British Journal of Haematology, 2000, **111**, 1035–1044

Historical Review

MULTIPLE MYELOMA: AN ODYSSEY OF DISCOVERY

Early cases

Multiple myeloma has probably been present for centuries. Morse *et al* (1974) reported four cases of possible multiple myeloma in American Indian skeletons from AD 200–1300. They described discrete lytic lesions with sharply demarcated borders and no evidence of sclerosis or formation of new bone. One skeleton was that of a 45-year-old man, but the fact that the other three were less than 40 years of age cast doubt on the diagnosis of multiple myeloma (Morse *et al*, 1974).

It is probable that 39-year-old Sarah Newbury, the second patient described by Samuel Solly (1844), had multiple myeloma. In May 1840, she experienced severe back pain while stooping and a strange sensation in her right leg. Eighteen months later, she described progressive bone pain in her limbs. Walking was difficult because of weakness of the right leg. Excruciating pain developed in her thighs in April 1842 while her husband was lifting her from the fireplace to carry her to bed. Her thighs gave way and she was confined to her bed. Fractures of both clavicles occurred (Fig 1), and deformities of the ribs and spine became evident. A simple bitter infusion was prescribed for her failing appetite, but she refused to take it and forbade any further visits by Dr Solly. The disease progressed and, on 15 April 1844, her husband requested that she be admitted to St. Thomas' Hospital. The right humerus had fractured. She was allowed wine and arrow-root, a mutton chop and a pint of porter daily. She was given an infusion of orange peel, a rhubarb pill when necessary, as well as an opiate. She died 5 d after admission, apparently from asphyxia. Autopsy revealed fractures of the right radius and ulna, left tibia and fibula, and both femurs. The thoracic cavity was markedly reduced and it compressed the right lung to one-quarter of its normal size. Sections of the bones revealed a 'red grumous matter', ranging from a deep Modena red to a bright scarlet crimson. Marked destruction and thinning of the bones was noted (Figs 2 and 3). The red matter was examined by Dr Solly and Mr Birkett of Guy's Hospital. The majority of the nucleated cells had a clear, oval outline and one or, rarely, two bright central nucleoli. Solly believed that the process was inflammatory and that it had begun 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' (Solly, 1844). Little did he know that more than one and a half centuries later, anti-angiogenesis drugs would be used for the treatment of multiple myeloma (Singhal *et al*, 1999).

'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, 1847).

This note and a urine sample were sent by a leading general practitioner of London, Dr Thomas Watson, to Henry Bence Jones, a 31-year-old physician at St. George's Hospital who had already established a reputation as a chemical pathologist. The patient, Thomas Alexander McBean, was identified by examining the Register of Deaths and searching for males 45–47 years old whose name began with an M and who died in London on 1 or 2 January 1846 (Clamp, 1967). Mr McBean was seen in consultation on 30 October 1845 by Dr William Macintyre, a 53-year-old Harley Street consultant and physician to the Metropolitan Convalescent Institution and to the Western General Dispensary, St. Marylebone (Clamp, 1967). In 1843, Mr McBean, 44 years of age and a highly respectable grocer of 'temperate habits and exemplary conduct' experienced easy fatigue and was noted to stoop when walking. He complained of 'frequent calls to make water' and noted that his body linen was stiffened by his urine although there was no urethral discharge. He took a vacation in the country in September 1844 to regain his strength. While vaulting out of an underground cavern on his country vacation, he suddenly 'felt as if something had snapped or given way within the chest', and for some minutes he lay, unable to stir because of severe pain. After he had a night's rest at a neighbouring inn, the chest pain resolved (Macintyre, 1850). Dr Macintyre subsequently applied a strengthening plaster to the chest because movement of the arms produced chest pain. The application of the plaster and his carefully abstaining from bodily exertion allowed the patient to resume work. A month later, he had an acute episode of chest pain, for which a surgeon removed a pound of blood and applied leeches and blisters topically. The pain abated, but he was weak for 2 or 3 months.

In the spring of 1845, Mr McBean had an episode of right pleuritic pain that was treated unsuccessfully by cupping. Therapeutic bleeding produced marked weakness. Wasting, loss of colour, and puffiness of the face and ankles led to consultation with Dr Watson, who gave the patient a course of steel and quinine. He improved rapidly and, by the middle

Correspondence: Dr Robert A. Kyle, Division of Hematology and Internal Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA. E-mail: kyle.robert@mayo.edu

Fig 1. Sarah Newbury. Fractures of femurs and right humerus. From Solly (1844).

of the summer, was able to travel to Scotland, where, on the sea coast, his improvement continued and he was able to take active exercise on foot during the greater part of the day, 'bounding over the hills', to use his own expression, as

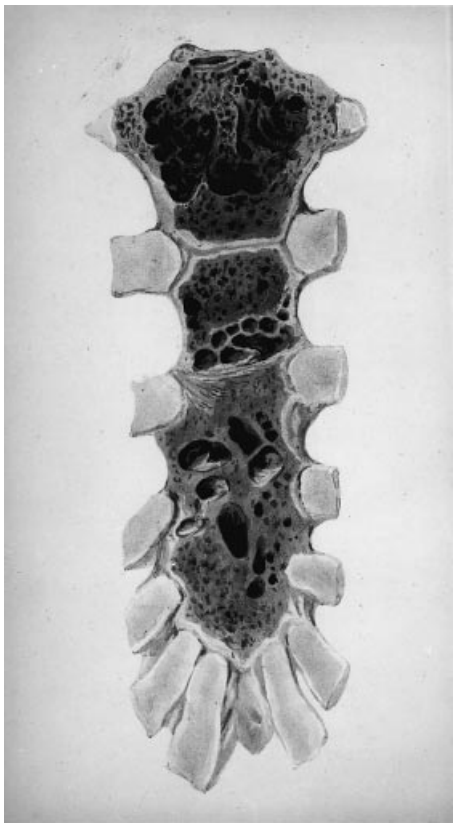
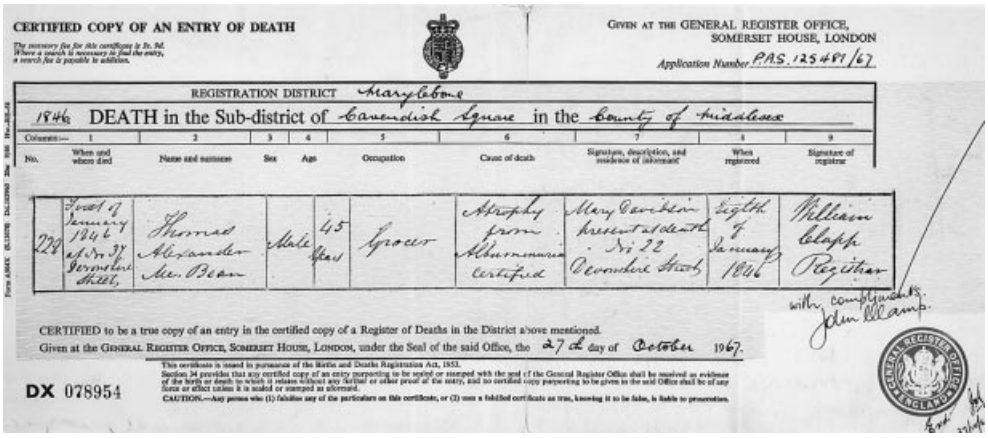


Fig 2. Sternum of Sarah Newbury showing destruction of bone. From Solly (1844).

