History of Multiple Myeloma

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Abstract Multiple Myeloma has been recognized since Ancient Times. The first well-documented case was reported in 1844 by Samuel Solly. The most commonly recognized case is that of Thomas Alexander McBean, a highly respectable tradesman from London in 1850. Mr. McBean excreted a large amount of protein that was described by Henry Bence Jones in the middle of the 19th century. Jones was a well-known physician and made many contributions to medicine. One of the best known cases of multiple myeloma was that of Dr. Loos that was reported by Otto Kahler. The recognition of plasma cells and subsequently their product, a monoclonal protein has been described in detail. The authors have reviewed the treatment of multiple myeloma including the novel agents, thalidomide, bortezomib and lenalidomide.

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1.1 Ancient Origins

Although the first well-documented cases of multiple myeloma were described in the 1840s, the disease has undoubtedly existed for centuries and perhaps even for eons. Spheroid skeletal lesions that are "purely lytic," with sharply demarcated borders and without evidence of sclerosis or formation of new bone, are suggestive of multiple myeloma — especially when such lesions are multiple and occur in the axial skeleton and proximal long bones (Rothschild et al. 1998). Two human skeletons with this bony lesion pattern — both males, with estimated ages at death of between 40 and 60 years — were identified from among 905 individuals in necropoles excavated at Thebes-West and Abydos in Upper Egypt, dating from 3200 BC to 500 BC (Zink et al. 1999), while two similarly affected skeletons were found among 2,547 individuals entombed in a rural South German ossuary between AD 1400 and AD 1800 (Nerlich et al. 2006).

Additional possible multiple myeloma cases identified by paleopathologists include the skeleton of a middle-aged female from AD 1000 to AD 1400 recently discovered in Iceland (Gestsdottir and Eyjolfsson 2005), two calvaria from medieval Britain (Wells 1964), four American Indian skeletons from AD 200 to AD 1300 (Morse et al. 1974), and 14 pre-Columbian American skeletons dating back to 3300 BC (Steinbock 1976). Recently, the Wellcome Collection in London featured an exhibit on skeletons; the museum curators highlighted myeloma-like lesions in the bones of a 45-year-old Roman soldier. The remains of George Grenville (1712–1770), the Whig Prime Minister whose administration passed the notorious Stamp Act of 1765 that first alienated American colonists from Great Britain, reveal lytic lesions resembling those of multiple myeloma.

Multiple myeloma with Bence Jones proteinuria (see below) occurs spontaneously in contemporary animals (Hanna 2005), raising questions about whether myelomatous lesions might be reliably identified in prehistoric non-human fossils. Paleontologists have detected multiple lytic defects without evidence of bony remodeling in a few dinosaur skeletons from the Jurassic and Cretaceous periods, and these have been interpreted as evidence of an origin of multiple myeloma in the Mesozoic era or earlier, but caution is indicated in interpretation of such ancient specimens (Capasso 2005).

1.1.1 Early Well-Documented Cases

The first well-documented case of multiple myeloma was the second patient in a series of cases of "mollities ossium" (i.e., pathological bony softness and fragility) published in 1844 by Samuel Solly (1805–1871), a distinguished London surgeon (Solly 1844). The patient's name was Sarah Newbury, a 39-year-old housewife, who developed fatigue and severe back pain while stooping 4 years before her death. Two years later, pain in Mrs. Newbury's limbs increased, making movement difficult, and she was eventually confined to her room. On one occasion, she developed fractures of her femurs when her husband lifted her and carried her to the bed. This event was followed by fractures of the clavicles, right humerus, and right radius and ulna (Fig. 1.1).

On April 15, 1844, Mrs. Newbury was hospitalized at St. Thomas' Hospital in Southwark, London, where Dr. Solly was a lecturer on anatomy. Treatment consisted of an infusion of orange peel and a rhubarb pill, as well as opiates at night. She also received wine and arrowroot, a mutton chop, and a pint of porter daily. Arrowroot was an easily digestible starch from the roots of tubers imported from the West Indies to England in the eighteenth century (Stephens 1994). It was considered to be bland, and

Fig. 1.1 Sarah Newbury. Fractures of femurs and right humerus

appropriate for persons who had difficulty with their digestion and were in poor condition (Felter and Lloyd 1898–1900). Porter, a dark, bitter ale made from black malted barley, was a popular drink among London working classes (especially porters and draymen) during the early eighteenth century, a time when clean, safe drinking water was difficult to obtain. Orange-based preparations, such as *infusum aurantii* made from oranges or orange peels, were often used to change the flavor of a medication. Rhubarb is a traditional gastrointestinal cathartic employed to treat dyspepsia and constipation, while opium compounds have been used since ancient times to produce pain relief.

Despite these ministrations, Mrs. Newbury died suddenly on April 20, 1844. At autopsy, Dr. Solly found that the cancellous portion of her sternum had been replaced by a peculiar red matter. The bone marrow cells were examined by Dr. Solly and a Mr. Burkett, who described the cells as "very clear, their edge being remarkably distinct and the clear oval outline enclosed one bright central nucleolus, rarely two, never more." Solly thought that the disease was an inflammatory process, and that it began with a "morbid action" of the blood vessels in which the "earthy matter of the bone is absorbed and thrown out by the kidneys in the urine" — remarkably prescient. Little did he know that, 150 years later, antiangiogenesis drugs such as thalidomide would be used for the treatment of multiple myeloma (Kyle 2000). Was Solly perhaps contemplating the role of angiogenesis in the pathophysiology of Mrs. Newbury's disease?

The best-known early case of multiple myeloma is that of Thomas Alexander McBean, "a highly respectable tradesman" in London, who was 45 years of age when he became ill. The patient developed fatigue and noted that his "body linen was stiffened by his urine." While on holiday in September 1844, he vaulted out of an underground cavern and suddenly "felt as if something had snapped or given way within the chest" and, for some minutes, he lay unable to move because of severe pain. A "strengthening plaster" was applied to the chest and the pain was temporarily relieved, but symptoms recurred 3 to 4 weeks later. Subsequently, "a pound of blood" (a pint — approximately one unit of red cells) was removed, and leeches were applied for "maintenance therapy."

