Medical Chemists and the Origins of Clinical Chemistry in Britain (circa 1750–1850)

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In this history, I review developments leading toward the establishment of clinical chemistry in Britain. Chemical research by certain physicians occurred in the context of medical traditions founded on vitalism, distillation analysis, and limited chemical knowledge. Urine chemistry figured prominently in this period together with the analysis of kidney and bladder stones. Bright's team studying albuminuria was the first clinical research school in Britain, whereas Prout's survey of physiological chemistry, based on meticulous attention to analysis, was the best summary of human metabolism before Liebig's *Animal Chemistry*. Liebig's ideas influenced all physicians who were interested in chemistry. Henry Bence Jones based his medical practice on Liebig's theories. His research relating urinary phosphates to diet and exercise revealed the so-called Bence Jones proteins and investigated the distribution and persistence of drugs in the body. J.L.W. Thudichum used analytical skills learned from Liebig in his brain chemistry work. George Owen Rees investigated urine analysis and the relationship between urine and blood, using Liebig's practical methods while condemning an uncritical acceptance of his theories. These and similar studies showed that chemistry could improve clinical medicine, and because it could also reveal the onset of disease even before clinical symptoms developed, it offered valuable support to preventive medicine. However, so many physicians resisted the introduction of chemistry that progress toward the establishment of clinical chemistry in nineteenth-century Britain was slow.
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In the eighteenth century various London physicians offered private lectures on aspects of medicine and med-

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ical practice in efforts to compensate for the lack of organized medical education in the capital. Some of these private medical courses included chemistry lectures that often extended well beyond the limited knowledge needed for the preparation of drugs and medicines, and it was from such small beginnings that the transformation of English medicine from an empirical art to a science-based discipline began. George Fordyce (1736–1802) offered one of the earliest of these chemistry lecture courses at his London home in Essex Street, Strand *(1)*. Fordyce began in 1760, and 6 years later William Saunders (1743–1817) also offered chemistry lectures at Red Lion Court, Fleet Street. Both had been pupils of William Cullen in Edinburgh, from whom they had gained their enthusiasm for chemistry. Their lecture courses were transferred to London medical schools around 1770 when Fordyce was appointed physician to St. Thomas's Hospital and Saunders joined Guy's Hospital, where a new lecture theatre and laboratory specifically designed for chemistry teaching had been built *(2)*. As more such courses began to feature in London medical schools the growing importance of the subject for the practicing physician led a few pioneers to advocate chemical tests as an aid to diagnosis *(3)*.

Fordyce continued to lecture in his own home on topics ranging widely over contemporary chemistry, including industrial and agricultural topics as well as medical studies. Saunders, on the other hand, ceased his private lectures and confined his chemistry teaching at Guy's mainly to apothecary arts and the materia medica *(4)*. Some years later George Pearson (1751–1828), a pupil of Joseph Black, also began to lecture on chemistry at his London home where he followed a plan similar to that of Fordyce. He was appointed physician to St. George's Hospital in 1787, but like Fordyce he continued his private chemistry courses in addition to his lectures at the medical school *(5)*. Pearson's lectures became widely known, and he later numbered prominent American chemists such as Benjamin Silliman, the first professor of chemistry at Yale, and William Peck, professor of chemistry at Harvard, among his students. Silliman and Peck also

attended Friedrich Accum's chemical lectures at the Surrey Institution, Blackfriars Road, London (6).

In 1792 the chemistry course at Guy's was taken over by William Babington (1756–1833), apothecary and later physician to the hospital (7); during the next 10 years Babington delivered these lectures (8) until 1802 when the Quaker pharmacist William Allen (1770–1843) joined him (9). Allen had his own chemical laboratory at his pharmacy in Plough Court on Lombard Street where, in addition to experimental work on medicines and drugs, a wide range of chemical topics was investigated (10). Allen's experimental work was highly regarded by leading European chemists, including Humphry Davy (1778–1829) and the Swedish chemist Jöns Jacob Berzelius (1779–1848) (11).

The subject matter of eighteenth-century chemistry remained a loose collection of data dominated by G.E. Stahl's phlogiston theory. In addition to the common acids and alkalis, metals and mineral compounds, all of which were studied for their uses in industry and assaying, there was much interest in plant and animal extracts. The latter were invaluable in the pharmacy, where chemistry traditionally made its chief contributions to medicine. In living organisms, however, the doctrine of vitalism held sway. Hypothetical vital forces were invoked to explain the functions of living organs, nerves, and tissues and the special properties of growth, repair, and reproduction common to all living things. To most physicians these vital forces were patently obvious, and it seemed unlikely that the physiology and pathology of living human organs could ever be fully accounted for by chemistry and physics. Chemists were also held in thrall to vitalism in one form or another throughout the greater part of the nineteenth century, although many thought that the importance of the vital forces would decline and ultimately vanish with the growth of organic chemistry (12).