Fig 3. Sarah Newbury. Destruction of femurs by myeloma tumour. From Solly (1844).

nimbly as any of his companions (Macintyre, 1850). His appetite improved, so much so that he dreamed of eating dogs and cats (Bence Jones, 1847). He had an episode of obstinate diarrhoea that reduced his strength considerably. He returned to London in September 1845 in a very debilitated state, but free of the excruciating pains that he had had during the spring. He was again treated by Dr Watson, who prescribed a course of tonics. He seemed to improve, but then, in October 1845, was seized with severe lumbar sciatic pain. Warm baths, Dover's powder, acetate of ammonia, camphor julap and compound tincture of camphor were prescribed, but did not help. Dr Macintyre saw him in consultation on 30 October and, because of the oedema, personally examined the urine. The specimen was opaque, acidic and of high density (specific gravity 1·035). When heated, the urine was found to 'abound in animal matter.' With the addition of nitric acid, the urine became clear, but a precipitate developed after an hour. This precipitate 'underwent complete solution on the application of heat, but again consolidated on cooling' (Macintyre, 1850). [Dr Macintyre had independently sent a urine sample to Dr Bence Jones following his examination.]

The exertion of getting into the bath produced such acute pain that the practice was discontinued. A slight catarrh developed and was treated with tartrate of potash with ipecacuanha. During the day, every motion of the trunk produced excruciating pain. Cautious manoeuvring allowed him to 'get in and out of bed on all-fours.' The febrile episode



CERTIFIED COPY OF AN ENTRY OF DEATH

GIVEN AT THE GENERAL REGISTER OFFICE, SOMERSET HOUSE, LONDON

Application Number PAS 125491/67

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
229	Fourth January 1846 at No 37 Devonshire Street,	Thomas Alexander Mc. Bean	Male	45 Years	Grocer	Atrophy from Albuminuria certified	Mary Davison present at death No 22 Devonshire Street	Eighth January 1846	William Clapp Registrar

with compliments John Clamp.

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.

DX 078954

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.

GENERAL REGISTER OFFICE ENGLAND

Fig 4. Death certificate of Thomas Alexander McBean. From Kyle (1996), by permission of Churchill Livingstone. (Courtesy of General Register Office, London, UK.)

resolved, but the patient became weaker and was unable to sit or stand. Flatulence of the abdomen developed, and the patient noted fullness and hardness in the region of the liver. He was given citrate of iron and quinine, along with opiates. His pain improved, and he slept well for two nights and was able to sit up and walk about the room. Unfortunately, a cough developed along with phlegm in his chest, and he had another episode of diarrhoea precipitated by a dose of rhubarb and soda. Dover's powder was prescribed, but he became weaker and looked more anaemic.

On 15 November, Dr Bence Jones saw him in consultation and advised alum with the 'view of checking the exhausting excretion of animal matter' (Macintyre, 1850). There appeared to be a reduction in these excretions and a decrease in pain that allowed him to sit up for an hour or two each day. However, he became weaker and on 7 December had a 'dreadful aggravation' of lumbar pain. Crude opium and morphia were given, but produced confusion. Weakness and emaciation progressed and, almost constantly racked with pain, he was unable to leave his bed. He took no nourishment, and on 1 January 1846 he died, exhausted, but in full possession of his mental faculties.

The cause of death was listed as 'atrophy from albuminuria' (Clamp, 1967) (Fig 4). Involvement of the bones, aside from pain, was not recognized during the patient's illness. The autopsy was carried out by a Mr Shaw in the presence of Drs Watson, Jones and Macintyre. The 'ribs crumbled under the heel of the scalpel.' They were soft and so brittle that they 'could be easily cut by the knife, and readily broken.' The interior of the ribs was filled with a soft 'gelatiniform substance of a blood-red colour and unctuous feel.' The sternum was soft and fragile and snapped when raised and turned back. The bones had the same appearance as those of Sarah Newbury. The heart and lungs were not remarkable. 'The liver was voluminous, but of healthy structure; the gall bladder was full of bile.' The thoracic and lumbar vertebrae had the same changes as were found in the ribs and sternum, but the sacrum, pelvis, humeri and femurs resisted 'all efforts to bend or break them by manual force' (Macintyre, 1850).

Bright's disease was considered in the differential diagnosis because of the albuminous matter in the urine, but there was no dropsy. Furthermore, the kidneys appeared normal on both gross and microscopic examination. They had 'proved equal to the novel office assigned them' and had 'discharged the task without sustaining, on their part, the slightest danger' (Macintyre, 1850).

The possibility of amyloidosis in addition to multiple myeloma is suggested by diarrhoea, weakness, emaciation, hepatic enlargement, flatulence, dyspepsia, oedema of the ankles, puffiness of the face and large amounts of Bence Jones protein in the urine. However, the autopsy findings of a normal heart and kidneys and a 'voluminous' liver of 'healthy structure' make the presence of amyloidosis improbable. It is unlikely that amyloidosis would have been overlooked because the waxy changes of amyloidosis in the liver were commonly recognized at the time.

The modest Dr Macintyre stated that his 'share in this part of the inquiry, it must have been seen, was very humble.' He went on to say that 'I shall be content if I have succeeded in pointing out to future observers, gifted with the requisite qualifications for conducting researches of a higher order, certain definite and distinctive characters by which a peculiar and hitherto unrecorded pathological condition of the urine may be recognized and identified' (Macintyre, 1850).

John Dalrymple, surgeon to the Royal Ophthalmic Hospital, Moorfields, London, and member of the Microscopical Society, examined two lumbar vertebrae and a rib of Mr McBean. The disease began in cancellous bone and produced irregularly sized, round, red projections visible through the periosteum. The cancellous cavities were filled by a red gelatiniform substance consisting of nucleated cells. Most of the cells were round, but some were oval and were 1·5–2 times larger than the average red blood cell. The oval cells frequently included two nuclei, each with a bright nucleolus. Some of the larger and more irregular cells contained three nuclei. A description of the soft matter in the bone 'accords very nearly with the description given by Mr Birkett, in Dr Solly's paper on Mollities Ossium'

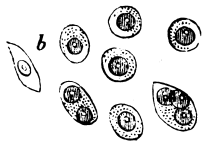


Fig 5. Plasma cells (wood engravings made from drawings by Mr Dalrymple). From Dalrymple (1846).

