

Historical Note

What's in a name? Bence Jones protein

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Introduction

Plasma cell disorders are important in the differential diagnosis of acute kidney injury and of renal impairment with proteinuria. One or more of several mechanisms can be involved, such as cast nephropathy, deposition of monoclonal immunoglobulins, formation of amyloid fibrils, hypercalcaemia, hyperuricaemia and a variety of tubular syndromes. Various tests, such as serum electrophoresis and immunofixation, assays for serum immunoglobulins and free light chains and tests for urinary paraproteins, also known as 'Bence Jones protein', are routinely employed in clinical practice. Scribbling these two words on a laboratory form (or ticking a box on a computer screen) raises questions: what is being tested and who is 'Bence Jones'. Does this eponym honour one physician or two, or perhaps a patient? Here, we provide some insights into the history of this commonly used eponym and aim to put it into context.

The mysterious illness of a wealthy London grocer

The story of this eponym begins with Thomas Alexander McBean, a 38-year-old London grocer, who, while on vacation in Scotland in 1844, suddenly developed pain in his chest after vaulting over an underground cavern. McBean, a man of 'temperate habits and exemplary conduct' described the pain 'as if something had snapped or given way within the chest'[1]. A number of traditional remedies were tried, such as blistering, leeches and cupping. These remedies gave some relief but the pain kept returning. McBean had also noted that 'body linen was stiffened by his urine'.

On Friday, 30 October 1845, persistent pain and emaciation led his general practitioner to refer to Dr William MacIntyre (circa 1791/1792–1857) in 84 Harley Street in the Marylebone area of central London (Figure 1) [2]. Today, this address carries an air of elegance and stands for the best tradition of British consultative medicine, but in the mid-19th century the area was still very much in development. Interestingly, MacIntyre seems to have been equally committed to serving the poor, in that he worked as a physician in the Metropolitan Convalescent Institution and in the Western General Dispensary, St Marylebone [3]. The two charitable institutions had been

established following a rapid increase in the population of the North West area of St Marylebone and the parish of Paddington in the 1830s. The situation of the sick and/or poor has been aptly described in Charles Dickens' *Oliver Twist*, published in 1838. It comes as no surprise that Dickens (whom we will encounter again later on in the story) supported the efforts of others [4], including outspoken reformist Thomas Wakley [5], to improve the healthcare of the poor and the workhouse infirmaries, in particular [6].

MacIntyre noted the severe bone pains and the presence of considerable peripheral oedema. Considering the possibility of nephrosis, MacIntyre tested the urine for albumin. The standard test used to precipitate albumin was to heat urine just below the boiling point and then allowing it to cool down. Addition of nitric acid to the urine also precipitated albumin. On heating the sample of urine to just below the boiling point, he was able to isolate albumin. However, on the addition of nitric acid to the urine sample, no immediate precipitation took place, on the contrary, the previously cloudy or turbid urine became instantly clear and retained its transparency for an hour to hour and a half after which it formed into a firm yellow substance. To his consternation, this yellow substance re-dissolved when heated. William MacIntyre sent a sample of the patient's urine to Henry Bence Jones, MD, chemical pathologist at St George's Hospital in London. Remarkably, and similar to today's frequent duplication of tests and investigations [7], the patient's general practitioner, Dr Thomas Watson, had 'independently' submitted another urine sample to Henry Bence Jones for analysis [8]. His cover letter received by Henry Bence Jones on 1 November 1845 reads as follows:

Dear Dr Jones, [...] the tube contains urine of very high specific gravity. When boiled, it becomes slightly opaque. On addition of nitric acid, it effervesces, assumes a reddish hue, and becomes quite clear, but as it cools, assumes the consistency and appearance which you see. Heat relieves it. What is it? [2]

Henry Bence Jones (1813–1873)

Henry Bence Jones was born in Suffolk on 31 December 1813, the son of Lt Col William Jones, who had served in the Peninsular War [9]. Young Bence Jones was educated

at Harrow and Trinity College, Cambridge and attended lectures in history and geology. He obtained a certificate for ordination, but decided not to join the Church. Instead, he entered St George's Hospital in 1837 to study, initially as an apothecary's apprentice, a time Bence Jones later regarded as of 'utmost use to me all my life' [9].