The Chemistry of the Urine and Its Deposits

There was, however, one human secretion that provided an exception to the universal influence of vitalism, the urine. Physicians, apothecaries, and quacks had practiced urology, a superficial examination of the urine to divine the state of health or sickness of patients, since antiquity. Closer to astrology than to medical diagnosis urology began to give way in the eighteenth century to simple chemical analysis. As a waste product of the animal system, urine was released from the influence of vital force. The main chemical constituents of the urine apart from water were known to be crystalline compounds and mineral salts. Numerous early workers identified urea, its commonest organic component. Antoine François de Fourcroy (1755–1809) and Nicolas Louis Vauquelin (1763–1829) in Paris evaporated the water from fresh urine to leave a solid residue containing ammonium chloride and urea (13). Urea behaved as a base, was converted to ammonium carbonate on gentle heating, and gave off

Table 1. Berzelius's analysis of human urine.[a]

Component	Parts per 1000 by weight
Water	933.00
Urea	30.10
Potassium sulfate	3.71
Sodium sulfate	3.16
Sodium phosphate	2.94
Sodium chloride	4.45
Ammonium phosphate	1.65
Ammonium chloride	1.50
Lactic acid; ammonium lactate; alcohol-soluble and -insoluble animal matter	17.14
Earthy phosphates and calcium fluoride	1.00
Uric acid	1.00
Mucus of the bladder	0.32
Silex	0.03
Total	1000.00

[a] Source: Berzelius JJ. General views of the composition of animal fluids (pp. 270–271). (16).

ammonia with alkalis. Fourcroy thought that the urine contained a higher proportion of azote (nitrogen) than other animal fluids (14).

When Berzelius completed his two-volume textbook of animal chemistry in 1808 (15), he sent a copy to Humphry Davy who suggested that an English translation should be made. This was never successfully achieved, but the Swiss émigré Alexander Marcet (1770–1822) persuaded Berzelius to publish some of his analyses of animal fluids, including the urine, in *Medico-Chirurgical Transactions*, (16) the journal of the Medico-Chirurgical Society founded in 1805 after a dispute within the Medical Society of London. It is now the Royal Society of Medicine (17). In the urine Berzelius identified lactates, muriates (chlorides), and earthy phosphates as well as uric acid; he even noted a small quantity of calcium fluoride (Table 1). His analysis became the standard and was still being quoted in the late 1840s (18). It provided basic information on the composition of healthy urine that was useful for the diagnosis of certain diseases because changes in the proportions of urea and uric acid, the end products of the metabolism of proteins, indicated the state of the vital functions themselves.

The urine sometimes contained excessive quantities of salts, which formed crystalline deposits first in the kidney, then in the bladder, where a stone might grow by accretion. Bladder stone was a scourge in eighteenth-century Europe, and there was no known cure except surgery (19). Lithotomy was a fairly common surgical procedure, and many hospitals held collections of bladder stones taken from patients; the operation was risky, however, and many patients died following it (20). A safer, less traumatic form of treatment was clearly highly desirable.

In 1780 Carl Wilhelm Scheele (1742–1786), the Swedish apothecary, had found that in addition to phosphates and

other mineral salts, all kidney and bladder stones contained a mildly acidic compound that he named "lithic acid" (uric acid). It seemed that chemical analysis could determine the composition of these stones, and there was hope that it might also show how they could be dissolved, or prevented from forming *(21)*. In 1797 William Hyde Wollaston (1766–1828), then a physician at Bury St. Edmunds in Suffolk, described the chemical properties of four types of urinary stones *(22)*, and later, in 1810 he discovered a new compound in bladder stones that he named cystic oxide (cystine) *(23)*. This encouraged George Pearson to examine more than 300 urinary stones in the collection at St. George's Hospital in London *(24)*. Henry Bence Jones would later analyze and catalog the same collection of stones. Pearson found Scheele's lithic acid in all of them, and among its properties he noted the pink color produced by evaporation with strong nitric acid. In Paris Fourcroy had already reviewed analyses of bladder stones; Pearson's paper revived his interest, and during the next 5 years, with Vauquelin, he analyzed at least 600 human calculi and some animal stones *(25)*. It was Fourcroy who introduced the name uric acid to replace Scheele's lithic acid. In England others who studied the chemical composition of bladder stones included William Henry (1774–1836), who examined the collection of urinary stones in the Manchester Infirmary *(26)*, and John Yelloly (1774–1842), a contemporary and friend of Alexander Marcet. Yelloly was appointed physician at the London Hospital in 1807, but he moved to the Norfolk and Norwich Hospital in 1818. The county of Norfolk had long been plagued by an unusually high incidence of this disease, and the Hospital had become a center for its treatment *(27)*. In the 1820s Yelloly analyzed nearly 1500 urinary stones in the Norfolk and Norwich Hospital collection *(28)*.

At Guy's Hospital, Saunders investigated the structure and functions of the liver *(29)*. He advocated drinking large quantities of warm water as a treatment for liver complaints, and this led him to investigate the chemical composition of natural mineral waters, a subject that had long occupied the attention of physicians *(30)*. Mineral waters offered a safe and relatively pleasant treatment for liver and renal diseases. Each mineral spa boasted special medicinal properties, and many eighteenth-century English physicians attempted to analyze these waters *(31)*. Other European chemists also worked on the chemical analysis of mineral waters, often with the aim of manufacturing them in the laboratory *(32)*. It was on Saunders's recommendation that Marcet was appointed physician at Guy's in 1804 *(33)*. As a pupil of Joseph Black he had a good knowledge of chemistry, and when Saunders introduced him to mineral water analysis, he contributed an account of the Brighton chalybeate spring to Saunders's book on mineral waters *(34)*.

Marcet began to lecture in chemistry at Guy's medical school in 1807 *(35)*. At the students' request he introduced lectures on the composition of bladder stones *(35)*, and in 1817 he wrote a book describing all of the known types of urinary calculi and explaining how their chief constituents could be identified by simple chemical tests *(36)*. His reagents included dilute solutions of mineral and acetic acids, caustic alkalis and the alkali carbonates, ammonium hydroxide, ammonium oxalate, and potassium cyanide. He proposed a portable chemical kit to be carried by physicians to the patient's bedside. It included small bottles containing the necessary reagents, test tubes, a spirit lamp, blowpipes, and other simple apparatus enabling chemical tests on urinary deposits to be made as an aid to diagnosis (Table 2).