(Dalrymple, 1846). Dalrymple postulated that the nucleated cells had a limited duration of life in mollities ossium and disintegrated and were 'carried out of the system by the circulation of the kidneys.' Wood engravings made from the very accurate drawings by Dalrymple are consistent with the appearance of myeloma cells (Fig 5) (Dalrymple, 1846). The lumbar vertebrae were scarcely thicker than the intervertebral disks and had lost one-third of their normal bulk. Both Dalrymple and Macintyre believed that the disorder was a malignant disease of bone.

Henry Bence Jones, who had received urine specimens from both Watson and MacIntyre, corroborated the finding that the addition of nitric acid produced a precipitate that was re-dissolved by heat and formed again on cooling. He calculated that the patient excreted more than 60 g/d. Jones concluded that the protein was an oxide of 'albumen', specifically 'hydrated deutoxide of albumen' (Bence Jones, 1848). He postulated that chlorine caused this new protein to form from the albumen. Bence Jones calculated that there were 66·97 parts of 'hydrated deutoxide of albumen' per 1000 parts of urine and that this amount was equal to the proportion of albumen in healthy blood, so that every ounce of urine secreted was equivalent to the protein loss of an equal quantity of blood (Bence Jones, 1847, 1848). It should be noted that the term 'protein' had only been introduced 9 years before in a letter from Berzelius to Mulder and that the word 'albumen' originated about the same time.

Some justification exists for changing the name 'multiple myeloma' to 'McBean's disease with Macintyre's proteinuria.' Although Macintyre described the heat properties of the urine, Bence Jones emphasized its place in the diagnosis of myeloma, for he said, 'I need hardly remark on the importance of seeking for this oxide of albumen in other cases of mollities ossium' (Bence Jones, 1847).

Macintyre died 7 years after reporting his findings. Thomas Watson later became a baronet and physician-in-ordinary to the queen. He was president of the Royal College of Physicians for 5 years and his popular book *Principles and Practice of Physic* earned him the title 'the British Cicero.'

Later cases

In 1867, Hermann Weber (Weber, 1867) reported on a 40-year-old man with mollities ossium who suffered frequent colds and then experienced sternal pain. The sternum became deformed. He also had severe lumbar pain, and movement of his head produced pain in his neck and arms. He died 3.5 months after the onset of pain. Post-mortem examination revealed that the sternum had almost completely been replaced by a reddish–grey substance that had the microscopic appearance of a sarcoma. Two fractures of the sternum were also seen. Several round defects in the skull had been replaced by the same substance as that found in the sternum. Many of the ribs, several vertebrae and parts of the pelvis were involved. Amyloid was found in the kidneys and spleen. William Adams (1872) described a female patient with intense, dull, aching pain in the long bones of the upper and lower extremities. A fracture of the right humerus developed without undue trauma. Fever and weight loss occurred. While the body was being placed on the table for the post-mortem examination, the left humerus and femur 'snapped off without any very great strain having been put upon them' (Adams, 1872). The cortex of the long bone was thinned to one-quarter of normal and the cancellous bone was replaced by a homogeneous, soft, gelatinoid substance. Microscopic examination revealed that the substance consisted of spherical and oval cells containing one oval nucleus, or rarely, two, with a bright nucleolus. The nucleus nearly filled the cell in many instances. Both the liver and the kidneys had lardaceous changes.

The term 'multiple myeloma' was introduced by J. von Rustizky (1873) while he was working in the institute of Professor F. D. von Recklinghausen. The patient, a 47-year-old man, had had a history of a right temple mass that had been increasing in size since May 1872. The fist-sized mass had produced right ophthalmoplegia. The sixth thoracic vertebrae had been involved and total paraplegia from two fingers above the umbilicus had developed. At autopsy, eight separate tumours, soft in consistency and reddish in colour, were found and were designated as 'multiple myelomas.' The right temporal mass was twice the size of an apple and extended into the orbital fossa. A small apple-sized tumour was seen in the right fifth rib, and swelling of the left seventh rib had produced a fracture. A fourth tumour involved the manubrium, and a fifth involved the sixth to eighth thoracic vertebrae and extended into the spinal canal. There were three separate tumours of the right humerus. Microscopic examination revealed round, vesicle-like cells with a single nucleus. The nucleus was located at the periphery close to the cell membrane. Unfortunately, there were no drawings of the cells and von Rustizky did not mention the case report of Macintyre or the work of Bence Jones.

W. Kühne, a pupil of Claude Bernard, described in detail the urinary findings of a patient who he believed had acute osteomalacia (Kühne, 1883). On physical examination, the 40-year-old man had a curvature of the spine and marked tenderness in the cervical and thoracic areas. Paralysis of the seventh nerve developed and he had difficulty swallowing. He was unable to lie on his back and had to remain on his side. He died on 27 August 1869, 9 months after onset of the symptoms. Interestingly, his younger brother died of the same condition (said to be acute osteomalacia of the spine), but there was no autopsy. The specific gravity of the urine was 1·022–1·025 and the urine foamed with shaking. Heating the urine produced turbidity at 40°C and a precipitate at 45°C−50°C. The urine became clear with boiling, but when it was placed in cold water, a precipitate appeared. Kühne isolated the protein and named it 'albumosurie.' He found that the carbon, hydrogen and

Fig 6. Otto Kahler. From Kyle (1996), by permission of Churchill Livingstone. (Courtesy of Dr Heinz Ludwig, Vienna.)

nitrogen levels were similar to those described by Bence Jones. Kühne thought that any difference was as a result of the fact that his preparation was purer than that of Bence Jones.

In 1889, Professor Otto Kahler described a case involving a 46-year-old physician named Dr Loos (Kahler, 1889). Sudden severe pain developed in this patient's right upper thorax in July 1879. The pain recurred 6 months later and was localized to the right third rib. During the next 2 years, intermittent pain, aggravated by exercise, occurred in the ribs, spine, left shoulder, upper arm and right clavicle. Albuminuria was first noted in 1881 and pallor was recognized in 1883. The skeletal pain, made worse by movement, continued to occur intermittently. He had an episode of pneumonia in February 1884. In December 1885, Dr Loos was first seen by Professor Kahler, who noted anaemia, severe kyphosis and tenderness of many bones. When the patient stood, his lower ribs touched the iliac crest. He had recurrent bronchial infections and intermittent haemoptysis. Kahler recognized that the urinary protein had the same characteristics that Bence Jones had described. Kyphosis of the upper thoracic spine increased, and the patient's chin pressed against the sternum and produced a decubitus ulcer. His height decreased monthly until he became dwarf-like. Dr Loos died on 26 August 1887, 8 years after the onset of symptoms. At autopsy, the ribs were soft and could be broken with minimal effort. Soft, grey–reddish masses were noted in the ribs and thoracic vertebrae. Microscopic examination showed large, round cells, consistent with myeloma. Examination of Dr Loos's urine by Huppert (1889) showed that the protein precipitated at 53–59°F, cleared with heating to boiling and then precipitated during cooling. The 24 h urine specimen contained 6·7 g of protein, but there was no albumin. It is of interest that the patient had a high fluid intake and took sodium bicarbonate on a regular basis. This regimen may have helped prevent renal failure.