Mr. McBean's bony pain eventually resolved, but he had considerable weakness for 2 to 3 months after this initial event. In the spring of 1845, his chest pain recurred; cupping and therapeutic phlebotomy were not helpful, and made him feel weaker. Dr. Thomas Watson, his physician, then prescribed steel and quinine, which was associated with rapid symptomatic improvement. Iron compounds had been used as tonics since the time of Paracelsus in the 1500s, while quinine was introduced to Europe in the late 1630s. Although quinine was given as a specific treatment for malaria in the early nineteenth

century, many physicians recommended it for virtually every febrile illness, and the combination of quinine and iron was considered appropriate for severely debilitated patients (Day 1870).

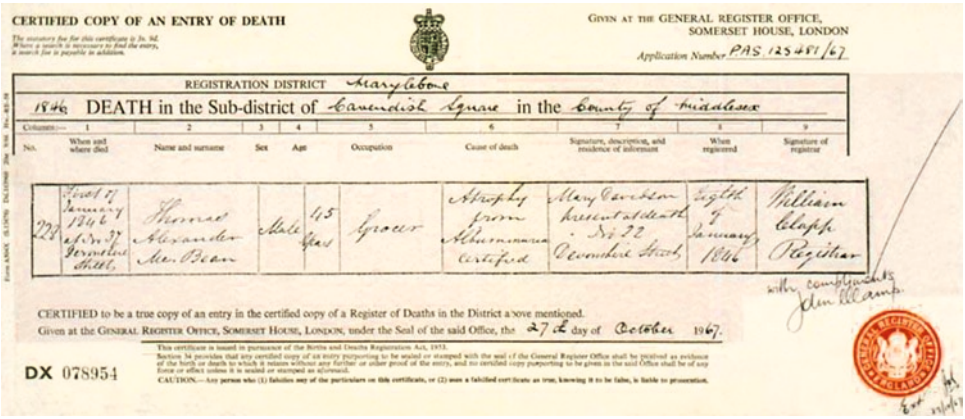
The patient traveled to Scotland in the summer of 1845, where "he bounded over hills as nimbly as any of his companions" (Macintyre 1850). Unfortunately, after returning to London, he developed lumbar and sciatic pain. He was seen in consultation on October 30, 1845, by Dr. William Macintyre (*c.*1791–1857), a Harley Street consultant. Macintyre personally examined the urine because edema had been observed, and he found that it "abounded in animal matter." The following note and a sample of urine were sent to Henry Bence Jones, a chemist at St. George's Hospital:

> Saturday, Nov. 1st, 1845
>
> "Dear Dr. Jones,
>
> The tube contains urine of very high specific gravity. When boiled, it becomes slightly opaque. On the addition of nitric acid, it effervesces, assumes a reddish hue, and becomes quite clear; but as it cools, assumes the consistence and appearance which you see. Heat reliquifies it. What is it?"

Bence Jones confirmed the findings of Macintyre with respect to the urine, and calculated that the patient had excreted more than 60 g/day of protein. He concluded that the strange new protein was an oxide of albumin, specifically "hydrated deutoxide of albumen," and thought that chlorine caused this new protein to form from albumen (Bence Jones 1848). The connection between congealable protein in the urine, dropsy (edema), and kidney disease had been emphasized 20 years earlier by Richard Bright (1789–1858), a physician at Guy's Hospital in London, who published three classic papers on proteinuria and kidney disease beginning in 1827 (Steensma and Kyle 2007). Dr. Bright's practice was to use a spoon to detect protein in the urine, heating fresh urine over a candle and watching for the development of opacity.

Mr. McBean's pain persisted, despite a variety of attempted therapies, and he died on January 1, 1846 (Fig. 1.2). At autopsy, his bones were found to be soft, brittle, and readily fractured, and to contain "a gelatiniform substance of a blood-red colour and unctuous feel." Histologic examination of the bone marrow revealed round and oval-shaped cells that were one-half to twice as large as an average blood cell and contained one or two nuclei and a bright-colored nucleolus (Kyle 2000).

Because Macintyre, rather than Bence Jones, first identified the chemical properties of the


CERTIFIED COPY OF AN ENTRY OF DEATH

GIVEN AT THE GENERAL REGISTER OFFICE, SOMERSET HOUSE, LONDON

Application Number PAS 125481/67

REGISTRATION DISTRICT Marylebone

1846 DEATH in the Sub-district of Cavendish Square in the County of Middlesex

No.	When and where died	Name and surname	Sex	Age	Occupation	Cause of death	Signature, description, and residence of informant	When registered	Signature of registrar
228	Great Portland Street in the Parish of St Marylebone	Thomas Alexander McBean	Male	45 Years	Grocer	Atrophy from Albuminuria certified	Mary Davison present at death 22 December Street	Eighth January 1846	William Clapp Registrar

with compliments John Williams

CERTIFIED to be a true copy of an entry in the certified copy of a Register of Deaths in the District above mentioned.
Given at the GENERAL REGISTER OFFICE, SOMERSET HOUSE, LONDON, under the Seal of the said Office, the 27th day of October 1967

This certificate is issued in pursuance of the Births and Deaths Registration Act, 1953.
Section 34 provides that any certified copy of an entry purporting to be sealed or stamped with the seal of the General Register Office shall be received as evidence of the birth or death to which it relates without any further or other proof of the entry, and no certified copy purporting to be given in the said Office shall be of any force or effect unless it is sealed or stamped as aforesaid.
CAUTION:— Any person who (1) falsifies any of the particulars on this certificate, or (2) uses a falsified certificate as true, knowing it to be false, is liable to prosecution.

DX 078954

Fig. 1.2 Death certificate of Thomas Alexander McBean

unusual protein found in Mr. McBean's urine, some might suggest changing the common term "Bence Jones proteinuria" to "Macintyre proteinuria." However, although Macintyre described the heat properties of the urine, his case report describing Mr. McBean focused on the clinical course rather than the novel urinary findings (Macintyre 1850), and it was Bence Jones who emphasized the place of the new protein in the diagnosis of multiple myeloma generally: "I need hardly remark on the importance of seeking for this oxide of albumen in other cases of mollities ossium (softening of the bone)" (Bence Jones 1847).