On 1 October 1838, Bence Jones became a pupil in the medical school at St George's Hospital, which had been established only 4 years earlier. It is tempting to think that it was the air of novelty and innovation that attracted him to this institution. Here, Bence Jones continued his varied interests [9], from attending Faraday's lectures on electricity to learning from Dr James Hope [10] all he could about the use of the recently invented (but still very controversial) stethoscope. Bence Jones also developed a keen interest in chemistry and decided to study this subject under Prof. Thomas Graham at the University College of London. Mr George Fownes, Prof. Graham's assistant, became a close friend and associate.



Fig. 1. Façade of 84 Harley Street, London, today (image in the public domain). The property still houses private clinics and consulting rooms.

During this period, Bence Jones came to analysing cystine oxide stones, resulting in his first medical paper [11]. Bence Jones also learnt about Justus Liebig and his pioneering work in Giessen, Germany. He left London on Easter Sunday 1841 for Giessen. There, Bence Jones studied in Liebig's laboratory (Figure 2) for 6 months. He was clearly an admirer of Liebig's ideas, stating:

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 [12]

Ironically, Liebig himself had been fundamentally wrong when he proposed a rather simplistic theory of 'animal chemistry', whereby digestion and assimilation converted food into muscle and other tissues and that during physical exertion these were degraded and oxidised in the lungs to produce energy [12]. While this school of thought was still deeply rooted in vitalism, it nonetheless paved the way for a period of experimental study that eventually led to the rational, experimental approach we know today [13]. Liebig, who was appointed Prof. in Giessen at the incredible age of 21, made numerous pioneering discoveries, from the invention of the bouillon cube and yeast extract to agriculture. Again, it is tempting to speculate that it was this hotbed of novelty and discovery that attracted Bence Jones. From Liebig, Bence Jones learned advanced analytical methods and analysed proteins, which led to another paper, this time in Liebig's 'Annalen'.

On his return from Giessen, Bence Jones took a post at St George's hospital. He also married his second cousin, Lady Millicent, daughter of the Earl of Gosford in May 1842. He began his work on analysing renal calculi in the Museum of University College Hospital and published a second paper on this topic. Not long after, in the autumn of 1843, Fownes arranged for Bence Jones to be appointed as a lecturer in Medicinal Chemistry at Middlesex Hospital. In his new post, Bence Jones continued his systematic study of the composition of urine in health and



Fig. 2. Laboratory in Giessen. Bildarchiv Preussischer Kulturbesitz, bpk-Bildagentur für Kunst, Kultur und Geschichte, Berlin, Germany, with permission.

disease. In December 1845, aged 32, he was appointed as an assistant physician and lecturer at St George’s hospital. It was in this role that he received McBean’s urine sample.

that it was different from albumin; however, from its chemical composition, he presumed it to be a ‘deutoxide of albumin’ and suggested that this substance may be represented by $C_{48}, H_{38}, N_6, O_{18}$ or by $C_{40}, H_{31}, N_5, O_{15}$.

More urine tests

Bence Jones first confirmed the observations of MacIntyre [14, 15] who had noted the ability of the heat-precipitated protein to re-dissolve upon continued heating of the urine. After a series of further experiments, Bence Jones found that this specimen of urine was slightly acidic and that the urine sediment consisted of crystalline phosphate of lime and oxalate of lime [15] (at the time these terms were used for calcium phosphate and oxalate, respectively). From further experiments, Bence Jones deduced its physical properties and determined

Autopsy findings, Bright’s disease and publications

Thomas Alexander McBean passed away on New Year’s Day in 1846, leaving his wife Margaret and 11 children behind. His death followed after a prolonged period of suffering and numerous treatment options being pursued (Table 1). There was a keen interest in the post-mortem findings. MacIntyre recalls:

The post-mortem examination was made, thirty-six hours after death, by Mr. Shaw, in the presence of Dr Watson, Dr Bence Jones, Dr Ridge, and myself. [1]

At autopsy, soft and brittle ribs were noted to the extent that ‘the osseous ribs crumbled under the heel of the scalpel’ [1]. Despite these remarkable findings, the death certificate denotes, perhaps for want of a better diagnosis, ‘Atrophy from Albuminuria, certified’ [8] (Figure 3). A correlation between oedema, albuminuria and diseased kidneys at autopsy had been found by Dr Richard Bright, Guys Hospital London in 1827 [16] and MacIntyre et al. were clearly aware of Bright’s work. However, on reflection MacIntyre himself was quick to refute a diagnosis of Bright’s disease on the account that