At that time most chemists thought that the chemical properties of substances depended on the quantity of material, but Marcet, following Wollaston's analytical techniques, used minute quantities of material and was convinced that such small samples showed precisely the same chemical properties as larger quantities. Marcet also discovered a new compound in certain stones that he called xanthic oxide because it was soluble in alkalis and turned yellow on evaporation with nitric acid *(32)*. It is now called xanthine. Marcet's work was potentially an important contribution to clinical chemistry, but the tests were not easy to perform in the sickroom, the results were disappointing, and most physicians, doubting their value, eschewed them.

The First Medical Research School at Guy's

Albuminuria, another life-threatening urinary disease, was common in the early nineteenth century, and Richard Bright (1789–1858), who entered Guy's Hospital as a physician in 1811, devoted his life's work to it *(38)*. Regarding each new case as a clinical problem to be explored by the experimental method, Bright established a dedicated team of young physicians. Combining chemical analysis with clinical and pathologic studies of the disease and confirmatory evidence from postmortem examinations, Bright and his team showed how physicians and chemists working together could achieve a more scientific approach to clinical medicine *(39)*. They aimed to construct complete clinical and pathologic case histories to provide the basis for appropriate medical treatment at each stage of the disease. After following this method for several years Bright persuaded the Hospital to grant him two wards with a total of 42 beds for a 6-month intensive study of the disease. In this unit a room where the physicians could meet to discuss the cases separated a male ward from a female ward. There was also a laboratory fitted out specifically for conducting microscopic and chemical examinations of tissue samples and secretions. The results were correlated with the clinical observations and with postmortem examinations of the diseased kidney. Between 1827 and 1840 Bright published the results of these studies illustrated by colored lithographs showing diseased kidneys *(40)*. Later he published tabulated details of many cases of albuminous urine that had been treated by his group *(41, 42)*.

Table 2. Marcet's experimental tests on urinary calculi.[a]

Name of calculus	Appearance	Reaction with blowpipe	Acids	Alkalis	Chemical composition
Lithic	Smooth	Blackens and burns with characteristic smell	Insoluble; pink color with HNO_3	Soluble	Uric acid
Bone-earth	White friable	Infusible	Soluble if powdered. Calcium oxalate precipitate with ammonium oxalate	Insoluble	Calcium phosphate
Triple phosphate	White crystals	Yields NH_3 and white residue	Insoluble	Soluble; NH_3 evolved	Magnesium ammonium phosphate
Fusible	White	Melts to form a near-white globule	Soluble in HCl. Calcium oxalate precipitate with ammonium oxalate	Partially soluble; NH_3 evolved	Mixture of 2 and 3
Mulberry	Rough brown as a mulberry	Swells to leave CaO	Slowly dissolves	Insoluble	Calcium oxalate
Cystic oxide	Waxy	Decomposes with characteristic smell	Readily soluble	Readily soluble	Cystic oxide (cystine)

[a] Source: Marcet A. An essay on the chemical history and medical treatment of calculous disorders (36).

Bright was the first in Britain to establish a medical research group concentrating on one particular disease. His first collaborator was John Bostock (1773–1846), the son of a Liverpool doctor and a pupil of Joseph Black at Edinburgh. Bostock moved to London in 1817, gave up medical practice, and began to make his name in medical chemistry and physiology (43). The team also included George Hilaro Barlow (1806–1866), George Owen Rees (1813–1889), George Robinson (1821–1875), and Frederick William Pavy (1829–1911). Their experiences under Bright's guidance enabled each of them to make further important contributions to renal and urinary studies. Barlow and Rees wrote an account of the work of Bright's team (44, 45). These studies of albuminuria marked the beginnings of the specialized hospital unit and the first clinical laboratory in England. Pamela Bright describes this laboratory in her biography of Richard Bright (46). Unfortunately, because of great reluctance among British clinicians to accept chemistry in the hospital, Bright's enterprise was allowed to lapse, and Britain was slow to develop the ideas he had pioneered.

In 1831 when William Prout (1785–1850) was elected to deliver the Gulstonian Lectures at the Royal College of Physicians, he chose to discuss the applications of chemistry to physiology, pathology, and medical practice, insisting on the need for physiologists to become chemists to ensure progress (47). This provoked the vitalist physician Alexander Philip Wilson Philip (1770?-1851?) to object strongly. He said that "Chemistry and the science of the vital functions are of so different a nature, that [. . .] the one will tend constantly to abstract the mind from, and perhaps in some degree unfit it for the other" (48). Such resistance to the applications of chemistry in medicine persisted, and 17 years later the Dublin clinician Robert James Graves (1796–1853) could still say that "Few and scanty indeed, are the rays of light which chemistry has flung on the vital mysteries" (49). In Germany by contrast, clinicians recognized the value of chemistry, and laboratories for clinical chemistry began to appear from the middle of the nineteenth century (50).

Organic Analysis and Metabolism

Studies of specific diseases were important, but a broader understanding of physiological chemistry was essential for the advancement of scientific medicine. William Prout, who also entered Guy's in 1811, understood this clearly. After securing his license from the Royal College of Physicians Prout left the hospital to set up in private practice (51, 52) Marcet's chemical lectures had inspired him, and once established Prout began his own course of evening lectures on animal chemistry at his London home.