1.2 Henry Bence Jones (1813–1873)

Henry Bence Jones was born on December 31, 1813, at Thorington Hall, in the parish of Thorington, just north of Yoxford in Suffolk, England (Kyle 2001). (The more famous Thorington Hall that is a National Trust property in Stoke-on-Nayland in the Stour River Valley is a different structure.) His childhood home had been loaned to his parents, Matilda Bence and Lieutenant Colonel William Jones (Dragoon guards), by Bence Jones' maternal grandfather, Reverend Mr. Bence Sparrow (d. 1824). Bence Jones' grandfather — the rector (parish priest) of Beccles, a village 10 miles north of Thorington — was sometimes known as Rev. Bence Bence, because he adopted the surname Bence in May 1804 upon inheriting Thorington Hall from his first cousin Anne Bence Golding.

Young Henry attended boarding school in Putney, a borough in south west London, in preparation for Harrow, one of the great English public schools. He said that he had learned little at Putney, but did enjoy walking in nearby Wimbledon Park. At Harrow, he was an accomplished cricketer and football and racquet player. He entered Trinity College, Cambridge, in 1831, where he rowed crew, and was a passable student, taking a second-class degree in January 1836. Although he attended Divinity lectures and attained a certificate for ordination, he decided not to pursue a career in the church.

Uncertain about his future, the young Bence Jones tried to find work with a relative in Liverpool, and also seriously considered immigrating to New Zealand (even proceeding with the necessary paperwork), but for unknown reasons, he did not leave England. His father suggested that he study medicine, and in 1836, he began working in the apothecary shop of John Hammerton where he prepared medicines under Hammerton's direction for 6 months. Years later, he said that this experience "was of the utmost use to me all my life" (Bence Jones 1929). He entered the Medical School at St. George's Hospital on October 1, 1838, where he began attending lectures in the dissecting room. Subsequently, he worked as a dresser in the surgeons' ward and then he turned to the physicians' ward. During medical school, he attended the lectures of the physicist Michael Faraday (1791–1867) on electricity at the Royal Institution, while Dr. James Hope, an assistant physician at St. George's, taught him use of the stethoscope. Bence Jones also noted that at the time he was a student, "the glorious discoveries of Dr. Bright [about renal disease] were not valued by any of our medical men" (Bence Jones 1929).

St. George's Hospital, where Bence Jones studied, had been established as a teaching facility and public infirmary in 1733 in what was then the open countryside outside the village of Knightsbridge — a site noted for its clean air, in stark contrast to the nearby overcrowded and filthy conditions prevalent in the city of London. Its faculty has included John Hunter, Edward Jenner, Thomas Young and Henry Gray (anatomist). After post–World War II reorganization as part of the National Health Service, St. George's Hospital moved to Tooting in South London in 1980; by then, the

medical school had become a constituent institution of the University of London system. The Lanesborough Hotel is presently on the original hospital site at Hyde Park Corner. When the hospital was rebuilt and expanded in the 1820s into the Classical neo-Grecian structure that Bence Jones would have known, noted architect William Wilkins (1778–1839) was responsible for the design; Wilkins also designed the National Gallery in Trafalgar Square, and University College London.

Bence Jones's medical studies were interrupted when he developed rheumatic fever in the spring of 1839 and returned home for 6 weeks. Fortunately, he "recovered without complications of disease of the heart" (Bence Jones 1929) — at least none that were detectable at that time. Upon his return to London, he enrolled as a private pupil to Professor Thomas Graham (1805–1869), the "father of colloid chemistry" and discoverer of the principle of dialysis, at University College. Most of the teaching was done by Graham's assistant, George Fownes (1815–1849), a brilliant researcher who published his own chemistry textbook in 1844, and won the prestigious Royal Medal of the Royal Society in 1847 before ill health caused him to have to give up his research. Fownes, in turn, had studied with Justus von Liebig (1803–1873) in Giessen, Germany; von Liebig was a leading chemist of the age and a strident advocate of applying chemistry to the study of plant and animal physiology, against the opposition of others, including the vitalists, who advocated strict separation between inorganic and organic chemistry. The cost of a year's tuition for the course with Graham was £50. Bence Jones learned the principles of organic chemical analysis from Fownes and Graham, and analysis of the sulfur content in a cystine oxide calculus represented his first medical publication (Bence Jones 1842).

Bence Jones was admitted in the spring of 1841 as a licentiate of the College of Physicians, which allowed him to practice, but he had no University medical degree as of yet. On Easter Sunday in 1841, he left for Giessen, Germany, where he studied in von Liebig's laboratory for 6 months. There he learned some advanced analytical methods, and analyzed the proteins in the brain and egg yolk. Bence Jones remained in contact with von Liebig throughout his life, and shared von Liebig's passion for applying chemistry to medicine. Coincidentally, von Liebig and Bence Jones died 2 days apart in April 1873, and their obituaries appeared in the same issue of *Lancet*.

In May 1842, 28-year-old Bence Jones married a cousin, Lady Millicent Acheson (*c.*1812–1887), the youngest daughter of Mary Sparrow and Sir Archibald Acheson, the second Earl of Gosford, an Irish peer who had served as Governor General of British North America from 1835 to 1838. Together they would have seven children. The young couple settled at 30 Grosvenor Square, London, and Bence Jones began working at St. George's. He analyzed the calculi in the Museum of University College Hospital and published his second paper (Bence Jones 1845). He was asked to give a course of 100 lectures on chemistry at Middlesex Hospital, where he became known for insisting on the study of urine in diagnosis of disease. Three years later, he obtained an assistant physician position at St. George's Hospital, and became a full physician there the next year; he was affiliated with St. George's for the rest of his life. In 1846, he became a Fellow of the Royal Society and also received a doctoral degree in medicine from Cambridge. He became involved with the Royal Institution when he gave a series of lectures in 1851, and he served as secretary of that institution — dedicated to "diffusing science for the common purposes of life" — for more than 20 years.

Although his clinical practice grew quickly and was consuming, he vowed to "let no year pass without doing something original in natural science as applied to medicine" (Bence Jones 1929) (Fig. 1.3). Bence Jones was no classicist;

Fig. 1.3 (**a**, **b**) Portraits of Henry Bence Jones

he believed that medicine would be much better served if students spent more time acquiring knowledge of chemistry and physics, rather than memorizing Latin and Greek vocabulary and declensions. As a biochemist, he believed in nothing that he could not separate, test, and measure, scorning experience, tradition, and authority. His research resulted in a series of articles on the sediment, uric acid, calcium oxalate, and the alkaline and earthy phosphates of urine, but while his obituary in the *Medical Times and Gazette* listed 34 papers and six additional articles, no accurate, complete bibliography exists (obituary 1873). He believed that medication must diffuse throughout the tissues before they could produce any benefit and demonstrated that quinine reached its maximum level in tissues 3 h after ingestion.

