is at the end of the 17th century that we meet perhaps the first true clinical chemist. It is not at all surprising that he is also perhaps the first true analytic chemist, for in 1684 Robert Boyle, the first “skeptical chemist,” published a paper entitled Memoirs for the Natural History of Blood, Specially the Spirit of That Liquor (9). Boyle systemized wet analysis and introduced the term “analysis” to describe those chemical reactions by which individual substances could be distinguished from one another. He initiated and elaborated the use of indicators, utilizing plant juices such as litmus and the juice of violets, and recognized that a change of color rather than the color itself might be significant (10). However, the idea that disease might produce specific chemical changes in the blood did not originate with Robert Boyle. Apparently, he was led to his investigation through discussions with his friend, the eminent philosopher and physician, John Locke, who like Goethe’s Faust recognized that “blood is a very special juice” (9). Using the crude methods of analysis which were available at that time, such as fractional distillation, sublimation, and quantitative gravimetric weighing, Boyle was able to demonstrate the presence of “sea salt” in the blood by a succession of tests, with silver nitrate as a test reagent. He also suggested that urine might be examined similarly (9). Although they evidently had no contact with each other, it was only 10 years after the publication of Boyle’s memoirs that Frederick Dekker of Leyden, in the Netherlands, reported a technic demonstrating the presence of albumin in urine (11). Dekker wrote that if urine was boiled in the presence of acetic acid, a precipitate would occur which
would be directly related to the albumin concentration in the urine. It was also around this time that Nicholas Lemery reported the presence of iron in the blood (12), Willis rediscovered the sweetish taste of diabetic urine (3), and DeGraff studied the contents of pancreatic fluid obtained from pancreatic fistulas (13).

In 1735, an English country physician by the name of Browne Langrish published a pamphlet on a series of chemical and physical analyses of the blood of patients with various types of fevers (14). He weighed the serum and clot and noted the proportion they bore to each other. He even invented an instrument to measure the toughness of the clot. He performed chemical analysis after the manner of Boyle, with whose work he was apparently familiar. Through the use of fractional distillation, he divided the blood into several components, many of which have no basis in our modern understanding of chemical analysis of blood. Matthew Dobson, in 1776, reported that the sweet taste of urine in a diabetic depended on a sugary substance (3). He was able to detect this by fermentation experiments and he reported sugar analysis on blood as well as urine. T. Cawley, in 1758, not only diagnosed diabetes by demonstrating sugar in the urine, but, for the first time, linked diabetes with pancreatic disease (3). Frank and Home, in 1778, also reported a fermentation test for sugar which could be applied easily to urine chemistry, and toward the end of the enlightened century (3), Wollaston discovered uric acid in gouty tophi and in the urine of patients with gout (15). In addition to the growing relationship between chemistry and medicine which occurred at this time, volumetric quantitative procedures began to make their appearance. Descroizillin, in 1787, described a titrimetric method of chlorine analysis, while Guyton DeMorveau, in 1784, used a graduated vessel for the first time for volumetric determination (10).

Although the foundation of the analysis of the "very special juices" was laid down during the 17th and 18th centuries, major impetus in the field of clinical chemistry was provided by the developing science of organic chemistry in the 19th century, for it is in that century that the giants of organic chemistry worked and wrote their voluminous and trenchant scientific reports. In fact, in 1806 Berzelius first used the term organic chemistry (16). Dumas, Leibig, and Kjeldahl all published in that century and all appeared to have influenced the physician-chemists who work in the field of clinical chemistry. Bischoff, in 1837 (17), was able to show that there was carbon dioxide and oxygen in blood, and Magnus, in the same year, reported that both venous and arterial blood contained these chemicals (18). In 1843, Andral, in Paris, published his famous essays on pathologic hematology (19). He was
able to demonstrate by some simple technics that the serum albumin level was low in cases of albuminuria and also in patients with edema; and in addition, that in certain hemorrhages, the blood fibrin level was reduced. It was about this time that chemical analysis of the urine was beginning to be practiced extensively, and though, as we have said, Dekker, back in the 17th century, reported the heat and acetic acid test for albumin, it was not until the 19th century that its significance was known: It was in the first decade of that century that W. C. Wells, an American colonial physician who re-emigrated to England, and J. Backall observed that albumin was present in the urine of patients with renal edema (20). This was clearly contrary to the observations of the 18th-century Dutch clinician, Boerhaave, who had not been able to observe albumin in urine of any of his patients. However, Boerhaave analyzed only normal urine samples and obviously the albumin concentrations were not sufficiently high to give positive tests (21). Wells and Backall’s studies were corroborated by the excellent work of Richard Bright at Guys Hospital, who firmly established the correlation of albuminuria and diseased kidneys (22), and by 1844, 17 years after Bright published his report, Golding Bird brought out a practical book on urine chemistry called Urinary Deposits, Their Diagnosis, Pathology and Therapeutic Indications. In addition to the already well established test for albumin, Bird described a nitric acid test for bile in the urine and a simple alkaline copper reagent for glycosuria (23). He also was able to recognize casts in the urine which had been described by H. B. Jones as being diagnostic of Bright’s disease. Quantitative analyses of 24-hr urine collections were done by Bird using a crude gravimetric technic, but they apparently yielded very little valuable information.