Otto Kahler, born in 1849 in Prague, was the son of a well-known physician. He received his doctorate of medicine at the University of Prague in 1871 and then worked as a physician in the medical department of Professor Halla (Fig 6). During a sabbatical in Paris, he met two famous French neurologists, Jean Martin Charcot and G. B. A. Duchenne (Duchenne de Boulogne), and worked with Arnold Pick. Kahler became interested in neurology and particularly in neuroanatomy. He contributed to our knowledge of the pathological anatomy of the central nervous system and of tabes dorsalis, localization of partial central oculomotor paralysis and slow compression of the spinal cord. In 1882, he was named Assistant Professor and, in 1886, he became head of the Second Medical Clinic at the German University of Prague following Halla's resignation. In 1889, Kahler was asked to succeed the famous physician Heinrich Bamberger as professor at the University of Vienna (Kraus, 1904). In his inaugural address, on 13 May 1889, Kahler paid tribute to Professor Bamberger and finished his lecture with a statement, 'Ars longa, vita brevis' (the art of medicine is long, life is short) (Feuilleton, 1889). Little did he realize that a tumour of his tongue biopsied in the summer of 1889 would prove to be malignant. The carcinoma of the tongue recurred the following year. A large tumour developed that caused paralysis of the vagus nerve and compression of the oesophagus and main bronchus. Kahler died on 24 January 1893, shortly after his 44th birthday (Nothnagel, 1893). Obituaries and eulogies emphasized his scientific contributions and noted his extreme kindness to his patients, and his excellence as a teacher and researcher. They made no mention of his famous case report. It is interesting that the landmark contributions of Henry Bence Jones and Otto Kahler were not recognized during their lifetimes.

It is probable that the 43-year-old engineer reported by Coats (1891) as having multiple sarcoma of bone actually had multiple myeloma. A large tumour of the sternum had developed 5 years before, along with tumours in the right clavicle, right humerus and left hip. The patient had back pain radiating to the lower extremities and experienced weakness of his legs and, later, a fracture of the right humerus. Post-mortem examination revealed multiple tumours and involvement of the ribs and vertebral bodies. Microscopic examination showed round or polygonal cells with oval nuclei constituting more than half the diameter of the cells.

Probably the first reported case of multiple myeloma in the United States was that published by Herrick & Hektoen (1894). A 40-year-old woman had lumbar pain for

Fig 7. J. F. Heller. From Kyle (1996), by permission of Churchill Livingstone, New York.

16 months before painless nodules developed on the sternum, face and chest. Albuminuria was noted. New nodules developed and she became weak and emaciated. The right clavicle enlarged and then fractured without trauma. The haemoglobin was reported as 45%. An antemortem diagnosis of myeloma was made by the noted surgeon, Dr Christian Fenger. The patient died on 1 July 1892, 18 months after the onset of symptoms. Autopsy revealed tumours involving the sternum, ribs, spine, right clavicle, both humeri and skull. Two of the dorsal vertebral bodies were largely replaced by tumour. Microscopic examination revealed round, lymphoid cells with large nuclei (Herrick & Hektoen, 1894).

F. P. Weber (1898) reported on a 61-year-old man with progressive bone pain and kyphosis who was treated with various agents, including arsenic, but who died of multiple myeloma on 18 January 1897. Microscopic examination showed that the tumour consisted of small, mononuclear round cells. He stated that, in the future, the diagnosis would be 'greatly facilitated by the employment of Röntgen's rays.' Weber *et al* (1903) subsequently described a 50-year-old man with myeloma in whom 15 g of Bence Jones protein was excreted daily. The tumour cells were polyhedral, with an eccentrically placed nucleus. The authors concluded that the bone marrow was the site of production of the Bence Jones protein, that its presence was of 'fatal significance' and that it 'nearly always, if not always, indicates that the patient is suffering from "multiple myeloma"' (Weber *et al*, 1903). Weber & Ledingham (1909) stated that about 40 cases of Bence Jones proteinuria had been reported. They published another case and postulated that Bence Jones protein resulted from the cytoplasmic residua of karyolysed plasma cells.

Geschickter & Copeland (1928) reported on 13 cases of multiple myeloma and reviewed the 412 cases reported in the literature since 1848. They estimated that multiple myeloma accounted for only 0·3% of all malignancies. Today, multiple myeloma constitutes 1% of all malignancies. The peak incidence was at age 55 years and only five cases had occurred under the age of 35 years. The incidence in men was almost twice that in women. The overall survival was 2 years. They emphasized six cardinal features: (i) involvement by tumour of the skeletal trunk, (ii) pathological fractures of ribs, (iii) Bence Jones proteinuria in 65% of cases, (iv) backache with early paraplegia, (v) anaemia in 77% of cases, and (vi) chronic renal disease. They did not recognize abnormalities of blood protein or elevation of the erythrocyte sedimentation rate.

Bayrd & Heck (1947) described 83 patients with histological proof of multiple myeloma who were seen at the Mayo Clinic throughout 1945. Duration of survival ranged from 1 month to 84 months (median 15 months).

Plasma cells

The term 'plasma cell' was used by Waldeyer (1875). He described large cells with granular cytoplasm, but did not mention the presence of the hof or eccentric nuclei. It is probable that he was describing tissue mast cells. Plasma cells were described accurately by Ramón y Cajal in 1890 (Ramón y Cajal, 1896) during study of syphilitic condylomas. He stated that the unstained perinuclear area (hof) contained the Golgi apparatus. He believed that plasma cells were normal constituents of connective tissue. Unna (1891) used the term 'plasma cell' while describing cells seen in the skin of patients with lupus erythematosus, but it is not known whether he actually saw plasma cells. Marschalkó (1895) described the characteristics of plasma cells, including blocked chromatin, eccentric position of the nucleus, a perinuclear pale area (hof) and a spherical or irregular cytoplasm.