Bence Jones' work habits were somewhat unusual. He began his laboratory work at 6 a.m. and then arrived at the hospital at approximately 1 p.m. for ward rounds. However, few students sought a clerkship with him because of his unpunctuality. He frequently chided students with the phrase, "Oh! Medical facts! Medical facts!" He taught students to "be as long as you like in forming your opinion on a case, but when you have thoroughly formed it, stick to it" (obituary 1873). His chief aim in the wards was to make therapeutics more scientific. He was unwilling to mix several medications together, a common practice of the day, and instead used simple, precise prescriptions. He was also skeptical of most of the therapeutic drugs of his day. Philosopher Herbert Spencer (1820–1903) wrote in his autobiography, "Speaking of drugs, Bence Jones said that there is scarcely one which may not, under different conditions, produce opposite effects…" (Rosenbloom 1919).

Bence Jones' medical practice grew rapidly and eventually became large and lucrative. In 1 year, his profits from practice were £7,400 — an enormous income for the time — and he bought a house at 84 Brook Street on one of the "grand avenues" of the posh Mayfair neighborhood in West London (obituary 1873). He was recognized widely as a "chemical" doctor, and thus, his practice drew the interest of other scientists. Charles Darwin (1809–1882), the great naturalist, was one of his patients. For Darwin, a noted hypochondriac, Bence Jones prescribed a "severe" diet for his indigestion, which "half-starved him to death" (Rosenbloom 1919). Other famous patients included Michael Faraday, about whom he wrote an affectionate biography in 1870 (Bence Jones 1870) and the biologist, Thomas Huxley ("Darwin's bulldog") (1825–1895). Nursing pioneer Florence Nightingale (1820–1910) once stated that Bence Jones was "the best chemical doctor in London" (Putnam 1993).

In the 1860s, Bence Jones' health began to fail. He noted frequent palpitations and diagnosed rheumatic heart disease in himself after hearing a mitral systolic murmur with his stethoscope in 1861. Reversing his earlier claim that he had suffered no ill effects from his bout of rheumatic fever in 1839, he realized that this illness and its sequelae had "done permanent damage to one of the valves" (Bence Jones 1929). In early 1866, congestive heart failure became more obvious; upon listening to his own lungs with a stethoscope, he stated, "I fancied that one side was half full of fluid" (Bence Jones 1929). His energy decreased, and by August 1870, in a letter to physicist John Tyndall (1820–1893), Bence Jones stated, "I am very lazy and feel unfit for any work and as neither eating, drinking, or sleeping come pleasantly to me, I am a useless mortal and had better be helping the worms and the grass to grow faster than they otherwise would do…" (Putnam 1993). Congestive hepatomegaly, ascites, and anasarca followed, and finally in 1873, Bence Jones was forced to both give up his clinical practice and resign as secretary of the Royal Institution. On April 20, 1873, he died at his home at 84 Brook Street in London of congestive heart failure, and was buried at Kensal Green Cemetery.

A Bence Jones ward exists at St. George's Hospital in Tooting, but it is devoted to gynecology patients rather than patients with multiple myeloma or kidney disease. Interestingly, Bence Jones' obituary in *Medical Times and Gazette* described his work on renal stones, diabetes mellitus, and malignant and tuberculous involvement of the kidney, as well as his emphasis on the clinical value of microscopic analysis of the urine, but there was no mention of the unique urinary protein that bears his name and would preserve that name for posterity (obituary 1873). Henry Bence Jones did not hyphenate his name, and a hyphen is not used in any of his papers or books published during his lifetime. The Royal College of Physicians and the *Dictionary of National Biography* enter him under "Jones." He signed his correspondence, "H. Bence Jones", and apparently did not like the name "Henry." His descendants added a hyphen more than a half-century after his death (Rosenfeld 1987).

1.3 Other Contributions to Bence Jones Proteinuria

In 1846, an Austrian clinical chemist, Johann Florian Heller (1813–1871), described a protein in the urine that precipitated when warmed above 50°C and then dissolved again on further heating (Heller 1846). Heller distinguished this protein from albumin and casein, and it is almost certain that this was Bence Jones protein, despite Heller's failure to recognize the reprecipitation of the protein when the urine cooled again. R. Fleischer, in 1880, is credited with the first publication to use the term "Bence Jones protein." (Fleischer 1880).

W. Kühne described a 40-year-old man with acute osteomalacia and an unusual urinary protein in 1883 (Kühne 1883). The patient's urine precipitated on warming to between 40°C and 50°C and cleared at 100°C. Kühne isolated the urinary protein, which he called "albumosurie," and found that the carbon, hydrogen, and nitrogen levels were similar to those described by Bence Jones, attributing minor differences in composition to the fact that his preparation was more pure than that of Henry Bence Jones.

Bence Jones recognized only a single type of protein, but in 1922, Stanhope Bayne-Jones (1888–1970) and D.W. Wilson at Johns Hopkins found that there are actually two distinct groups of Bence Jones proteins (Bayne-Jones and Wilson 1922). Leonhard Korngold and Rose Lipari, at Memorial Cancer Institute in New York, demonstrated a relationship between Bence Jones protein and the serum proteins of multiple myeloma in 1956 (Korngold and Lipari 1956). The two major classes of Bence Jones protein have been designated kappa and lambda in honor of Korngold and Lipari. Gerald Edelman (1929–) and Joseph A. Gally at the Rockefeller Institute in New York, 117 years after the description of the unique heat properties of Bence Jones protein, proved that the light chains prepared from an IgG myeloma protein and the Bence Jones protein from the same patient's urine had an identical amino acid sequence; similar spectrofluorometric behavior; identical appearance on chromatography with carboxymethylcellulose; and, on starch gel electrophoresis after reduction and alkylation, the same ultracentrifugal pattern, identical thermosolubility, and the same molecular weight (Edelman and Gally 1962). The light chains examined by Edelman and Galley precipitated when heated to between 40°C and 60°C, dissolved on boiling and reprecipitated when cooled to between 40°C and 60°C — identical to the physicochemical properties of Bence Jones protein.