With the realization that chemistry and medicine were intimately related, the years of the 1830s, 1840s, and 1850s were miraculous in the number of contributions in the field of clinical chemistry. Penttenkoffer, in 1844, described a technic for the detection of bile acids in which he used a concentrated sulfuric acid solution mixed with a sugar solution. He apparently measured the development of the pink or violet color of furfural, which would result from a mixture of bile acid and carbo-hydrate (24). The biuret test for albumin was reported by Heinrich Rose in 1831 (24). In 1844, Heller described a ring test for albumin that is still used in some laboratories (24). He also was able to provide some information about urinary secretions. Von Fehling, in 1848, developed his quantitative test for reducing sugars in the urine, which eventually developed into the commonly used Benedict’s test for urinary sugar (24). Perhaps the most important advancement in the 1840s
and 1850s was a series of reports by the eminent chemical pathologist Bence Jones. The most significant contribution was the one dealing with the presence of an unusual protein in the urine of patients with certain types of bone disease. Bence Jones had been influenced by several years of study with Leibig, the great organic chemist, and probably most of his original ideas were developed from this period of study. In 1845, Bence Jones became a physician at the St. George Hospital in London and delivered lectures there on chemistry. In 1850, he published an article on animal chemistry and its relationship to stomach and renal disease. Certainly he had become an authority on chemical pathology by that time. Thus, it was not surprising, in 1848, that a Scottish physician by the name of Watson sent him a urine specimen with the following letter:

Dear Dr. Jones:

The tube contains urine of a very high specific gravity. When boiled, it becomes opaque. On the addition of nitric acid, it effervescs, and assumes a reddish hue and becomes quite clear; but as it cools, assumes a consistence and appearance which you see. Heat reliquifies it. What is it? (26)

Evidently, Dr. Jones felt it was an unusual material and wrote a paper on it which was published in Lancet (26). This, of course, was the first report of the famous Watson/Bence Jones protein, and it was this study which has laid the basic foundation for the development of the very sophisticated, modern investigations of immunoochemistry and immunoglobulin study. I could go on quoting other original work: Beaumont’s physiologic and biochemical observation of gastric juice (27); Millon’s work with mercury and its effect on protein reagents, and eventually on barbiturate evaluations (24); the development by Bunsen, the famous flame maker, of spectroanalysis and the concept of extinction coefficients (15); the German physiologic chemist Hoppe-Seylers’ studies of the spectrum of oxyhemoglobin and methemoglobin (28). These and many others were discovered and reported during the 19th century. Although most of the individuals who worked in this field would have been considered more physician than chemist on the basis of their training, it is obvious that many of them thought of themselves as more chemist than physician. It is evident, therefore, that these two disciplines are intimately related and that those of us who work as clinical chemists have something definite to contribute to the field of medicine and to analytic and clinical diagnosis. The clinical chemist, more than any other medical scientist, has the opportunity to understand and appreciate physiologic and biochemical variations, the ability to recognize the limitations and vagaries of biochemical analytic procedures, and finally, the capability to provide objective information which, in its
proper framework, can be used for subjective diagnosis by the clinical medical scientist.

I would like to conclude with a paraphrase of a quote of Johann Joachim Becker (29):

The clinical chemists are a strange class of mortals held by an almost insane impulse to seek their pleasures among blood and urine, physicians and patients, soot and flame, poisons and poverty. Yet among all these evils, he seems to live so sweetly that he may die if he would change places with even a modern Greek shipping magnate.

References