Atrocious pains [...] constitute no part of Bright’s disease[1]

MacIntyre also acknowledged remarkable similarity to the case of 39-year-old Sarah Newbury, which Samuel Solly, Surgeon at St Thomas’ Hospital, had reported in 1844 [17]. The histological examination was made by John Dalrymple (1803–1852) [18] who was first to publish the histological findings [19]. MacIntyre had noted many important features of the disease and also

Table 1. Treatments used in the case of Mr McBean [1]

Strengthening plaster to the chest	Pain relief
Leeches	Derived from humoral medicine, to release toxins
Steel (iron citrate) and quinine	Used as a tonic, often in wine
Dover’s powder (ipecacuana with opium), with or without aromatic cretaceous mixture or with guaiac	Traditional remedy for cold and fever, also to induce sweating
Acetate of ammonia	Sedative
Camphor julap	Antiemetic
Camphor tincture (presumably of opium)	Analgesic, with anti-diarrhoeal properties
Cupping, vesicatories and counter-irritants, blisters, incl. those over the kidney	Derived from humoral medicine, to release toxins
Rhubarb and Soda	To treat constipation, induce flatulence
Alum (potassium aluminium sulphate)	‘with the view of checking the exhausting excretion of animal matter’ (Bence Jones)
Crude opium and preparations of morphia	Analgesic
Alcoholic tincture of aconite	Sedative, with analgesic properties

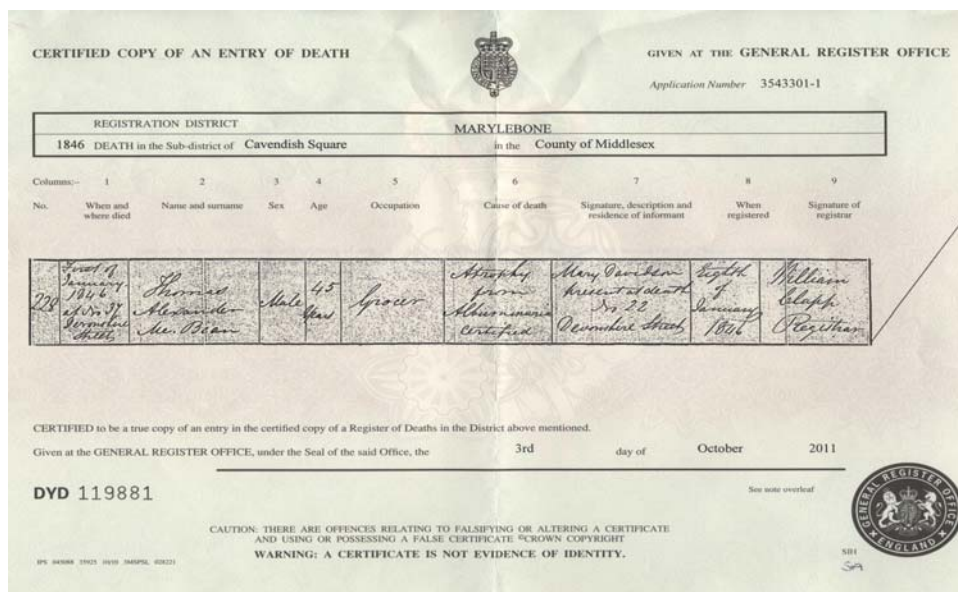


Fig. 3. Death certificate of Thomas Alexander McBean stating ‘Atrophy from Albuminuria’ as a cause of death (Crown copyright, with permission).