Wright (1900a) reported on a 54-year-old man hospitalized on 24 February 1898, with a 1-year history of a tumour of the chest wall and pain in the axilla. Radiographs (Röntgen rays had been discovered only 3 years before) showed changes in the 5th, 6th, 7th, 8th, 11th and 12th ribs posteriorly on the left side and in the 7th and 8th ribs on the right side. Large amounts of albumosuria and anaemia (haemoglobin 60%) were present. Multiple tumours of the ribs and a skull lesion developed. At autopsy, the tumours consisted of cells with eccentric nuclei with intensively staining chromatin masses. Some of the cells were binucleated. Wright emphasized the presence of numerous thin-walled blood vessels in the tumours. He concluded that the tumour cells were plasma cells or immediate descendants of these cells. He also described plasma cells in the normal bone marrow and emphasized that multiple myeloma was 'a neoplasm originating, not in the red marrow cells collectively, but in only one of the varieties of the cells of the red marrow, i.e. in the "plasma cells"' (Wright, 1900b). The diagnosis of multiple myeloma was facilitated by reports of bone-marrow aspiration by Arinkin in 1927 (Arinkin, 1929). Rosenthal & Vogel (1938) reported that only three cases of multiple myeloma had been

recognized at the Mt. Sinai Hospital from 1916 to 1935, but that 13 cases were found in the ensuing 2.5 years. They attributed this marked increase in recognition to the use of sternal punctures in patients with obscure anaemia or skeletal abnormalities and stated that many cases had been missed in the past. They emphasized that hyperproteinaemia, positive formol-gel reaction, Bence Jones proteinuria and abnormal X-rays suggested the diagnosis, which, they said, should be proved by sternal puncture.

Bence Jones proteinuria

A number of other persons were involved in the story of Bence Jones proteinuria. In 1846, J. F. Heller (Fig 7) described a protein in the urine that precipitated when warmed a little above 50°C and then disappeared on further heating. Although Heller did not recognize the precipitation of the protein when the urine was cooled, it is nearly certain that this was Bence Jones protein. He distinguished this new protein from albumin and casein (Heller, 1846). Fleischer (1880) was the first to use the term 'Bence Jones protein.' Kühne (1883) described Bence Jones protein in a patient who died in 1869. The urine of Kahler's patient was described in detail by Huppert (1889).

Bradshaw (1898) found that meals had little or no influence on the amount of Bence Jones proteinuria. There was no nocturnal variation and Bradshaw believed that the rate of excretion was fairly constant throughout the day. In 1917, Jacobson reported on a patient with bone pain, lytic lesions, anaemia, Bence Jones proteinuria, renal failure and large numbers of plasma cells in the bone marrow at autopsy. Heating of the blood during inactivation of complement for the Wassermann test produced a heavy precipitate. The washed precipitate almost entirely dissolved at 100°C and reappeared on cooling. The author postulated that the Bence Jones protein was 'dammed back' in the bloodstream because of renal failure (Jacobson, 1917).

Walters (1921) made a study of three patients and reported that the quantity of Bence Jones proteinuria was independent of the protein intake. Furthermore, no diurnal variation was found. The intravenous injection of Bence Jones protein in one patient appeared to increase the amount of Bence Jones proteinuria. Bence Jones protein was demonstrated in the blood of one patient and in the bronchial secretions of another. Walters concluded that Bence Jones protein was of endogenous origin and was probably derived from blood proteins through the action of the abnormal cells in the bone marrow.

Two distinct groups of Bence Jones proteins were recognized by Bayne-Jones and Wilson (1922). They demonstrated that Bence Jones proteins consisted of a group of similar, but not identical, proteins. They made 12 preparations of Bence Jones proteins from five patients, two of whom had previously been reported on by Walters. Rabbits were immunized by intravenous injection of the Bence Jones protein and precipitin tests were done with the Bence Jones preparations. Two distinct groups were found and were designated group I and group II. Korngold & Lipari (1956), using the Ouchterlony test, identified three different Bence Jones proteins, but two were always found together in the urine of the same patient. They showed that antisera to Bence Jones protein also reacted with myeloma proteins. As a tribute to Korngold and Lipari, the two classes of Bence Jones proteins have been designated kappa and lambda. Using ^{13}C-labelled glycine, Putnam & Hardy (1955) demonstrated that synthesis of the abnormal serum globulin and that of Bence Jones protein were independent processes. Bence Jones protein was found to be rapidly excreted and was thought to be derived from the nitrogen pool rather than from the plasma or a tissue protein precursor.

One hundred and seventeen years after the description of the unique heat properties, Edelman & Gally (1962) showed that the light chains prepared from an IgG monoclonal protein and the Bence Jones protein from the same patient's urine had an identical amino-acid composition, similar spectrofluorometric behaviour, identical appearance on chromatography on carboxymethylcellulose and on starch gel electrophoresis after reduction and alkylation, the same ultracentrifugal pattern, identical thermal solubility and the same molecular weight. These light chains precipitated when heated to between 40°C and 60°C, dissolved on boiling and re-precipitated with cooling to between 40°C and 60°C, which is identical with the heat properties of Bence Jones proteins. Hilschmann & Craig (1965) and Titani *et al* (1966) showed that Bence Jones proteins were not only related to the light chains of gamma globulin, but that each light chain was divided into a 'variable' or V region and a 'constant' or C region. This accounts for the heterogeneity of normal gamma globulins, and for antibody specificity and diversity.

Serum globulins

Von Behring & Kisato (1890) described a specific neutralizing substance (antibody) in the blood of animals immunized with diphtheria and tetanus toxin. These antibodies were found after the injection of most foreign proteins. Although Jacobson had reported Bence Jones protein in the serum in 1917, it was not until 11 years later that Perlzweig *et al* (1928) recognized hyperproteinaemia when they described a patient with multiple myeloma who had 9–11 g of globulin in the serum. The patient also had Bence Jones proteinuria and probably a small amount of Bence Jones protein in the plasma. They also noted that it was almost impossible to obtain serum from clotted blood because the clot failed to retract, even with prolonged centrifugation. Cryoglobulinaemia was recognized by Wintrobe and Buell (1933) and the term 'cryoglobulin' was introduced by Lerner and Watson (1947). The patient described by Lerner and Watson had previously been reported as having allergic purpura with hypersensitivity to cold (Peters & Horton, 1941). von Bonsdorff *et al* (1938) described a patient with cryoglobulinaemia in which the globulins crystallized after exposure to cold for 24 h.

Tiselius used the moving-boundary method of electrophoresis in his doctoral dissertation in 1930 to demonstrate the homogeneity of serum globulins. His manuscript describing the apparatus for electrophoresis (Tiselius, 1968) was not accepted by the journal to which it was first sent, because it was too 'physical'; it was subsequently

published in the *Transactions of the Faraday Society* (Tiselius, 1937a). Later that same year, Tiselius described the separation of serum globulins into three components, which he designated α, β and γ (Tiselius, 1937b). Two years later, Tiselius & Kabat (1939) localized antibody activity to the γ globulin fraction of plasma proteins. They noted that antibodies to *Pneumococcus* type I were found in the area of γ mobility in rabbit serum and that antibodies to pneumococcal organisms migrated between β and γ in horse serum.

