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Thudichum and the Medical Chemistry of the 1860s to 1880s

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JOHANN LUDWIG WILHELM THUDICHUM (1828–1901) has been claimed as the father of neurochemistry; in this sphere I see him as a notable successor to many previous workers (McIlwain, 1958), and here I wish first to indicate his position in the medical chemistry of the mid-nineteenth century.

Sudhoff (1932; Table I) describes how, when Thudichum was about 18 years old, his

TABLE I.—J. L. W. THUDICHUM 1828–1901: SYNOPSIS OF CAREER AND PUBLICATIONS

1847	Meets Liebig; enters the University of Giessen.
1851	M.D.Giessen. Thesis: "Fractures of the upper end of the humerus".
1854	M.R.C.S.London.
1856	Physician, St. Pancras Dispensary.
1858–63	Lecturer in Chemistry, Grosvenor Place School of Medicine.
1858	A Treatise on the Pathology of the Urine (Churchill, London: 2nd edit., 1877).
1863	A Treatise on Gall-stones (Churchill, London).
1865	Lecturer in Pathological Chemistry, St. Thomas' Hospital.
1866–82	Research for the Medical Officer to the Privy Council and later to the Local Government Board, appearing in the Public Health Reports.
1872	A Manual of Chemical Physiology including its points of contact with pathology (Longmans, Green, Reader & Dyer, London).
1872	A Treatise on the Origin, Nature and Varieties of Wine (with A. Dupré. Macmillan, London).
1879–81	*Annals of Chemical Medicine, including the application of chemistry to physiology, pathology, therapeutics, pharmacy toxicology and hygiene* (Longmans, Green, London).
1884	A Treatise on the Chemical Constitution of the Brain (Baillière, Tindall & Cox, London).
1886	Anatomischen und Klinischen Chemie (Berlin).
1894	A Treatise on Wines. Their Origin, Nature and Varieties, with Practical Directions for Viticulture and Vinification (Bell, London).
1895	The Spirit of Cookery (Baillière, Tindall & Cox, London).
1901	Die chemische Konstitution des Gehirns des Menschen und der Tiere (Pietzcker, Tübingen).

father consulted Justus Liebig about the analysis of mineral waters from a newly discovered spring. The son Ludwig met the great chemist and was oriented towards chemistry before he entered the University of Giessen as a medical student. Here he obtained his doctorate in 1851 with a thesis on an anatomical subject; but even before this he had worked with Liebig in the inspiring environment of his busy and pioneering laboratory; he regarded himself throughout his life as Liebig's pupil. His position in Giessen (in Hesse) was, however, made difficult because a few years earlier during war with Denmark he had served voluntarily in a medical capacity in the army of Schleswig-Holstein. In this situation he left for London where a family he already knew well had recently established themselves: in particular Augustus Dupré who had become Lecturer in Chemistry at Westminster Hospital Medical School, and his sister Charlotte who married Thudichum soon after he arrived in London. Thudichum also promptly obtained his M.R.C.S.; then an appointment as physician, and he was in medical practice throughout his life, especially as an otologist and rhinologist. He contributed papers in this specialty, and devised a "Thudichum nasal speculum" but these activities form a small part only of his scientific output.

Thudichum's chemical interests first found official expression in England in 1858 through his appointment as lecturer in Chemistry at the Grosvenor Place School of Medicine. Later he was lecturer in pathological chemistry at St. Thomas's Hospital, and director there of the newly founded pathological and chemical laboratory (Obituary, 1901). He was thus concerned just a hundred years ago, with teaching to medical students the rapidly expanding subject of medical chemistry. In 1858 he published his first book, on the analysis of urine.

Teaching and writing in medical chemistry underwent a considerable change in the second quarter of the nineteenth century: during, that is, the period between Thudichum's birth and his beginning as a lecturer. At the beginning of the 1800s, chemistry was being taught to students of medicine in some if not all the medical schools in Britain, but taught in much

the same fashion as chemistry would be taught to students in science. Paris's (1825) "Medical Chemistry" is an example. Though addressed very specifically to students of medicine, the book has throughout an entirely chemical framework and a large part concerns purely inorganic chemistry. Much of the material taught was in fact that of our present school chemistry (and physics) which of course is still taught with a purely chemical logic, as a means of introducing chemical principles and discovery, whether or not the students concerned are later to be trained in medicine or another subject.