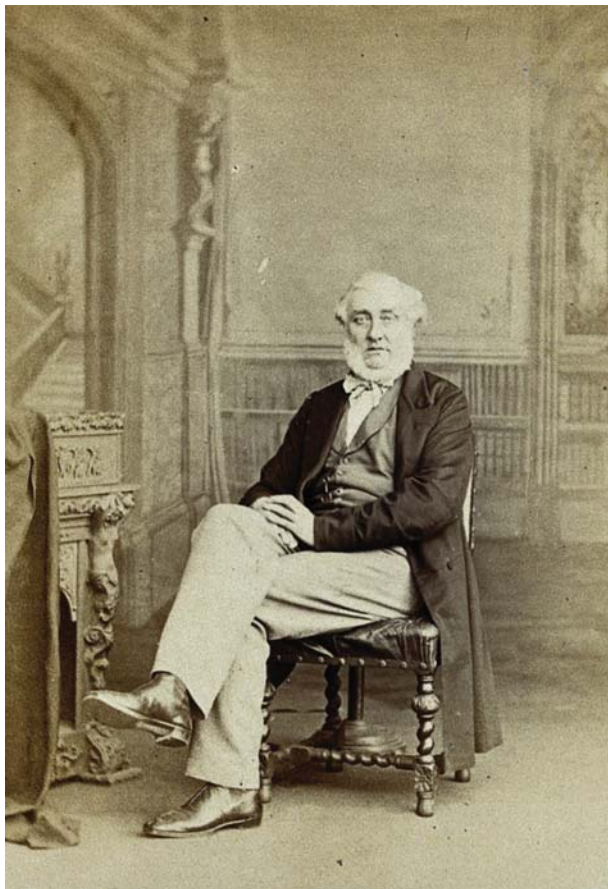


Fig. 4. Photograph of Henry Bence Jones (photograph by Ernest Edwards, 1868, courtesy of Wellcome Library). Reprinted with permission.

published the case although it took him until 1850 to do so [1]. Remarkably, by that time, Bence Jones had already published two articles on the urinary findings and what he regarded as an oxide of albumin [14, 15]. In his 1847 paper, he concluded

I need hardly remark on the importance of seeking for this oxide of albumen [sic] in other cases of mollities ossium. [15]

Further career and the birth of the ‘chemical doctor’

In 1846, aged 33, Bence Jones was elected as a Fellow of the Royal Society. Bence Jones was also invited to deliver the prestigious Goulstonian Lectures at the Royal College of Physicians of London in 1845, and he used this platform to formulate his ideas regarding ‘chemical pathology’. He also lectured on a broad variety of topics, ranging from ‘animal chemistry’ to alcohol, sugar and acid content in wines and ventilation. Some of his lectures were published in a monograph entitled ‘Of Animal Chemistry’. It is probably fair to say that he, together with other pupils of Liebig, was instrumental for the development of clinical chemistry as a specialty [12]. In 1866, when elected as the president of the chemistry section of the British Association for the Advancement of Science, Bence Jones proclaimed:

Whatever sets forth the union of chemistry and medicine tends to promote not only the good of science but also the welfare of mankind [20]

He went on to deliver the hugely prestigious Croonian lecture at the Royal College of Physicians in 1868. Not