Among chemists Prout is best remembered for his observation that the atomic weights of the elements are whole-number multiples of that of hydrogen. Prout's hypothesis, stated in 1815, caused controversy, and chemists repeatedly sought to determine ever more accurate

atomic weights throughout the nineteenth century *(53)*. His work in physiological chemistry, begun about the same time, has always been much less known. He began with an experimental study of respiration, performing experiments on himself to determine the quantity of carbon dioxide exhaled at different times of the day and under various circumstances. Prout was also interested in the process of digestion, and believing that its main purpose was to fabricate blood, he published his investigations *(54)*, completed 3 years later with experiments on the development of the chicken embryo *(55)*. In human physiology Prout identified four stages in the formation of blood: digestion in the stomach, chymification in the duodenum, chylification in the lacteals, and sanguification proper in the blood vessels. His aim was to investigate human physiology not merely as an intellectual exercise but for the daily benefit of practicing physicians.

Prout recognized that the first essential was to determine the elementary composition of natural substances as precisely as possible *(56)*. Until the beginning of the nineteenth century the "analysis" of natural substances had involved destructive distillation, an unreliable process yielding spirits, oils, salts, and earths, all complex mixtures and compounds. The nature and proportions of the products depended on the temperature reached during the distillation process. Other analytical procedures involved solvents, but such extraction processes nearly always produced complex mixtures of variable proportions *(57)*.

In 1810 Joseph Louis Gay-Lussac (1778–1850) and Louis Jacques Thenard (1777–1857) in Paris devised a new method of organic analysis by which carbon and hydrogen, common to all organic matter, were oxidized quantitatively to carbon dioxide and water. Their first oxidizing agent was potassium chlorate, but later they used copper oxide. From the weights of the products the proportions of the fundamental elements in the organic matter could be determined *(58)*. Nitrogen, generally present in animal matter, was estimated by calculation; other elements, such as phosphorus or sulfur, required special methods. Berzelius adapted the method for laboratory use *(59)*, but Prout, dissatisfied with the reliability of the results, set to work to improve the technique. Realizing that moisture would cause serious errors by boosting the proportions of hydrogen and oxygen in his results, he took steps to dry both his reagents and the organic material to be analyzed by use of concentrated sulfuric acid in a vacuum apparatus he designed himself. He spared no expense in the pursuit of accuracy; his methods were laborious and exacting, but by 1820 he was able to say "I [. . .] have at length extended my researches to almost every distinct and well-defined [organized] substance" *(60)*. Unfortunately, he published very few of his results, unwilling to make them public until he was convinced that they could not be improved further. In 1827, still seeking increased accuracy, he began to use

pure oxygen gas in a specially constructed analytical apparatus *(61)*.

In common with many of his contemporaries, Prout spent much time on urine analysis. In 1814 he isolated a pure sample of urea, and his method of purifying it by use of animal charcoal became the standard procedure described in chemical textbooks. He also showed that the excrement of a boa constrictor, then on exhibition in the Strand, was 90% pure uric acid, an important physiologic observation. He determined the empirical formulae of these compounds and gave figures for their empirical formula weights. In the course of this work Prout discovered two new acids. The first was discovered around 1818 when he examined the purple color produced by the action of nitric acid on uric acid. He thought this was the ammonium salt of a new acid he named purpuric acid. Presented to the Royal Society in a paper read by Wollaston, this led to Prout's election as FRS in 1819. The other new acid was discovered in 1822 when Marcet gave him a sample of urine that had turned black (alkaptonuria). Prout decided that the black color was attributable to the ammonium salt of an unknown acid that he named melanic acid. It has since been shown to be homogentisic acid [2:5 dihydroxy-phenyl acetic acid— $C_6H_3(OH)_2CH_2COOH$—a product of faulty protein metabolism *(62)*]. Prout's work on urine chemistry, first published in 1821, was intended as a handbook for the practicing physician and made an important contribution to clinical chemistry *(63)*. Like Marcet, Prout also introduced a portable chemical kit for physicians to use at the patient's bedside. There were five editions of this book, each with extensions and improvements. The fifth and last appeared in 1848, but by then the book had fallen out of favor *(64)* because, as a result of his increasing deafness, Prout had not kept up with newer developments in chemistry and physiology.

In 1824 Prout discovered hydrochloric acid in the stomach rather than acetic acid or lactic acid as had generally been thought *(65)*. Twice in 1823 he had advertised his forthcoming book on digestion, but this new discovery so changed his views that he now abandoned the project. The presence of such a strong mineral acid in the stomach was hotly contended, but others soon confirmed his discovery. Friedrich Tiedemann (1781–1861) and Leopold Gmelin (1788–1853) in Germany found hydrochloric acid in stomach fluids in February 1824, only 1 month after Prout's announcement, of which they were unaware *(66)*, and William Beaumont (1785–1853) in America was later able to make a lengthy and detailed series of experiments on the gastric juice in vivo *(67)*. These experimental discoveries supported the use of chemical methods in physiologic investigations, but they did not wholly explain the digestive process. The acid alone was found incapable of digesting food, and it was clear that the digestive juice must also contain an unknown "ferment". Pepsin, the first enzyme to be discov-

ered, was found in gastric juice by Theodor Schwann (1810–1882) in 1838 (68).