It can thus be seen that the type of medical chemistry on which Thudichum began to publish in 1858 was a relatively new subject: representing a stage in the formation of what became the typical physiological chemistry as it was taught in medical schools in the decades around 1900. I would like therefore to look more closely at the environment in which this first book appeared.

Firstly, Thudichum's was one of several books on the same general subject published in the middle of the last century. In the decade 1854–1865, the Surgeon-General's Catalogues and other sources indicate the books of Table II, concerning analysis of urine, to have appeared together with about an equal number of publications in thesis or analogous form.

TABLE II.—THUDICHUM'S FIRST BOOK WITH COGNATE PUBLICATIONS

Neubauer, C. (1854) Anleitung zur qualitativen und quantitativen Analyse des Harns. Wiesbaden.

Hellerman, J. F. (1855) Pathological Chemistry of the Urine. Trans. L. Dahl. Dublin.

Beale, L. S. (1856) Tables for the chemical and microscopical examination of urine in health and disease. London.

Thudichum, J. L. W. (1858) A Treatise on the Pathology of the Urine, including a complete guide to its analysis. London.

Parkes, E. A. (1860) The composition of the Urine in health and disease and under the action of remedies. London.

Beale, L. S. (1861) On Urine, Urinary deposits and calculi, their microscopic and chemical examination. London.

Hassall, A. H. (1863) The Urine in health and disease, being an exposition of the composition of the urine and of the pathology and treatment of urinary and renal disorders. London (1st Edition, 1859).

Neubauer, C. and Vogel, J. (1863) A Guide to the qualitative and quantitative Analysis of the Urine, designed especially for the use of medical men. Transl. Markham, New Sydenham Society, London.

All these were practical handbooks dealing with this relatively narrow subject, and before and after this especially prolific decade such publications were less frequent. Thudichum's deals with urinary constituents and does not, for instance, begin with a general statement of kidney function or the role of the urine or its relationship to the blood. Although these subjects are touched on in dealing with individual constituents, they form a very small and disconnected part of the whole, as also do the book's pathological aspects.

Now both before and since the 1850s, many more general books on physiological chemistry appeared. An example, very relevant to Thudichum in London, was the "Practical Handbook of Medical Chemistry" of J. E. Bowman of King's College, London, which went through three editions between 1850 and 1855; designed as a "small manual giving instruction for the examination and analysis of urine, blood, and a few other of the more important animal products, healthy and morbid; and comprising also, directions for the detection of poisons in inorganic mixtures and in the tissues". Nearly half of this book deals with urine, but from a practical point of view it is very different from its successors of Table II. The methods both for urine and blood in Bowman's book are very cumbersome, depending largely on actually separating and weighing constituents, including urea. An analysis begins with 10 or 12 oz. of blood.

By contrast, the manuals of what we may call the new analytical specialists of Table II were excellently businesslike. Several volumetric methods are described, which are much more speedy than gravimetric ones. Thudichum with the other authors was, in effect, presenting some fifty years' research by many investigators on the application of analytical methods to bodily materials, with the object of aiding diagnosis and treatment. To appreciate this, it may be noted, firstly, that Fourcroy at the end of the eighteenth century began the section on the animal kingdom in his "Elements of Natural History and Chemistry" (1790) by saying how the analysis of animal substances in general was in a much more imperfect state than other branches of the science. With respect to urine, he writes "The state of the stomach, and particular humours . . . cause infinite diversity of changes in this fluid, to ascertain and estimate which, a long series of experiments would be requisite, which have, as yet, only been pointed out as necessary."