1.4 Other Early Cases of Multiple Myeloma

In 1867, Hermann Weber reported a 40-year-old man with pain, tenderness, and deformity of the sternum. The patient also had severe pain in the lumbar area, and he died 3.5 months after the onset of pain. At postmortem examination, the patient's sternum was almost entirely replaced by a grayish-red substance that had the microscopic appearance of a sarcoma. There were several round defects in the skull, many of the ribs, several vertebrae and parts of the pelvis. Amyloid — described by Rudolf Virchow (1821–1902) in Berlin in 1854 — was found in the kidneys and spleen (Weber 1867).

Five years later, William Adams described a similar patient to Weber's with bone pain and fractures. At autopsy, it was observed that the cancellous portions of the bones had been replaced by a homogenous soft gelatinous substance consisting of small spherical and oval cells containing one oval nucleus (rarely two) with a bright nucleolus. "Lardaceous changes" (likely amyloidosis) were found in the liver and kidneys (Adams 1872).

J. Von Rustizky, a Russian pathologist working in the laboratory of Friedrich von Recklinghausen (1833–1910) in Strassburg in 1873, introduced the term "multiple myeloma." At autopsy, a 47-year-old patient examined had eight separate tumors of bone marrow, which Von Rustizky called "multiple myelomas," and he noted that the nucleus of the tumor cells was located in the periphery of the cell membrane — a morphology highly suggestive of plasma cells.

1.4.1 The Case of Dr. Loos

The term "Kahler's disease" was once used to describe myeloma; this eponym resulted from a case report of a physician named Dr. Loos by

Professor Otto Kahler of Prague. The patient, Dr. Loos, was a 46-year-old physician who developed severe thoracic pain in July 1879. During the next 2 years, intermittent pain aggravated by exercise occurred in Dr. Loos' ribs, spine, left shoulder, upper arm, and right clavicle. Albuminuria was found in September 1881, and pallor was seen 2 years later. Dr. Loos was first seen by Professor Kahler in 1885. Kahler found anemia, severe kyphosis, tenderness of many bones, and albumosuria. The urine of Dr. Loos was described in detail in 1889 by Karl Hugo Huppert (1832–1904), a German chemist and physician who was the Professor of Medicinal Chemistry in Prague. Kyphosis of the upper thoracic spine increased and the patient's chin pressed against the sternum producing a pressure ulcer. Dr. Loos died on August 26, 1887, 8 years after the onset of symptoms. At autopsy, soft gray-reddish masses were noted in the ribs and microscopic examination revealed large, round cells consistent with myeloma. The patient sustained a high fluid intake and took sodium bicarbonate on a regular basis, which may have helped prevent renal failure.

Otto Kahler, born in 1849, was the son of a well-known physician in Prague. After receiving his M.D. degree from the University of Prague in 1871, Kahler studied in Paris, where he met the French neurologists Jean Martin Charcot (1825–1893) and Guillaume-Benjamin-Amand Duchenne (1806–1875). Kahler became interested in neurology, particularly in neuroanatomy. He contributed to the understanding of the pathological anatomy of tabes dorsalis, localization of parietal central oculomotor paralysis, and the symptoms of gradual compression of the spinal cord. He then returned to Prague where he became head of the second medical clinic at the German University of Prague. In 1889, Kahler succeeded the Austrian internist Heinrich von Bamberger (1822–1888), as Professor at the University of Vienna (Fig. 1.4). Kahler finished his inaugural address in Vienna on May 13, 1889, with a statement, "Ars longa vita brevis" (the art [of medicine] is long, life is short) — words that proved prophetic in 1889, when he developed a malignant tumor of the tongue. Despite an attempted excision, carcinoma of the tongue recurred the following year, and Kahler died on January 24, 1893 (Nothnagel 1893). Kahler was known for being extremely kind to his patients and an excellent teacher. Incidentally, his obituaries and eulogies made no mention of his famous case report of Dr. Loos (Kahler 1889); the contributions of both Henry Bence Jones and Otto Kahler to multiple myeloma were not recognized during their lifetimes.

Fig. 1.4 Otto Kahler

1.4.2 The First Myeloma Case in America

Probably the first reported case of multiple myeloma in the United States was published by

James Herrick (1861–1954) and Ludvig Hektoen at Rush Medical College in Chicago in 1894 (Herrick and Hektoen 1894). A 40-year-old woman had lumbar pain for 16 months before painless nodules developed on the sternum, face, and chest. The right clavicle enlarged and then fractured without trauma. The hemoglobin level was less than half normal. The patient died 18 months after the onset of symptoms. Autopsy revealed tumors involving the sternum, ribs, spine, right clavicle, both humeri, and the skull, and microscopic examination revealed the round, lymphoid cells with large nuclei described in other reports.

1.4.3 Recognition of the Poor Prognosis Associated with Bence Jones Protein

Frederick Parkes Weber (1863–1962), an English physician who is the "Weber" in Klippel–Trenauney–Weber syndrome and Rendu–Osler–Weber disease, reported a case of multiple myeloma in 1898 and stated that in the future, the diagnosis might be "greatly facilitated by the employment of Röntgen's rays" (Weber 1898). Weber also claimed that bone marrow was the site of production of the Bence Jones protein and that its presence was of "fatal significance" and that it "nearly always, if not always, indicated that the patient was suffering from multiple myeloma" (Weber et al. 1903).

1.4.4 Case Series

In the first half of the twentieth century, case reports gave way to case series. In 1928, Charles F. Geschickter (1901–1987) and Murray M. Copeland (1902–1982) at Georgetown University in Washington, DC, presented an analysis of all 425 cases of multiple myeloma reported since 1848 (Geschickter and Copeland 1928). They emphasized six major features consisting of multiple involvement of the skeleton by tumors, pathologic fractures, Bence Jones proteinuria, back pain, anemia, and renal insufficiency. They did not recognize abnormalities of blood protein or elevation of the erythrocyte sedimentation rate. Bone marrow aspiration, described in 1929 by Mikahael Arinkin in Leningrad, greatly increased the antemortem recognition of multiple myeloma (Arinkin 1929). Rosenthal and Vogel reported that only three cases of multiple myeloma had been recognized in Mount Sinai Hospital in New York from 1916 to 1935, but that 13 cases were found in the succeeding 2.5 years (Rosenthal and Vogel 1938). Edwin Bayrd (1917–2007) and Frank Heck described 83 patients with histological proof of multiple myeloma who were seen at Mayo Clinic through 1945. Duration of survival ranged from 1 to 84 months (median 15 months) (Bayrd and Heck 1947).