Prout's last purely chemical paper was published in 1827; it was intended as the first of three dealing with the main alimentary groups, saccharinous (carbohydrates), oleaginous (fats), and albuminous (proteins) (69). The other papers were never published, but Prout was awarded the Royal Society's Copley Medal for the method of combustion analysis using gaseous oxygen described in this paper. Prout's important contributions to clinical chemistry include, in addition to accurate analyses of many natural substances, his insistence on chemistry as essential for understanding physiology and a comprehensive scheme of human physiological chemistry. This was published in 1834, but curiously it appeared as an apologia for the religious doctrine of Natural Theology (70). It was not widely understood, especially because those most likely to read were mainly nonscientists. Prout's speculative metabolic theory, however, remained the broadest survey of this field until Liebig's *Animal Chemistry* appeared in 1842.

The Urine and the Blood

The tradition for medical chemistry at Guy's was maintained in the work of George Owen Rees (71). Despite a long and successful career as a practicing physician, Rees always preferred the chemical laboratory to hospital wards. He became well known as a chemical analyst and was a founding member of the London Chemical Society. In 1833 he published an English translation of a small French manual of inorganic analysis based on Berzelius's rules for analyzing gases, salts, and mineral waters (72). Common reagents and simple gravimetric procedures were introduced, and Rees's own practical hints, emphasizing the need for close observation, made it a useful laboratory guide for chemistry students. Rees also supplied quantitative analyses of blood serum, urine, and other animal fluids with a study of the chemical properties and corpuscular structure of the blood in six cases of albuminuria for a joint report with Barlow on the work of Bright's team mentioned above (44).

Rees also recognized the value of microscopic observations and was one of the first to notice that red blood corpuscles remained unchanged in a saline solution with specific gravity equal to that of healthy blood serum, an observation predating the introduction of the "normal saline solution" (73). As a skilled chemical analyst he remarked on the need for pure reagents and had a very low opinion of the quality of the materials sold by the average chemist and druggist. He found that their distilled water often contained chlorides and that hydrochloric acid always contained iron and often contained sulfuric acid. Nitric acid usually contained sulfuric acid; the latter was often contaminated with arsenic and lead, whereas liquor potassae (caustic potash solution) usually contained lime. In view of these and other contaminants

Rees always purified reagents purchased from chemists and druggists before using them for analysis.

His analytical skills also led to collaboration with another colleague at Guy's, the forensic toxicologist Alfred Swaine Taylor (1806–1880). Taylor was renowned for his work as a medical jurist and was frequently called as an expert witness in murder trials involving poisoning (74). Rees assisted Taylor by supplying him with reliable analytical data to be used in conjunction with clinical and postmortem observations in criminal trials. Taylor always insisted on the primacy of clinical observations and presented the analytical results as supporting evidence. This was particularly true in cases of poisoning when alkaloids such as morphine, strychnine, and brucine were used. They were extremely difficult to identify by chemical tests although their physiologic effects were well known, and Taylor was sometimes convinced on the basis of clinical reports alone that poisoning was attributable to these alkaloids even when there was no postmortem chemical evidence to support this conclusion. Nevertheless, the combined efforts of Taylor and Rees produced major contributions to this special branch of clinical pathology.

Urine analysis was Rees's forte, and following his work with Bright he became especially interested in the identification of albumin in the urine. He showed how it could be detected in the presence of other substances that interfered in the tests. It was known that both nitric acid and heating to the boiling point would yield a precipitate from albuminous urine, but heat might also produce a precipitate of earthy phosphates. Nitric acid dissolves this precipitate, and Rees, like Bright, advocated the use of both tests to confirm the presence of albumin. The urine of patients taking certain vegetable substances, such as copaiba or cubebs, becomes cloudy with nitric acid, but unlike albumin the cloudiness does not subside. Other complicating factors led Rees to return to the problem until he had developed a more comprehensive method for identifying albumin that involved potassium ferrocyanide and mercury perchloride, in addition to the traditional tests. Rees showed how such simple chemical tests could improve diagnosis. Many clinicians disagreed, but the surgeon Bransby Blake Cooper (1768–1853) boldly declared that "no medical practitioner should consider himself competent to undertake the treatment of urinary diseases who is not able to investigate the chemical characters of abnormal urine" (75).

Rees also turned his attention to the blood, arguing that the composition of healthy blood should first be determined to act as a standard when noticeable changes occurred (76). Thus, in cholera the proportion of water in the blood decreased, and in diabetes there was an excess of fatty matter as well as urea. Other foreign matter sometimes found in the blood included the coloring matter of the bile, cholesterine, and even free carbon, although these substances had often been confused with others or missed altogether. Rees insisted that the proportions of each constituent of a blood sample should be

Table 3. Liebig on the degradation of protein and starch (C = 6 and O = 8).[a]

5 atoms proteine		9 atoms choleic acid
15 atoms starch	$=$	9 atoms urea
12 atoms water		3 atoms ammonia
5 atoms oxygen		60 atoms carbonic acid

5 atoms proteine: $5(C_{48}N_6H_{36}O_{14})$	$=$	$C_{240}N_{30}H_{180}O_{70}$
15 atoms starch: $15(C_{12}H_{10}P_{10})$	$=$	$C_{180} \quad H_{150}O_{150}$
12 atoms water: $12(HO)$	$=$	$H_{12} \, O_{12}$
5 atoms oxygen:	$=$	O_5
Total		$\mathbf{C_{420}N_{30}H_{342}O_{237}}$
9 atoms choleic acid: $9(C_{38}NH_{33}O_{11})$	$=$	$C_{342}N_9 \, H_{237} \, O_{99}$
9 atoms urea: $9(C_2N_2H_4O_2)$	$=$	$C_{18} \, N_{18}H_{36} \, O_{18}$
3 atoms ammonia: $3(NH_3)$	$=$	$N_3 \, H_9$
60 atoms carbonic acid: $60(CO_2)$	$=$	$C_{60} \qquad O_{120}$
Total		$\mathbf{C_{420}N_{30}H_{342}O_{237}}$