Secondly, if we look at the achievements of the years before the publications of Table II, we find they had been unusually prolific, and feature many subjects and names still familiar in physiological chemistry. Thus, though the volume and sweetness of the urine had long

been prominent in diabetes mellitus, Trommer first developed a chemical test for the sugar, depending on oxidation by alkaline copper salts, in 1841; Fehling's quantitative method came only in 1850. The peculiar smell of the breath in this condition was definitely ascribed to acetone, and a test for this in urine devised by Petters in 1857. Albumin was noted as an abnormal constituent of urine in 1812, and the biuret test for urinary albumin described in 1833; Millon's reaction for proteins dates from 1849. In 1848 Bence-Jones reported the urinary proteins associated with a particular softening of the bones. Pettenkofer's test for bile-salts in urine came in 1844.

Chemical analysis was thus making real contributions to the understanding and diagnosis of disease and this new, applied medical chemistry largely concerned the urine. The nature of the urine makes it understandable that it, rather than other body fluids or tissues, should first have received the large attention indicated by Table II. It contains relatively little of the proteins, mucilages and formed elements which make blood, milk or flesh more difficult to examine. Simple substances such as urea and inorganic salts form a large part of its solid matter. Apart from the examination of the urine to aid the diagnosis or treatment of disease, two other stimuli to its study can be recognized in the first half of the 1800s, perhaps especially in Thudichum's work. First, the examination represented part of the growing organic chemistry of the times: a wide variety of materials associated with living organisms were being ransacked for their chemical constituents, which were being analysed and the analyses collated to yield chemical patterns. These had not in Thudichum's book of 1858 become the structural or even empirical formulæ of to-day: the subject was in his time still in course of development. Secondly, the analyses of foodstuffs, tissues and excreta were giving real enlightenment in physiology and here Liebig, with the new concept of metabolism expressed chemically, was a pioneer.

The books of Table II, which reflect this first major application of chemical analysis in medicine, appear from this distance to represent the type of technical elaboration through which a new specialty frequently passes before taking its place as a valuable but limited tool, available with the minimum of trouble to those who are to apply it to practical problems. Of all the books, Thudichum's probably represents the greatest chemical elaboration. Its organisation is purely chemical, with some 50 chapters, mostly of a few pages and dealing with an individual urinary constituent or group of constituents. These chapters are usually excellent, brief, well-documented monographs on the constituents concerned, giving, for instance, their chemical nature, discovery, chemical and physical properties, isolation or determination. But often less than half of the account deals with the substance as it occurs in urine. Thus there are described the crystallography of sodium chloride, the solubility of creatine, the chemical synthesis of urea: information for which one would now consult texts on inorganic chemistry, physics, or organic chemistry. On the other hand, it is to be emphasized that knowing as much as possible about the chemistry of all urinary constituents did give the basis for the discovery of new constituents and for the development of new analytical methods. Thus Thudichum's book might have been a manual for those who were hoping to make new chemical discovery regarding the urine in pathological conditions, though actual achievement in this respect formed only a small part of it.

Thudichum's next major work concerned a second subject which was typical of the growing chemical pathology of the time: "A Treatise on Gall Stones: their Chemistry, Pathology and Treatment" (1863). It has fewer compeers than his book on urine; in his Introduction Thudichum states his aim of giving an account of the chemistry of gall stones comparable to Morgagni's description of their physical nature. The book displays Thudichum not only as a chemist, but also as a microscopist, for he found casts of bile ducts in the centre of the stones; and as a theorist, for he writes fifty pages on previous chemical work, and in a final section nearly as long he debates both chemical and physical factors in the formation of the stones. Here he emphasizes the presence of the bile acids as binding materials and concludes the stones to be formed "by a decomposition of the bile akin to putrefaction". But this is too early a date to expect adequate experiments in such matters; Thudichum's experiments on the changes occurring on standing bile for some years are not impressive. More noteworthy are his isolation of bile pigments from the stones, and his contribution to their chemical classification. Also, two similarities between the investigation of urine and gall stones are worth bearing in mind in relation to Thudichum's subsequent work. First, presumably in his search for chemically tractable materials, Thudichum has chosen to study a very limited part of the body. Second, he is working within a limited range of chemical study, being primarily concerned with the isolation and analysis of chemical substances.