1.4.5 Plasma Cells

The term "plasma cell" was first used in 1875 by Heinrich Wilhelm Gottfried von Waldeyer-Hartz (1836–1921), a German anatomist, but from the detailed description, it seems likely that he was observing tissue mast cells, rather than the antibody-producing cells that we currently call by that name (Waldeyer 1875). Plasma cells were described accurately by the great Spanish anatomist Santiago Ramón y Cajal (1852–1934) in 1890 during a study of syphilitic condylomas (Cajal 1896). Cajal believed that the unstained perinuclear area ("hof") contained the Golgi apparatus, and he felt that the plasma cells were likely normal constituents of connective tissue. T. von Marschalkó, a Hungarian pathologist, described the key characteristics of plasma cells in 1895, including blocked chromatin, eccentric position of the

nucleus, a perinuclear pale area, and a spherical or irregular cytoplasm (Marschalko 1895). J.H. Wright thought that the tumor cells of myeloma consisted of plasma cells or their immediate descendants (Wright 1900).

1.4.6 Antibodies

In 1890, Emil Adolf von Behring (1854–1917), a German physiologist, and Japanese bacteriologist Shibasaburō Kisato (1853–1931) described a specific neutralizing substance in the blood of animals immunized with diphtheria and tetanus toxin — an observation that won them the first Nobel Prize in physiology or medicine in 1901. von Behring and Kisato and their successors noted that antitoxins — later called antibodies — could be found after the injection of most foreign proteins (von Behring and Kisato 1890). Although a Bence Jones protein had been detected in the serum by Jacobsen in 1917, it was not until 1928 that William A. Perlzweig (1891–1949) and his colleagues at Johns Hopkins recognized hyperproteinemia, when they described a patient with multiple myeloma who had 9 to 11 g of globulin in the serum (Perlzweig et al. 1928). The Johns Hopkins team also noted that it was almost impossible to obtain serum from clotted blood drawn from a hyperproteinemic patient, because the clot failed to retract even with prolonged centrifugation. Maxwell Wintrobe (1901–1986) and M.V. Buell, also at Johns Hopkins, recognized cryglobulinemia in 1933 (Wintrobe and Buell 1933), but the term "cryoglobulin" was introduced by medical student Aaron Lerner (1920–2007) and his research preceptor, C.J. Watson, at the University of Minnesota 14 years later (Lerner and Watson 1947). The patient described by Lerner and Watson had previously been reported as having allergic purpura with hypersensitivity to cold (Peters and Horton 1941).

1.4.7 Electrophoresis

Separation of serum proteins by electrophoresis was described by Swedish biochemist Arne Tiselius (1902–1971) in his doctoral dissertation in 1930; he published expanded observations using the moving boundary method of electrophoresis in 1937 (Tiselius 1937b). Interestingly, this article, which led to his 1948 Nobel Prize in chemistry and later to the Presidency of the Nobel Foundation, was rejected by the *Biochemical Journal* (Putnam 1993) — perhaps a note of encouragement for other frustrated authors. Later in 1937, Tiselius described the separation of serum globulins into three major protein components, which he termed alpha, beta, and gamma according to their electrophoretic mobility (Tiselius 1937a, b). Tiselius and an American postdoctoral fellow, Elvin A. Kabat (1914–2000), localized antibody activity to the gamma globulin region of the plasma proteins (Tiselius and Kabat 1939). However, they quickly recognized that some antibodies migrated in the fast gamma region and others in the slow gamma region, and that some sedimented in the ultracentrifuge as 7S and others as 19S molecules, suggesting further heterogeneity. The concept of a family of proteins with antibody activity was described by Belgian immunologist Joseph-Félix Heremans (d. 1975) in 1959 (Heremans 1959). Before 1960, the term "gamma globulin" was used for any protein that migrated in the gamma mobility region of the electrophoretic pattern; these gamma globulins are now referred to as immunoglobulins: IgG, IgA, IgM, IgD, and IgE.

In 1939, Lewis G. Longsworth and his colleagues at the Rockefeller Institute applied electrophoresis to the study of multiple myeloma, and demonstrated the tall, narrow-based "church spire peak" (Longsworth et al. 1939). The electrophoresis apparatus used by Longsworth and contemporaries was cumbersome and difficult

to use; the original commercial models were 20-ft long and 5-ft high, and often occupied a separate laboratory room. A single electrophoretic run required a full day, and results could only be interpreted by an experienced operator (Putnam 1993). Subsequent technical refinements made electrophoresis simpler and more widely available. For instance, the use of filter paper as a support permitted the separation of proteins into discrete zones that could be stained with various dyes (Kunkel and Tiselius 1951), and cellulose acetate replaced filter paper. Currently, most laboratories now use agarose gel electrophoresis.

Immunoelectrophoresis was described by Grabar and Williams in 1953 (Grabar and Williams 1953). Eleven years later, Wilson reported immunofixation or "direct immunoelectrophoresis," in which he applied antisera on the surface of the agarose immediately after completion of electrophoresis. Rowe and Fahey isolated IgD monoclonal protein from a myeloma patient (Rowe and Fahey 1965). A year later, Ishizaka et al. described the final immunoglobulin isotype, IgE (Ishizaka et al. 1966).

1.4.8 Monoclonal Versus Polyclonal Gammopathies

A critical milestone was the concept of monoclonal versus polyclonal gammopathies, first presented in the Harvey Lecture Series by Swedish physician Jan Gosta Waldenstrom (1906–1996) in 1961 (Waldenstrom 1960–1961). He described patients with a narrow band of hypergammaglobulinemia on electrophoresis as having a monoclonal protein, and those with a broad band on electrophoresis and hypergammaglobulinemia as having a polyclonal increase in proteins. While polyclonal hypergammaglobulinemia was associated with nonmalignant disorders including inflammation or infection, patients with monoclonal proteins typically had multiple myeloma or macroglobulinemia. However, others with a monoclonal pattern had no evidence of malignancy, and Waldenstrom considered them to have "essential hypergammaglobulinemia" or a "benign monoclonal protein." Today the preferred term for this phenomenon is monoclonal gammopathy of undetermined significance (MGUS), because some such proteins will remain stable for many years and not cause clinical problems, but in other patients with MGUS, multiple myeloma, macroglobulinemia, light chain (AL) amyloidosis, or a related disorder may subsequently develop (Kyle 1978).