[a] Source: Liebig J. *Animal chemistry or organic chemistry in its application to physiology and pathology (79).*

determined separately and emphasized the importance of correlating chemical and microscopic observations with older clinical methods *(77)*. Rees showed that the compositions of the urine and the blood are directly linked. In debility, anasarca, heart disease, chlorotic anemia, and hysteria he found components of the blood effused into the urine. Moreover, he observed that the concentrations of blood substances in the urine were usually greatest in the early stages of disease, even before physical symptoms had become obvious *(78)*. It followed, therefore, that chemical tests could alert the physician to the onset of disease and so contribute as much to preventive medicine as to the diagnosis and treatment of established diseases.

Liebig's *Animal Chemistry*
In 1842 Justus von Liebig (1803–1873) published his *Animal Chemistry (79)*. He argued that digestion and assimilation converted food into muscle and other tissues and that during physical exertion these were degraded and oxidized in the lungs to produce energy. Animal heat was distributed throughout the body by the circulation of the blood, and the end products, including urea and uric acid, were excreted. By analyzing the food taken in, the fluids in the alimentary canal, and the compounds excreted in the urine, Liebig thought it would be possible to explain the physiological chemistry of the animal body. He represented metabolic changes by balanced "equations" using empirical formulae in which atoms and molecules were added and subtracted as required to produce the end result (Table 3).

Superficially the method seemed plausible, and Liebig used it extensively in his account of animal chemistry. He dedicated his work to Berzelius in the hope that it would be recognized as an important extension of the great man's work in this field, but Berzelius criticized his arguments as facile. Nevertheless, Liebig's theories were welcomed by some for the simplicity they brought to physiological chemistry. Controversy stimulated research, and for 30 years chemists and physiologists in Germany, France, and Britain carried out intensive investigations to test Liebig's theory of oxidative metamorphosis *(80)*. By the 1870s his ideas had been found to be untenable, but the research they had provoked led to new discoveries in physiological chemistry and helped to advance clinical chemistry.

Henry Bence Jones (1813–1873), the most prominent nineteenth-century medical chemist in England, was an enthusiastic follower of Liebig *(81)*. Physician at St. George's Hospital, Secretary of the Royal Institution, Council Member of the Royal College of Chemistry, and Vice Chairman of the Chemical Society, Bence Jones had a high profile in nineteenth-century London *(82)*. At University College George Fownes (1815–1849), who had been a pupil of Liebig in 1839, introduced him to Liebig's theories and analytical methods. and after obtaining his License at the Royal College of Physicians in 1841, Bence Jones spent 6 months in Liebig's laboratory at Giessen. "My first conversation with professor Liebig on his new views on physiology" he said, "had filled me with admiration and appeared like a new light where all had been confusion and incomprehensible before" *(83)*. Indeed Bence Jones became so convinced by Liebig's theories that he determined to base his future work on them *(84)*. He argued that in urinary diseases the oxidation of uric acid should be encouraged and the degradation of muscular tissues reduced. Too much nonnitrogenous food led to the conversion of uric acid to ammonium urate, fat, and choleic acid instead of urea, and this was thought by Liebig to be the fundamental cause of gout. Bence Jones suggested that by promoting the circulation while moderating the diet this could be corrected, and it would be easy to monitor the progress of the treatment by regularly analyzing the urine. In general, he said, "the quantity of uric acid thrown out of the body varies inversely with the

quantity which undergoes change in the body" *(85)*. Using this principle, coupled with chemical analysis of the urine, he thought that the physician could gain a clearer picture of a patient's health.

Liebig argued that the oxidation of muscle tissue led to the release of alkaline phosphates in the urine, and to test this Bence Jones made a systematic study of the chemical composition of the urine of patients in the wards of St. George's Hospital. By correlating his observations with diet, the effects of exercise, and certain medicines, he began to reveal the potential of chemical methods in clinical medicine *(86)*. He found that patients restricted to two meals a day interspersed with moderate exercise excreted increased quantities of alkaline phosphates in proportion to the degree of muscular exertion, apparently confirming Liebig's theory. Unfortunately, it appeared that in delirium tremens and acute chorea (St. Vitus dance) when muscular exertions sometimes became so intense as to endanger life, there was no marked increase in the excretion of phosphates. However, in cases of acute inflammation of the nervous structures and of the brain the excretion of phosphates did increase. To explain these anomalous observations he suggested that in nervous disorders oxygen attacked phosphorus in cerebral matter, although there was no experimental evidence to support this idea. Thus, when faced with baffling clinical observations he speculated in the absence of firm evidence just as Liebig had done. Bence Jones's work on urine analysis was published in 1850 *(87)*.

In 1845 he had received some samples of urine from a patient suffering from mollities ossium. He found that they contained a high proportion of albuminous matter that, unlike ordinary albumin, was soluble in boiling dilute nitric acid, and in 1847 he announced the discovery of a new protein *(88)*. This albuminous urine had already been fully described in clinical terms by William McIntyre (1791–1857) *(89)*, but the significance of the Bence Jones proteins remained obscure for more than a century. Their biochemical importance was revealed in 1955 when F.W. Putnam found that Bence Jones proteins are not degradation products of protein metabolism but are biosynthesized in the cells *(90)*. Recent work has shown that the Bence Jones proteins consist of the "light-chain" components of the immunoglobulins. The sequence of amino acids in the chains is specific to each individual, and the complete amino acid sequences of some Bence Jones proteins have been worked out. They hold the key to antibody specificity.