Thudichum's Practical Work and Work on the Brain

Thudichum's book on the urine, and also his later "Manual of Chemical Physiology" (1872) are eminently practical books: they give excellent manipulative instructions and much quantitative data needed by a laboratory worker. I would now like to indicate the circum-

stances in which the greater part of Thudichum's laboratory work was carried out, for they were unusual in his day and would also be so in ours. Thudichum had received his training under Liebig who from the 1830s was a pioneer in teaching by laboratory investigations, and as such attracted workers from all over Europe and beyond. It is understandable that the facilities which Thudichum first obtained with his hospital or medical school appointment fell far below this standard, though in his second appointment, at St. Thomas's, he was director of a new pathological and chemical laboratory and some work published in 1869 is described as being performed there. The bulk of his work, however, both before and after that time, was carried out in a laboratory which he had established in his private house. More remarkable, Thudichum was given support or expenses from Government sources. This took place through his carrying out investigations for the Medical Officer to the Privy Council initially into the chemical pathology of infectious diseases. Such payment for work done was perhaps not fundamentally different from payments to medical consultants or to consultant analysts. With Thudichum, however, the arrangement was unusual in being primarily for research, in what became quite a broad and abstruse subject, and which lasted for some years. The Medical Officer concerned, whose attention had been attracted by Thudichum's work and who charged him with these investigations (Obituary, 1901; Sudhoff, 1932) was the notable Sir John Simon. Simon was initially responsible to the Privy Council and so in a relationship similar to that of the Medical Research Council established some forty or fifty years later. In the latter part of Thudichum's work Sir John Simon was responsible to the Local Government Board.

At first Thudichum carried out analyses on material on which Simon made other pathological studies but shortly Thudichum's work appears to have become entirely independent. Quite early he had qualified assistants. Throughout, his work appeared in the Annual Report of the Medical Officer, introduced by Simon but often carrying long technical supplements by Thudichum in which he gave theoretical and practical details of his work. Thudichum more than anyone else appears to have availed himself for sixteen years of this opportunity to make the Reports a medium for publishing in what we would now regard as the basic medical sciences. Moreover the Reports at least in one quarter almost became known as a periodical in biological chemistry: Chittenden (1930) in his history of physiological chemistry in the United States describes them as eagerly awaited there. On the other hand, this mode of publication probably contributed to some of Thudichum's work being overlooked. Much of it, however, was published a second time either in ordinary journals or, after a lapse of some years, in book form.

Thudichum's studies for the Medical Officer were clearly planned as a fundamental attack on a major medical problem of the time. He begins his first report: "The object of these researches, proposed to me on the 7th August 1866 by the Medical Officer of the Privy Council were as follows: 'By investigation of choleraic discharges, and of the diseased body after death, and by such auxiliary observations of the sick as may be needful, to ascertain *what successive chemical changes are undergone by the body in the progress of cholera, and what relation subsists between those changes and the symptoms presented by the patient during life*'." Thudichum's previous work clearly fitted him for such studies, and his report on this occasion covers some 50 pages, giving examinations of urine, blood, bile, stools, muscle and liver from many cases; describing new methods in detail including the use of the spectroscope in which Thudichum did pioneer work.[1]

In 1868 and in subsequent years the direct study of cholera has less prominence and Thudichum's section in the Reports is headed *Researches intended to promote an improved chemical identification of diseases.* Thudichum in 1868 argues this subject in general terms, not confining himself to his own researches but writing rather in textbook or monograph style, concluding, for example, that "Ultimate pathology cannot, I think, be cellular, as was claimed by Virchow". He notes that not enough is known of the constituents of bodily organs to make likely the detection of chemical change in pathological conditions. Here he instances the relatively well-investigated extract of muscle (Thudichum had written on Liebig's meat extract), pointing out that in spite of much investigation some five-sixths of its constituent material was still unidentified. This is the light in which we are to see Thudichum's detailed chemical studies: and very detailed they were. For example, he