1.5 Alkylator and Corticosteroid-Based Therapy

Therapy of multiple myeloma has improved markedly since the days of Sarah Newbury's treatment with rhubarb pills and infusion of orange peel, or the phlebotomy, leeches, steel, quinine, and other ministrations that Thomas McBean had to endure. Despite the therapeutic advances of the last half-century, however, the cure of myeloma has proven elusive, and there is much work yet to be done.

1.5.1 Urethane

Nils Alwall (1904–1986), a Swedish hemodialysis pioneer, reported in 1947 that a patient with multiple myeloma who was treated with urethane (ethyl carbamate) had a reduction in serum globulin concentration from 5.9 g/dL to 2.2 g/dL, an increase in hemoglobin from 60% to 87%, disappearance of proteinuria, and a reduction in bone marrow plasma cells from 33% to 0% (Alwall 1947). Urethane became the standard of treatment for myeloma for more than 15 years, until a randomized trial showed that it was not effective. In 1966, chemotherapy pioneer James

F. Holland and colleagues randomized 83 patients with treated or untreated multiple myeloma to receive urethane or a placebo consisting of cherry- and cola-flavored syrup (Holland et al. 1966). No difference was seen in the objective response or in survival between the two treatment groups.

1.5.2 Melphalan

In 1958, Nikolai Nikolaevich Blokhin and colleagues in Moscow reported that three of six patients with multiple myeloma obtained benefit from sacrolysin (L-phenylalanine mustard, melphalan) (Blokhin et al. 1958). Four years later, Daniel E. Bergsagel, at MD Anderson, and his colleagues confirmed these findings, reporting significant improvement in 8 of 24 patients with multiple myeloma who were treated with melphalan; 6 other patients had more modest objective improvements (Bergsagel et al. 1962). In a later report, melphalan given as a loading dose for 1 week followed by maintenance therapy produced responses in 78% of 64 patients with newly diagnosed or previously treated multiple myeloma (Hoogstraten et al. 1967).

1.5.3 Prednisone

Prednisone also was found to be effective for multiple myeloma at about the same time that melphalan debuted. In a placebo-controlled double-blind trial published in 1962, prednisone as a single agent produced significant decreases in serum globulin levels and an increase in hematocrit, but no improvement in survival when compared with a placebo (Mass 1962). In another study, prednisone, in a single dose of 200 mg every other morning, produced benefit in eight of ten patients with poor-risk myeloma (Salmon et al. 1967). In an analysis of two Cancer and Leukemia Group B (CALGB) myeloma treatment protocols, prednisone as a single agent produced a 44% objective response (MacIntyre et al. 1985). The classic regimen of melphalan plus prednisone (MP) was established in a randomized trial of 183 myeloma patients published in 1969. This study, led by Raymond Alexanian and colleagues, found that survival was 6 months longer with MP compared with melphalan alone (Alexanian et al. 1969). Later, dexamethasone was found to offer some advantages over prednisone.

1.5.4 Alkylator Combinations

Harley et al. first reported a combination of alkylating agents — melphalan, cyclophosphamide, and carmustine (BCNU) in 1972 (Harley et al. 1972). A combination of carmustine, cyclophosphamide, melphalan, vincristine, and prednisone (M-2 protocol) produced excellent subjective and objective responses in 60% of 36 myeloma patients (Lee et al. 1974). Likewise, in a series of 73 patients with myeloma, the M-2 protocol produced an 87% response rate in 73 myeloma patients (Case et al. 1977).

However, when the CALGB cooperative group studied the combination of carmustine (BCNU), cyclophosphamide, melphalan, and prednisone (BCMP regimen) to MP in 252 patients by J.B. Harley and colleagues in 1979; there was no survival benefit from the BCMP regimen above MP (Harley et al. 1979). Other trials had similar negative results in terms of survival, even when objective response rates improved. The Myeloma Trialists Collaborative Group described a large meta-analysis of individual data of 4,930 persons from 20 randomized trials comparing MP with various combinations of therapeutic agents (Myeloma Trialists' Collaborative Group 1998). Although the response rates were higher with combination chemotherapy (60% vs MP 53%,

$P < 0.0001$), there was no significant difference in response duration or overall survival. MP thus remained the mainstay of myeloma treatment for decades.

1.6 Stem Cell Transplantation

E. Donnall Thomas and his colleagues in Cooperstown, New York, treated six patients (one had multiple myeloma) with total body irradiation or chemotherapy followed by an intravenous infusion of bone marrow cells in 1957 (Thomas et al. 1957), but technical obstacles prevented successful results. Thomas moved to Seattle in 1963 and continued to modify approaches to stem cell transplantation, which ultimately led to his Nobel Prize in 1990. The first successful syngeneic bone marrow transplantation for myeloma was reported in 1982; two physician brothers were the patients (Osserman et al. 1982). In 1986, Alexander Fefer and colleagues in Seattle described five myeloma patients who received a syngeneic bone marrow transplant (Fefer et al. 1986). The following year, Gösta Gahrton and colleagues in Sweden reported that 10 of 14 patients with multiple myeloma who received an allogeneic bone marrow transplant from an HLA-compatible sibling donor survived for a median of 12 months (Gahrton et al. 1987).

The first reported autologous bone marrow transplantation in a patient with plasma cell leukemia was reported in 1983 by Timothy McElwain (1937–1990) and Ray Powles at the Royal Marsen Hospital in Sutton, England (McElwain and Powles 1983). The patient was given melphalan 140 mg/m^2 followed by platelet support and antibiotics; he relapsed 16 months later and was again given 140 mg/m^2 of melphalan followed by an intravenous autograft obtained from his remission marrow. Two of four previously untreated myeloma patients treated similarly obtained a complete response, whereas one of four previously treated patients had a complete response (McElwain and Powles 1983). Eleven (27%) of forty-one patients with previously untreated multiple myeloma obtained a complete remission after a single intravenous dose of melphalan 140 mg/m^2. Unfortunately, most of the patients relapsed with a median duration of remission of 19 months. In 1987, Bart Barlogie and colleagues at MD Anderson in Houston reported use of melphalan 140 mg/m^2 and total body irradiation (150 cGy), followed by autologous or allogeneic bone marrow transplantation, in six patients with multiple myeloma refractory to chemotherapy (Barlogie et al. 1987). Barlogie subsequently developed intense treatment programs using autologous transplantation, which he called "total therapy" (a term and concept pioneered for childhood leukemia at St. Jude's Hospital in Memphis), which eventually played a major role in establishing high-dose therapy and stem cell rescue as standard therapy for myeloma.