In another research project Bence Jones sought to trace sites in the organs and tissues where drugs became concentrated and to investigate rates of diffusion of drugs through the system to discover how long they remained effective. In this pioneering work he was assisted by August Dupré (1835–1907), who had studied with Liebig at Giessen and with Bunsen and Kirchhoff at Heidelberg. Dupré lectured on toxicology and was later appointed public analyst to the City of Westminster *(91)*. With Bence Jones he used spectrum analysis to detect the presence of certain metals. Measured doses of lithium carbonate were administered to guinea pigs that were then killed after various intervals ranging from a few minutes to several days. Parts of their organs were incinerated, and the soluble salts were extracted from the ash and examined for the presence of lithium. Spectrum analysis is extremely sensitive for lithium, and it was found that within 15 min the metal ions had diffused from the stomach to all of the vascular tissues, the cartilage of the hip joint and the humors of the eye. In 30 min, lithium was detectable in the lens of the eye, a part of the body furthest removed from the vascular system. Bence Jones also found that if the lithium salt was injected subcutaneously diffusion was much more rapid; within 4 min it could be detected in the lens of the eye. Lithium salts were found to persist in the urine up to 39 days after the initial dose.

To ensure the validity of his results for therapeutic use he needed to test similar procedures on human subjects, and he sought volunteers among the patients at St. George's Hospital. He found that doses of lithium carbonate given 4 h after food appeared within 10 min in the urine, but it took up to 18 h for the element to reach the fingernails or hair, although once present in these sites it persisted for 12 days or longer. To estimate the times taken to reach nonvascular sites in the body, Bence Jones examined the lenses removed from the eyes of cataract patients. Thirteen patients at the Royal Ophthalmic Hospital were involved in these tests, in addition to terminally ill patients who received injections of lithium salt solutions and whose tissues were tested for lithium in postmortem examinations. Lithium was found in the lens of the eye 3.5 h after the dose was administered, and traces were still detectable 4 days later *(92)*. The rates of diffusion of other metals, including rubidium, strontium, silver, and thallium, were also examined in this pioneer study of the distribution and fate of chemicals in the body.

To trace the rates of diffusion of the alkaloids Bence Jones used the fluorescence of quinine sulfate in ultraviolet light, a phenomenon already observed by the Irish-born physicist George Gabriel Stokes (1819–1903) *(93)*. The sensitivity of this test was much lower than that of the spectrum analysis procedure for lithium. Bence Jones began by determining the rate of diffusion of quinine into the organs of the guinea pig as before. The organs were boiled with dilute sulfuric acid, and the resulting solutions were made alkaline with potassium hydroxide and then extracted with ether. The residues were then tested for fluorescence. It was found that regardless of whether the animals had been dosed with quinine there was always some fluorescence and that the effect was most marked in the lens of the eye. Bence Jones managed to isolate the cause of this fluorescence, a substance whose properties were virtually identical to those of quinine. He called the new substance "animal quinoidine" and devised a standardization process to estimate the degree of fluorescence attributable to this common factor. A set of

standard solutions of quinine sulfate were prepared by which it became possible to estimate with reasonable accuracy the quantity of medicinal quinine in the tissues and the time required for quinine to diffuse into the various tissues and so become effective.

On the basis of his results Bence Jones suggested the concept of a chemical circulation depending partly on the circulation of the blood and partly on the osmotic diffusion of chemicals between the blood and the tissues. He proposed new lines of inquiry to investigate this chemical circulation, recognizing the experimental difficulties involved but suggesting that chemists should tackle them for the improvement of medicine. Commenting on Bence Jones's methods, Edward Long Fox *(94)*, one of his students, said that scientific truth, accuracy, and a dislike of empiricism marked him as a hospital physician. "His chief aim in the wards seemed to be towards making therapeutics scientific [. . .] and he insisted on his pupils analyzing the secretions pretty constantly" *(95)*. By the mid-1860s Bence Jones had come to regard the body as a complex, finely balanced system controlled by the interaction of chemical, physical, and nervous functions. Changes in the animal system caused detectable chemical errors, and the physician could prescribe the appropriate corrective medicines based on the results of chemical and physical experiments. In 1866 Bence Jones was elected Chairman of the Chemical Section of the British Association for the Advancement of Science meetings in Nottingham. In his address he remarked that chemistry was still neglected in most medical schools and called for physicians to pay more attention to the study of chemistry. He said that "accurate knowledge of the actions of medicines depends on exact chemical and physical experiments; and by the perfection of these alone will the practice of medicine lose its doubts and difficulties" *(96)*.