[1]An interesting sidelight on Thudichum's spectral analysis is described by Duncum (1947). During the 1860s Thudichum demonstrated its abilities to the Medical Society of London and used cylinders of compressed oxygen and hydrogen for his source of light. This was observed by Charles James Fox, who was seeking a way to make nitrous oxide manageable for anæsthesia. Fox persuaded the firm of Coxeter to compress nitrous oxide for anæsthetic use and from 1870 was using it widely in the Dental Hospital, London. At this point we have a reminder of Thudichum as a patriot and humanitarian, for during the Franco-Prussian War he is described as making an urgent newspaper appeal for the supply of nitrous oxide for military surgery. Over £180 was subscribed to a Nitrous Oxide Fund and Coxeter supplied over 5,000 gallons of the gas for this purpose, Thudichum going to the theatre of war to see it applied.

examined urinary pigments, and the pigments of bile and gall stones; reported on "a new series of yellow compounds contained in animals and plants" which Rosenheim (1930) later took as pioneering work in carotenoids. He studied proteins and amino acids, characterizing a new amino acid "glycoleucine", or norleucine.

Moreover, it was in this spirit and background that Thudichum carried out his major original work which was on chemical constituents of the brain. His first large report of his own investigations in this subject came in 1874 and his book, "The Chemical Constitution of the Brain," in 1884. It is clear from both these sources and also from John Simon's own Reports, that Thudichum was carrying out very extensive and purely chemical studies of the normal composition of the brain, usually of ox brain, in order to understand and control the deliria and coma of cholera, typhoid, and other infections. To appraise this we must recall the late 1860s when Thudichum's work on cholera began. Fevers with their prominent, distressing, mental symptoms, were the major medical problem of the day. Bacteriology had not begun. Microscopic observations of the brain were still rudimentary. Presumably it seemed reasonable to others as well as to Thudichum, that chemistry which could demonstrate abnormal glucose or urea in a normal-looking urine, might also help to specify the material basis for disorder in a normal-looking brain. At any rate one can imagine it worth trying. Thudichum, however, had a rather more rigid view and even in 1884 appears to be making little attempt to consider what was the most profitable line of attack. For he was primarily a chemist and had found great chemical complexity in the brain. As he wrote after his twelve years of investigations, "unforeseen complications arose". His list of chemical substances isolated from the brain, and either partly or completely characterized, runs to some 140 (Thudichum, 1901). I have appraised elsewhere something of the great enterprise and some shortcomings of this work (McIlwain, 1955, 1958; Page, 1937). Thudichum's purifications and analyses were very painstaking, and were carried out at a time when about a gram of material was required for adequate characterization and analysis. Much of this work, therefore, may never again be done in the same way or on the same scale; and we are fortunate that some of Thudichum's specimens have been preserved. In 1930 Dr. Rosenheim of the National Institute for Medical Research visited two daughters of Thudichum and was given laboratory records, other writings of Thudichum, and also a large collection of his chemical specimens. These were exhibited to the Biochemical Society in 1930 and are now at the National Institute, Mill Hill.

In the present setting we may note that Thudichum, although knowing how much more difficult would be his new task than that of the chemical understanding of urine or gall stones, nevertheless tackled it energetically. I wish to emphasize that Thudichum still, in 1884, wrote "When the normal composition of the brain shall be known to the uttermost item, then pathology can begin its search for abnormal compounds or derangements of quantities. . . . The knowledge of the composition and the properties of neuroplasm and of its constituents will also aid us in devising modes of medical treatment. . ." Here he was doing little more than restating his programme of twelve years ago, perhaps in the hope that others would continue his work. For he was then 56 years of age, still active in medical practice, with a family of six children and with many other interests. In the report dated December 1883, George Buchanan as Medical Officer wrote "Dr. Thudichum has now completed those profound researches into the chemistry of the brain, on which he has been so long engaged for the Board. . . His researches have shown, he says, the brain to be the most diversified chemical laboratory of the animal body; all other organs being much more simple and very much less specific in their chemical constitution than the organs producing and conducting nerve power". This conveys the enthusiasm of a specialist, with a turn of phrase about nerve power which betrays ignorance of a quarter century of physiological study of the nervous system. The phrase is Thudichum's; it appears in his book of 1884.