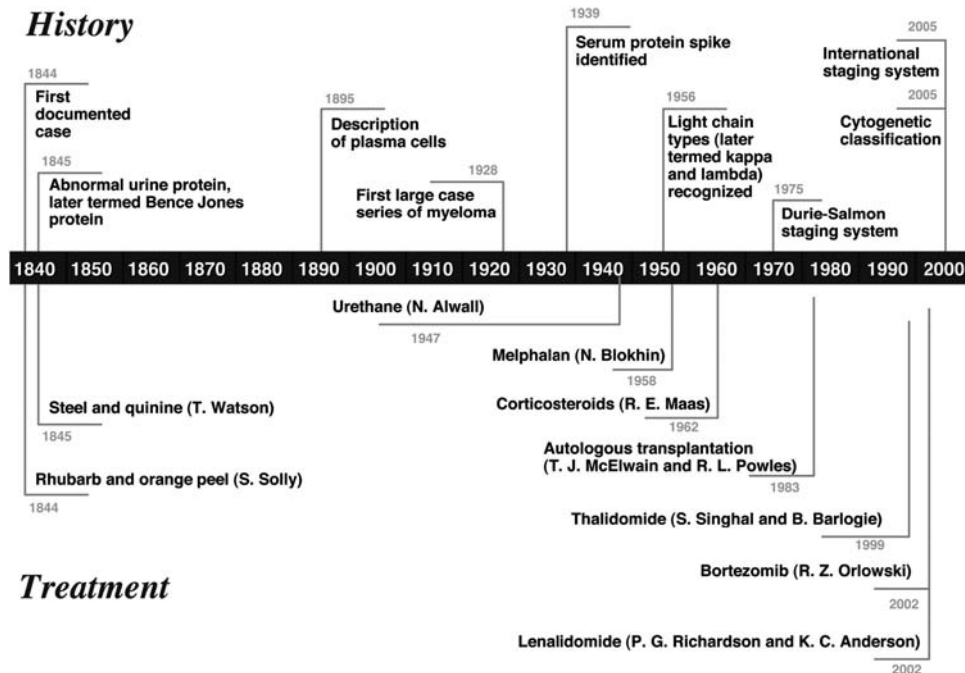


Fig. 5. Time line: the history of multiple myeloma. From [21], with permission.

surprisingly, a photo from this period shows a man at ease and full of self-confidence (Figure 4). He was also well connected within the society and had influential friends. Florence Nightingale, who knew him well, described Bence Jones the best ‘chemical doctor’ in London. His friends (and patients) included, among others, Charles Darwin, Thomas Huxley and Michael Faraday. There is also clear evidence that he was earning good money, as his profits in 1864–65 were estimated as £7400 [9] (an incredible £567 728 in today’s money, based on a comparison of annual income). His influential friends also allowed him to play a crucial role in the development of Great Ormond Hospital for Sick Children [12]. Bence Jones died of cardiac failure on 20 April 1873, aged 60, survived by his wife and five children. He is buried at Kensal Green cemetery in West London in grave 4327/59.

A very brief history of multiple myeloma

The complete history of multiple myeloma is narrated in great detail elsewhere [21] (Figure 5). Dalrymple in his histological findings of McBean described nucleated cells which were present in large numbers in the affected bones on post-mortem but it took another 30 years or so until Waldayer coined the term ‘plasma cell’ [21, 22]. Von Rustizky in Kiev 1876 first employed the term myeloma in describing the condition [23]. The term ‘Bence Jones protein’ was actually first used by Fleischer in Erlangen in Germany in 1880 [24].

The diagnosis of myeloma was greatly facilitated by the introduction of bone marrow aspiration by Russian M. I. Arinkin in 1929 [25]. The extra gradient in the serum electrophoresis was first described in 1939 [26]. In the 1950s, Leonard Korngold and his assistant Rose Lipari in New York identified different classes of Bence Jones proteins [27] designated, in their honour, as kappa and lambda. In 1961, Waldenström developed the concept of clonality [28], thus allowing us to arrive at today’s definition of Bence Jones protein as a monoclonal globulin protein found in the blood or urine. One year later Edelman and Gally showed that light chains and Bence Jones protein from the same patient had identical properties [29].

Treatment was first attempted by dialysis pioneer Nils Alwall in Lund in 1947 [30]. He used ethyl carbamate, an alkylating agent, later shown to be ineffective [31]. By that time, Blokhin et al. had reported success with melphalan [32]. Corticosteroids and alkylating agents came together in a regime devised by Alexanian in Houston in 1969 [33]. Stem cell transplantation was first performed in the 1980s, first in identical twins [34], and then by Barlogie et al. as allogeneic transplantation [35]. It was again Barlogie’s group who rediscovered, in 1999, thalidomide and its use in myeloma [36]. In 2002, Orlowski et al. first reported remarkable success with a new bortezomib [37], the same year in which first results were reported for lenalidomide [38].

Conclusion

A minute of reflection while ticking boxes on laboratory forms lead to an interesting detour into the history of medicine. Another remarkable facet of the case is that we can only speculate what prevented the three

physicians involved in Mr McBean’s care from publishing their case together, in one multi-authored paper (although they do mention each other in their acknowledgements) [39]. Perhaps the fact that Watson and MacIntyre ‘independently’ submitted urine samples to Bence Jones gives it away. We also gleaned interesting insights into society and health care in 1840s Dickensian London [6] and learned something about Thomas Wakley, the founding editor of ‘Lancet’ [5]. Every time we now write the ‘Urine for Bence Jones protein’ on a laboratory form, we will now be reminded of the story of the sick London grocer and of the early history of clinical chemistry as a specialty.

Conflict of interest statement. None declared.

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