Bence Jones gained a reputation as the best chemical physician in London. Few physicians were as easily persuaded of the value of Liebig's theories, although many chemists were inspired by his teaching and research methods. Prominent among Liebig's ardent followers in London was the German émigré Johann Louis Wilhelm Thudichum (1829–1901). Thudichum is best remembered for his work on the chemical composition of the brain *(97)*, but his interests were wide, extending from the therapeutic properties of the Turkish Bath to the chemistry of wine and cookery. He made many useful discoveries and isolated a large number of complex organic compounds. After studying chemistry and medicine at Giessen and Heidelberg, Thudichum arrived in London in 1853. He began to lecture on chemistry, and his early physiological researches were on urine *(98)* and gallstones *(99)*. He quickly established himself as a chemical pathologist and was recruited by John Simon (1816–1899), first Medical Officer of Health for London and Medical Officer to the Privy Council, to assist in Simon's scheme to extend the use of chemistry in medicine. Simon asked Thudichum to investigate the possibility that the brain

damage often caused by epidemic diseases such as cholera and typhus fever was attributable to chemical changes. Thus, Thudichum's researches on the chemical composition of the brain were themselves an aspect of clinical chemistry. Thudichum was meticulous, honest, and outspoken. His experimental results led him to challenge the contemporary view propounded by Oscar Liebreich (1839–1908), who was working in Hoppe-Seyler's laboratory at Tübingen, that the brain was composed of a single complex lipid called "protagon". Thudichum found a complex mixture of compounds in brain matter and concluded that protagon did not exist. Influential contemporary physiological chemists unjustly criticized his work, his reputation was damaged, Government financial support was withdrawn, and he was forced to pursue research at his own expense. After his death in 1901 he remained virtually unknown among chemists until 1930, when Otto Rosenheim (1871–1955) revealed him as a pioneer of biochemistry. A recent study of his life and work emphasizes his importance in clinical chemistry and public health *(100)*.

The "Fallacy of Theories"

Even those physicians who were convinced of the importance of chemistry in medicine were often doubtful about placing too much reliance on chemical theories. Warning that matters of fact should be carefully distinguished from speculation, Rees said, "further advances may very probably lead us to detect the fallacy of theories which it is to be feared, the present state of our knowledge may permit us to see in too attractive a form" *(101)*. Rees had entered physiological chemistry not in the heady atmosphere of Liebig's research school but through the busy wards of Guy's Hospital, where he had been daily confronted with urgent medical problems. Throughout a long medical career he sought to improve the reliability of analytical results for clinical diagnosis. His chemical ideas were well known in medical circles, but his methods, received with polite interest but little enthusiasm, were not much used. Thudichum too used Liebig's analytical methods with great skill, but he did not subscribe to his theories.

Golding Bird (1814–1854), another Guy's physician, also criticized Liebig's theories on the grounds that they were not borne out by clinical observations *(102)*. Like so many of his contemporaries, Bird studied the chemistry of the urine and its deposits by making chemical and microscopic observations to identify minute quantities of urinary deposits. He classified 342 stones in the collection at Guy's Hospital according to the composition of their nuclei *(103)*. His results were published in 1844 in an important book in which crystals of the different urinary deposits were illustrated by drawings using the microscope *(104)*. Bird discussed the formation of the components of urinary deposits by the rearrangement of their atoms in the manner of Liebig's chemical equations, but despite the convenience of this formulaic convention, he recognized that there was no certainty that such theoret-

ical rearrangements explained the mechanisms of the chemical reactions involved. Bird's book was very widely used, and there were five editions, the last of which appeared in 1857, three years after his death.

As Liebig had suggested it seemed reasonable to suppose that an increase in the circulation of the blood would cause more rapid oxidation of the tissues, but Bird doubted that the theory was universally true. He observed that in anemia the proportion of uric acid to urea in the urine decreased, whereas in fevers it increased in direct opposition to Liebig's theory. In addition, for Liebig the efficient agents in vital chemistry were wholly chemical, but like many other physicians, Bird argued that the nerves also played an important part in controlling the vital functions. His belief in the influence of the nerves was reinforced in 1836 when he was appointed to take charge of a new electrotherapy department. Some patients with nervous disorders were "electrified" by being connected to the positive pole of a battery while seated on a nonconducting stool. Weak electric currents were passed through the body in other cases, or mild electric shocks were administered. After using these techniques for 6 years Bird wrote a report of his work and later chose this topic for his lectures on the materia medica at the Royal College of Physicians in 1847, although some argued that electricity was ineligible for inclusion among drugs and medicines (105). Medical practitioners were reluctant to recognize this new therapy, and it fell into the hands of charlatans who, with no medical training, set themselves up as "medical electricians". Magnetic telegraph operators employed by the railway companies sometimes engaged in this practice.

Bird realized that a simple device for administering mild shocks and weak currents would be a useful therapeutic aid, and around 1850 he supported the claims made for Pulvermacher's chain, a device invented by a Viennese physicist that could be carried by physicians and used by patients themselves. It consisted of several small wooden cores, each carrying two wires, one of zinc and the other of gilded copper. The ends of the wires were formed into hooks so that a chain of any desired length could be made. The chain was first dipped in vinegar and would then produce electric shocks until the liquid evaporated; a chain of 50 links administered a sharp shock (106).

Summary

Marcet, Bright, Prout, Rees, Bence Jones, Thudichum, and Bird, all practicing physicians, began to establish some of the principles of clinical chemistry in England in the early years of the nineteenth century, but their work did not receive the recognition it deserved. Their aim was not to cause a revolution in medical practice but to integrate some of the newer chemical techniques with the older methods of traditional medicine. In his Lettsomian lectures at the Royal Society of Medicine in 1851 Rees insisted that chemical and microscopic observations should be used together with traditional clinical methods (77). In showing that in diseases components of the blood were often found in the urine, he also discovered that the concentrations of such substances were usually greater in the early stages of disease. Thus, the chemist could alert the physician to the onset of disease by revealing otherwise invisible chemical changes, giving the physician a better chance to make an early diagnosis. This gradually encouraged physicians to pay more attention to clinical chemistry, although resistance to the introduction of scientific methods in general and chemistry in particular persisted, and progress towards converting medicine into a science-based discipline remained slow in Britain throughout the nineteenth century.

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