Tiselius's moving-boundary electrophoresis apparatus using a U-tube soon became commercially available at a cost of $5000. E. J. Cohn from Harvard University ordered an instrument built in the Uppsala workshop. Cohn and his group did much to popularize electrophoresis through a series of papers on the wartime plasma-protein fractionation programme at Harvard (Putnam, 1993).

Longsworth *et al* (1939) applied electrophoresis to the study of multiple myeloma and demonstrated the tall, narrow-based 'church spire' peak. The Tiselius electrophoresis apparatus was cumbersome and difficult to use; the original commercial models were 20 feet long and 5 feet high and often occupied a separate laboratory room. A single electrophoresis run required a full day and the time and interpretation of an experienced operator (Putnam, 1993). The use of filter paper as a support permitted the separation of protein into distinct zones, which could be stained with various dyes (Kunkel & Tiselius, 1951). During the late 1950s, use of the technically simpler paper electrophoresis spread like an epidemic in clinical laboratories, replacing the more sophisticated moving-boundary electrophoresis that had been the domain of only the most advanced laboratories (Laurell, 1973). Subsequently, cellulose acetate supplanted filter paper (Kohn, 1957). Currently, high-resolution electrophoresis on agarose gel is employed in most laboratories.

Grabar & Williams (1953) described immunoelectrophoresis, which facilitated the diagnosis of multiple myeloma. Immunofixation or direct immunoelectrophoresis was described by Wilson (1964) when he applied antisera on the surface of the agar immediately after the completion of electrophoresis. Immunofixation is useful in the recognition of small monoclonal light chains when none are found with immunoelectrophoresis (Whicher *et al*, 1980). When combined with immunofixation, high-resolution agarose gel electrophoresis is more sensitive than immunoelectrophoresis in detecting small monoclonal proteins (Reichert *et al*, 1982).

Monoclonal proteins were considered abnormal because of their homogeneity, which is seen as a localized band or narrow spike with electrophoresis. Kunkel believed that monoclonal proteins were a product of malignant plasma cells and were the equivalent of normal antibodies produced by normal plasma cells. Thus, monoclonal proteins were said to be representative of a heterogeneous population of gamma globulins. He showed that each heavy chain subclass and light chain type in monoclonal proteins had its counterpart among normal immunoglobulins and also among antibodies. After the discovery of the two types of light chains, kappa and lambda, in monoclonal proteins in a ratio of approximately 2:1, the same light chains were detected in essentially the same ratio among normal immunoglobulins. Similarly, the IgG and IgA subclasses and the IgD class were discovered among myeloma proteins and were then found as normal serum components (Kunkel, 1968). Even the antigenic determinants ('idiotypic specificities' or 'individual antigenics specificities') that are associated with the binding sites were believed to be associated uniquely with myeloma proteins, but have been shown to occur among antibodies (Natvig & Kunkel, 1973). It was recognized that some antibodies migrate in the fast γ region and others in the slow γ region and that some sediment in the ultracentrifuge at 7S and others at 19S. The concept of a family of proteins with antibody activity was not proposed until the late 1950s (Heremans, 1959). Before 1960, the term 'gamma globulin' was used for any protein that migrated in the γ mobility region of the electrophoretic pattern. These gamma globulins are now referred to as immunoglobulins IgG, IgA, IgM, IgD and IgE. The concept of monoclonal vs. polyclonal gammopathies was lucidly presented in the Harvey Lecture series by Waldenström (1961). He clearly described patients with a narrow band of hypergammaglobulinaemia as having a monoclonal protein. Although many of these patients had multiple myeloma, others had no evidence of malignancy and were considered as having 'essential hypergammaglobulinaemia' or benign monoclonal gammopathy. Most physicians now use the term 'monoclonal gammopathy of undetermined significance' because, in some of these patients, multiple myeloma, macroglobulinaemia or a related disorder will eventually develop (Kyle, 1993). Waldenström further correctly regarded the broad band in hypergammaglobulinaemia as a polyclonal increase in proteins. This simple distinction is extremely important clinically because patients with a monoclonal gammopathy already have or may develop a neoplastic process, whereas patients with a polyclonal gammopathy have an inflammatory or reactive cause of their hypergammaglobulinaemia (Waldenström, 1961).

Treatment of multiple myeloma

Alwall (1947) reported that a patient with multiple myeloma had a reduction in serum globulin concentration from 5·9 to 2·2 g/dl, an increase in haemoglobin from 60% to 87%, disappearance of proteinuria and a reduction in bone-marrow plasma cells from 33% to 0% when treated with urethane. For almost 20 years, urethane was the standard treatment for multiple myeloma. Blokhin *et al* (1958) reported benefits in three out of six patients with multiple myeloma who were treated with sarcolysin (L-phenylalanine mustard). Four years later, Bergsagel *et al* (1962) reported significant improvement in eight out of 24 patients with multiple myeloma who were treated with L-phenylalanine mustard (melphalan). Six other patients improved in one or more objective criteria. Holland *et al* (1966) randomized 83 patients with treated or untreated multiple myeloma to receive urethane or a placebo consisting of a cherry- and cola-flavoured syrup. No

difference was seen in objective improvement or in survival in the two treatment groups. In fact, the urethane-treated patients died earlier on average than those treated with placebo. This difference was ascribed to the increased mortality of urethane-treated patients who were azotaemic. Patients with poorer prognostic features had a significantly shorter survival with urethane therapy. Various combinations of alkylating agents have been used for the treatment of multiple myeloma, but there is no evidence that they are superior to melphalan and prednisone (Myeloma Trialists' Collaborative Group, 1998).

Division of Hematology and Internal Medicine,
Mayo Clinic and Mayo Foundation,
Rochester, Minnesota, USA

ROBERT A. KYLE

ACKNOWLEDGMENTS

Portions of this manuscript were modified from Gahrton, G. & Durie, B. G. M. (eds.) (1996) *Multiple Myeloma*, Oxford University Press, New York, and Wiernik, P. H., Canellos, G. P., Ducher, J. P. & Kyle, R. A. (eds) (1996) *Neoplastic Diseases of the Blood*, 3rd edn. Churchill Livingstone, New York. I am indebted to Dr Dietland Wahner-Roedler for translating the German articles.

REFERENCES

Adams, W. (1872) Mollities ossium. *Transactions of the Pathological Society of London*, **23**, 186–188.

Alwall, N. (1947) Urethane and stilbamidine in multiple myeloma: report on two cases. *Lancet*, **2**, 388–389.

Arinkin, M.I. (1929) Die intravitale Untersuchungsmethodik des Knochenmarks. *Folia Haematologie*, **38**, 233–240.