Chemistry in Physiology and Medicine

In 1872 appeared his "Manual of Chemical Physiology including its points of contact with Pathology". Like his book on urine, this is one of a number of books on the same general subject produced by different authors at this time. Thudichum's begins in a familiar fashion with an account of digestion; of the chemical effects of saliva, gastric and pancreatic juices. He naturally has a section on the brain, but the most distinctive part is the relatively large and detailed "analytical guide" giving excellent laboratory descriptions of experiments to display the chemistry of the component tissues and substances of the animal body. Many experiments are of a type which has persisted through the subsequent eighty years, and one may suspect it to be Thudichum's medical school experience which prompted him to write in the book's preface ". . . I think it improbable that ordinary students of medicine will go easily through the whole of its matter in the laboratory. I hope therefore that teachers of chemistry who will make use of the guide will select the reactions and analyses to be performed by each student, according to his knowledge, ability and intentions". Conceivably because of its

good practical guide as well as the date of its publication, this was the first text on physiological chemistry to be used in the United States when, in 1874, the subject began to be taught with laboratory work at Yale (Chittenden, 1930).

Of very different character are the two volumes of Thudichum's *Annals of Chemical Medicine, including the application of chemistry to physiology, pathology, therapeutics, pharmacy, toxicology and hygiene* (1879, 1881). This was intended to be an abstract or review journal in the subjects named. It thus represented a considerable enterprise, and was the nearest approach in English to Maly's *Jahresbericht über die Fortschritte der Thierchemie* which had been published since 1873. In general, Thudichum's like Maly's consisted of annoted summaries of publications from all sources. It also, however, contained much of Thudichum's own work and was nearly all written by himself. Moreover, from time to time it displays Thudichum polemically defending details of his previous work. Thus he felt, probably rightly, that his work had been slighted or distorted by certain authors including Gamgee in this country and Hoppe-Seyler in Germany; here, in the *Annals*, Thudichum forcefully gave his opinions. Less excusably, the *Annals* also occasionally displays really splenetic views of work which Thudichum was not in a good position to judge. One treated so was Kühne on his discovery of the bleaching of visual pigments by light, observations which Thudichum disparaged and mocked (*see* McIlwain, 1958). For Thudichum was a protagonist not of all types of application of chemistry in medicine, but of one particular type: the separation, purification, and analysis of compounds from natural sources.

Thudichum must have realized a growing lack of sympathy with this aspect of his work and outlook. Only two volumes of the *Annals* were published. He had been a Vice-President of the Chemical Society, but at the Physiological Society was involved in polemical discussions. In these one may suspect Thudichum to have been right in chemical detail but narrow in outlook. In spite of his work, incidents such as these and such as his criticism of Kühne were a disservice to the furtherance of chemistry in physiology and medicine. They may contribute to explaining how Thudichum had no immediate successors. He was further isolated in that his medical practice was in a quite different specialty from that in which he did his major research. At least three of four people had collaborated in his work, but he appears to have had little opportunity for establishing a teaching laboratory, or perhaps by choice to have put his energies elsewhere. A wider, university atmosphere might have corrected his dogmatic and polemical tendencies.

In these circumstances it is understandable that Thudichum developed others of his many interests. Since the 1870s he had been concerned with the analysis of wines, making reports to the Pure Wine Association, London. A paper in 1870 has the intriguing title "On wines, origin, nature, analysis and uses; with special reference to a new alcoholic drink made from tea". In the 1890s, his development of this theme is seen by his books on food and wine (Table II). He also continued in medical practice. When in 1901 he published a German version of his book on the chemistry of the brain, there was little to add to his work of twenty years before. In one sense this is a measure of the magnitude of Thudichum's contributions; in this field he had worked assiduously even though he did not supersede the techniques of his predecessors. Here we come to a general point in the development of the sciences. In one sense biochemistry developed from the organic chemistry of the time of Liebig. In another sense it represented a sharp break, a refreshing and inspiring new way of approaching chemical problems in living organisms. There are few better demonstrations of this than the life of Thudichum.

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THUDICHUM, J. L. W. References are included in Table I (*see* p. 127); a complete or almost complete bibliography is at the library, National Institute for Medical Research, London.