1.6.1 Novel Agents

Beginning in the late 1990s, other active drug therapies emerged that finally supplanted MP as the standard of care for patients with multiple myeloma. These included thalidomide (Singhal et al. 1999), bortezomib (Richardson et al. 2003, 2005), and lenalidomide (Rajkumar et al. 2005; Richardson et al. 2006).

1.6.1.1 Thalidomide

Chemie Grünenthal, a German pharmaceutical company, introduced thalidomide (alpha-N-[phthalimidol] glutarimide) (as a sedative) on October 1, 1957. Three years later, it was sold in more than 40 countries, and became popular both as a sedative and as a treatment for morning sickness of pregnancy.

Widukind Lenz (1919–1995), a German pediatrician and geneticist, reported on November 18, 1961, that in utero thalidomide was associated with severe teratogenic malformations (Lenz 1962). Exposure to the drug during the first trimester of pregnancy produced the fetal malformations. Thalidomide was removed from the market in most countries by the end of 1961, but by then almost 10,000 infants had been affected. Dr. Francis Kelsey of the US Food and Drug Administration (FDA) was concerned about the lack of safety data and fortunately did not approve the drug for use in the USA. No significant activity was noted in two separate clinical trials for patients with advanced cancer (Grabstald and Golbey 1965; Olson et al. 1965). A few myeloma patients were admitted to these trials, but clinical activity was not apparent.

Despite removal from the market as a sedative, thalidomide continued to be used in the developing world for the treatment of leprosy and other ailments. Beginning in the 1980s, thalidomide was also found to be effective for Behçet disease, graft-versus-host disease, and HIV-associated oral ulcers and wasting. The FDA approved thalidomide for the treatment of erythema nodosum leprosum in 1998, with a prescribing and distribution safety system termed, "The System For Thalidomide Education and Prescribing Safety" program (STEPS).

The antiangiogenic properties of thalidomide in the rabbit cornea micropocket assay were described by Robert D'Amato and colleagues in Judah Folkman's laboratory in Boston (D'Amato et al. 1994). Based on the increasing awareness of angiogenesis and the pathogenesis of cancer, and the evidence of increased angiogenesis in myeloma, the spouse of an affected myeloma patient convinced Barlogie and colleagues at the University of Arkansas to initiate a compassionate-use trial of "antiangiogenic therapy." After a detailed telephone conversation with Folkman, Barlogie and colleagues designed a landmark trial that enrolled 84 myeloma patients for whom MP had failed (Singhal et al. 1999). Thirty-two percent of patients in this pilot study responded to thalidomide, making it the first new drug with single-agent activity for myeloma in more than three decades.

1.6.1.2 Bortezomib

The orderly degradation of eukaryocytic cellular proteins is mediated by the ubiquitin-proteasome pathway (Ciechanover 1994). The 26S proteasome consists of a core 20S catalytic complex and a 19S regulatory complex. Ubiquitin-tagged proteins are recognized by the 19S regulatory complex, where the ubiquitin tags are removed, and then the 20S proteasome cylinder hydrolyzes the formerly tagged proteins into small polypeptides. Inhibition of the proteasome leads to cellular apoptosis with malignant, transformed, and proliferating cells being particularly susceptible (Adams et al. 1999; Orlowski et al. 1998).

Several boronic acid–derived compounds, including bortezomib, were designed to inhibit the proteasome pathway in a specific manner (Adams et al. 1999; Orlowski et al. 1998). The initial clinical study with bortezomib in advanced hematologic malignancies was conducted by Robert Orlowski at the University of North Carolina (Orlowski et al. 2002). Leading up to the trial, Orlowski's laboratory was investigating the proteasome pathway — an area of research that his father, Marian Orlowski (1918–2006), had pioneered years earlier. Bortezomib demonstrated antimyeloma activity in the initial phase I study (Orlowski et al. 2002). It also showed activity against myeloma cells in several preclinical models in a series of experiments conducted in the laboratories of Kenneth Anderson at the Dana Farber Cancer Institute in Boston (Hideshima et al. 2001). Approximately one-third of the 202 patients with relapsed

refractory myeloma responded to bortezomib (Richardson et al. 2003). These results led to the approval of bortezomib by the FDA in May 2003. In a subsequent randomized trial, time to disease progression was superior with bortezomib compared with dexamethasone alone in patients with relapsed, refractory myeloma (Richardson et al. 2005).

1.6.1.3 Lenalidomide

Several analogs of thalidomide were synthesized to try to minimize some of the adverse events (including, perhaps, teratogenicity) associated with thalidomide. Lenalidomide, a 4-aminosubstituted analog of thalidomide formerly called CC-5013, belongs to a class of thalidomide analogs termed "immunomodulatory drugs" by the manufacturer, Celgene Corporation.

Lenalidomide was tested in phase I trials in relapsed refractory myeloma at the Dana Farber Cancer Institute by Paul Richardson and colleagues, and the compound showed promise (Richardson et al. 2002). A multicenter randomized phase II trial of lenalidomide, also led by Richardson, enrolled 102 patients with relapsed/refractory myeloma, with an overall response rate of 17% (Richardson et al. 2006). In a phase II trial conducted at Mayo Clinic, 31 of 34 patients (91%) with newly diagnosed myeloma achieved an objective response with thalidomide plus dexamethasone (Rajkumar et al. 2005). Two large phase III trials have shown a significantly superior time to progression with lenalidomide plus dexamethasone compared with placebo plus dexamethasone in patients with relapsed myeloma (Dimopoulos et al. 2007; Weber et al. 2007). The combination of lenalidomide and dexamethasone was approved by the FDA in June 2006 for the treatment of myeloma in patients who have failed one prior regimen.

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