Bayne-Jones, S. & Wilson, D.W. (1922) Immunological reactions of Bence-Jones proteins. II. Differences between Bence-Jones proteins from various sources. *Bulletin of the Johns Hopkins Hospital*, **33**, 119–125.

Bayrd, E.D. & Heck, F.J. (1947) Multiple myeloma: a review of eighty-three proved cases. *Journal of the American Medical Association*, **133**, 147–157.

Bence Jones, H. (1847) Chemical pathology. *Lancet*, **2**, 88–92.

Bence Jones, H. (1848) On a new substance occurring in the urine of a patient with mollities ossium. *Philosophical Transactions of the Royal Society of London (Biology)*, 55–62.

Bergsagel, D.E., Sprague, C.C., Austin, C. & Griffith, K.M. (1962) Evaluation of new chemotherapeutic agents in the treatment of multiple myeloma. IV. L-phenylalanine mustard (NSC-8806). *Cancer Chemotherapy Report*, **21**, 87–99.

Blokhin, N., Larionov, L., Perevodchikova, N., Chebotareva, L. & Merkulova, N. (1958) Clinical experiences with sarcolysin in neoplastic diseases. *Annals of the New York Academy of Sciences*, **68**, 1128–1132.

Bradshaw, T.R. (1898) A case of albumosuria in which the albumose was spontaneously precipitated. *Medical and Chirurgical Transactions of London*, **63**, 259.

Clamp, J.R. (1967) Some aspects of the first recorded case of multiple myeloma. *Lancet*, **2**, 1354–1356.

Coats, J. (1891) A case of multiple sarcoma of bone. *Glasgow Medical Journal*, **36**, 420–426.

Dalrymple, J. (1846) On the microscopical character of mollities ossium. *Dublin Quarterly Journal of Medical Science*, **2**, 85–95.

Edelman, G.M. & Gally, J.A. (1962) The nature of Bence-Jones proteins: chemical similarities to polypeptide chains of myeloma globulins and normal γ-globulins. *Journal of Experimental Medicine*, **116**, 207–227.

Feuilleton (1889) *Wiener Medizinische Wochenschrift*, **20**, 781–784.

Fleischer, R. (1880) XXIV. Ueber das Vorkommen des sogenannten Bence Jones' schen Eiweisskörpers im normalen Knochenmark. *Archiv für Pathologie Anatomie und Physiologie*, **80**, 482–489.

Geschickter, C.F. & Copeland, M.M. (1928) Multiple myeloma. *Archives of Surgery*, **16**, 807–863.

Grabar, P. & Williams, C.A. (1953) Méthode permettant l'étude conjuguée des propriétés électrophorétiques et immunochimiques d'un mélange de protéines. Application au sérum sanguin. *Biochimica et Biophysica Acta*, **10**, 193–194.

Heller, J.F. (1846) Die mikroskopisch-chemisch-pathologische untersuchung. In: *Physikalische Diagnostik und Deren Anwendung in der Medicin, Chirurgie, Oculistik, Otiatrik und Geburtshilfe, Enthaltend: Inspection, Mensuration, Palpation, Percussion und Auscultation, Nebst Einer Kurzen Diagnose der Krankheiten der Athmungs-und Kreislaufsorgane* (ed. by G. von Gaal), p. 576. Braumüller & Seidel, Vienna, Austria.

Heremans, J.F. (1959) Immunochemical studies on protein pathology. The immunoglobulin concept. *Clinica et Chimica Acta*, **4**, 639–646.

Herrick, J.B. & Hektoen, L. (1894) Myeloma: report of a case. *Medical News*, **65**, 239–242.

Hilschmann, N. & Craig, L.C. (1965) Amino acid sequence studies with Bence-Jones proteins. *Proceedings of the National Academy of Sciences of the United States of America*, **53**, 1403–1409.

Holland, J.R., Hosley, H., Scharlau, C., Carbone, P.P., Frei, III, E., Brindley, C.O., Hall, T.C., Shnider, B.I., Gold, G.L., Lasagna, L., Owens, Jr, A.H. & Miller, S.P. (1966) A controlled trial of urethane treatment in multiple myeloma. *Blood*, **27**, 328–342.

Huppert (1889) Ein Fall von Albumosurie. *Prager Medicinische Wochenschrift*, **14**, 35–36.

Jacobson, V.C. (1917) A case of multiple myelomata with chronic nephritis showing Bence-Jones protein in urine and blood serum. *Journal of Urology*, **1**, 167–178.

Kahler, O. (1889) Zur Symptomatologii des multiplen Myleoms; Beobachtung von Albumosurie. *Prager Medicinische Wochenschrift*, **14**, 45.

Kohn, J. (1957) A cellulose acetate supporting medium for zone electrophoresis. *Clinica et Chimica Acta*, **2**, 297–303.

Korngold, L. & Lipari, R. (1956) Multiple-myeloma proteins. III. The antigenic relationship of Bence Jones proteins to normal gamma-globulin and multiple-myeloma serum proteins. *Cancer*, **9**, 262–272.

Kraus, F. (1904) Gedächtnisrede auf Otto Kahler. *Wiener Klinische Wochenschrift*, **27**, 771–774.

Kühne, W. (1883) Ueber Hemialbumose im Harn. *Zeitschrift für Biologie*, **19**, 209–227.

Kunkel, H.G. (1968) The 'abnormality' of myeloma proteins. *Cancer Research*, **28**, 1351–1353.

Kunkel, H.G. & Tiselius, A. (1951) Electrophoresis of proteins on filter paper. *Journal of General Physiology*, **35**, 89–118.

Kyle, R.A. (1993) 'Benign' monoclonal gammopathy—after 20–35 years of follow-up. *Mayo Clinic Proceedings*, **68**, 26–36.

Kyle, R.A. (1996) History of multiple myeloma. In: *Neoplastic Diseases of the Blood* (ed. by P.H. Wiernik, G.P. Canellos, J.P. Duther & R.A. Kyle), 3rd edn, pp. 411–422. Churchill Livingstone, New York, USA.

Laurell, C.B. (1973) Electrophoresis, specific protein assays, or both

in measurement of plasma proteins? *Clinical Chemistry*, **19**, 99–102.

Lerner, A.B. & Watson, C.J. (1947) Studies of cryoglobulins. I. Unusual purpura associated with the presence of a high concentration of cryoglobulin (cold precipitable serum globulin). *American Journal of Medical Science*, **214**, 410–415.

Longsworth, L.G., Shedlovsky, T. & MacInnes, D.A. (1939) Electrophoretic patterns of normal and pathological human blood serum and plasma. *Journal of Experimental Medicine*, **70**, 399–413.

Macintyre, W. (1850) Case of mollities and fragilitas ossium, accompanied with urine strongly charged with animal matter. *Medical and Chirurgical Transactions of London*, **33**, 211–232.

Marschalkó, T. (1895) Ueber die sogenannten Plasmazellen, ein Beitrag zur Kenntniss der Herkunft der entzündlichen Infiltrationszellen. *Archives of Dermatology and Syphilology*, **30**, 241.

Morse, D., Dailey, R.C. & Bunn, J. (1974) Prehistoric multiple myeloma. *Bulletin of the New York Academy of Medicine*, **50**, 447–458.

Myeloma Trialists' Collaborative Group (1998) Combination chemotherapy versus melphalan plus prednisone as treatment for multiple myeloma: an overview of 6,633 patients from 27 randomized trials. *Journal of Clinical Oncology*, **16**, 3832–3842.

Natvig, J.B. & Kunkel, H.G. (1973) Human immunoglobulins: classes, subclasses, genetic variants, and idiotypes. *Advances in Immunology*, **16**, 1–59.

Nothnagel (1893) Hofrath Otto Kahler. *Wiener Klinische Wochenschrift*, **6**, 79–80.

Perlzweig, W.A., Delrue, G. & Geschickter, C. (1928) Hyperproteinemia associated with multiple myelomas: report of an unusual case. *Journal of the American Medical Association*, **90**, 755–757.

Peters, G.A. & Horton, B.T. (1941) Allergic purpura with special reference to hypersensitiveness to cold. *Proceedings of the Staff Meetings of the Mayo Clinic*, **16**, 631–636.

Putnam, F.W. (1993) Alpha-, beta-, gamma-globulin—Arne Tiselius and the advent of electrophoresis. *Perspectives on Biology and Medicine*, **36**, 323–337.

Putnam, F.W. & Hardy, S. (1955) Proteins in multiple myeloma. III. Origin of Bence-Jones protein. *Journal of Biological Chemistry*, **212**, 361–369.

Ramón y Cajal, S. (1896) Estudios histológicos sobre los tumores epiteliales. *Revista de Trimest Microgr*, **1**, 83.

Reichert, C.M., Everett, Jr, D.F., Nadler, P.I. & Papadopoulos, N.M. (1982) High-resolution zone electrophoresis, combined with immunofixation, in the detection of an occult myeloma paraprotein. *Clinical Chemistry*, **28**, 2312–2313.

Rosenthal, N. & Vogel, P. (1938) Value of the sternal puncture in the diagnosis of multiple myeloma. *Journal of Mount Sinai Hospital*, **4**, 1001–1019.

Singhal, S., Mehta, J., Desikan, R., Ayers, D., Roberson, P., Eddlemon, P., Munshi, N., Anaissie, E., Wilson, C., Dhodapkar, M., Zeddis, J. & Barlogie, B. (1999) Antitumor activity of thalidomide in refractory multiple myeloma. *New England Journal of Medicine*, **341**, 1565–1571.

Solly, S. (1844) Remarks on the pathology of mollities ossium with cases. *Medical and Chirurgical Transactions of London*, **27**, 435–461.

Tiselius, A. (1937a) A new apparatus for electrophoretic analysis of colloidal mixtures. *Transactions of the Faraday Society*, **33**, 524.

Tiselius, A. (1937b) Electrophoresis of serum globulin. II. Electrophoretic analysis of normal and immune sera. *Biochemistry Journal*, **31**, 1464–1477.

Tiselius, A. (1968) Reflections from both sides of the counter. *Annual Review of Biochemistry*, **37**, 1–24.

Tiselius, A. & Kabat, E.A. (1939) Electrophoretic study of immune sera and purified antibody preparations. *Journal of Experimental Medicine*, **69**, 119–131.

Titani, K., Whitley, Jr, E. & Putnam, F.W. (1966) Immunoglobulin structure: variation in the sequence of Bence Jones proteins. *Science*, **152**, 1513–1516.

Unna, P.G. (1891) Über plasmazellen, insbesondere beim Lupus. *Monattsschrift für Praktische Dermatologie*, **12**, 296.

von Behring, & Kisato (1890) Ueber das Zustandekommen der Diphtherie-Immunität und der Tetanus-Immunität bei Thieren. *Deutsche Medicinische Wochenschrift*, **49**, 1113–1114.

von Bonsdorff, B., Groth, H. & Packalén, T. (1938) On the presence of a high-molecular crystallizable protein in the blood serum in myeloma. *Folia Haematology*, **59**, 184–208.

von Rustizky, J. (1873) Multiples myelom. *Deutsche Zeitschrift für Chirurgie*, **3**, 162–172.

Waldenström, J. (1961) Studies on conditions associated with disturbed gamma globulin formation (gammopathies). *Harvey Lectures*, **56**, 211–231.

Waldeyer, W. (1875) Ueber Bindegewebszellen. *Archiv für Microbiologie und Anatomie*, **11**, 176–194.

Walters, W. (1921) Bence-Jones proteinuria: a report of three cases with metabolic studies. *Journal of the American Medical Association*, **76**, 641–645.

Weber, F.P. (1898) General lymphadenomatosis of bones, one form of 'multiple myeloma'. *Journal of Pathology*, **5**, 59–64.

Weber, F.P. & Ledingham, J.C.G. (1909) A note on the histology of a case of myelomatosis (multiple myeloma) with Bence-Jones protein in the urine (myelopathic albumosuria). *Proceedings of the Royal Society of Medicine*, **2**, 193–206.

Weber, F.P., Hutchison, R. & MacLeod, J.J.R. (1903) Multiple myeloma (myelomatosis), with Bence-Jones proteid in the urine: (myelopathic, albumosuria of Bradshaw, Kahler's disease). *American Journal of Medical Science*, **126**, 644–665.

Weber, H. (1867) Mollities ossium, doubtful whether carcinomatous or syphilitic. *Transactions of the Pathological Society of London*, **18**, 206–210.

Whicher, J.T., Hawkins, L. & Higginson, J. (1980) Clinical applications of immunofixation: a more sensitive technique for the detection of Bence Jones protein. *Journal of Clinical Pathology*, **33**, 779–780.

Wilson, A.T. (1964) Direct immunoelectrophoresis. *Journal of Immunology*, **92**, 431–434.

Wintrobe, M.M. & Buell, M.V. (1933) Hyperproteinemia associated with multiple myeloma, with report of a case in which an extraordinary hyperproteinemia was associated with thrombosis of the retinal veins and symptoms suggesting Raynaud's disease. *Bulletin of the Johns Hopkins Hospital*, **52**, 156–165.

Wright, J.H. (1900a) A case of multiple myeloma. *Transactions of the Association of American Physicians*, **15**, 137–147.

Wright, J.H. (1900b) A case of multiple myeloma. *Johns Hopkins Hospital Report*, **9**, 359–366.

Keywords: multiple myeloma, protein, proteinuria, plasma cells, gammopathy.