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Articoli/*Articles*

PARAPROTEINEMIAS AND PLASMA CELL DYSCRASIAS: A HISTORY LONG 150 YEARS

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SUMMARY

Bence Jones proteinuria, one of the main clinical manifestations of multiple myeloma, was first recognized and described 150 years ago. From 1847 until nowadays many advances have occurred in biology, epidemiology, treatment, and prognosis of the plasma cell dyscrasias. In the present note, the most important milestones on the road to the recognition of these diseases are traced, from Henry Bence Jones, the physician who first emphasized the presence in the urine of the protein that bears his name, to the more recent acquisitions in their biology and therapy.

1. The first cases of plasma cell dyscrasias

Saturday, November 1, 1845.
Dear Doctor Bence 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?[1]

This short note and a sample of urine were sent by a leading physician of London, Dr. Thomas Watson, maybe a poor assistant of Dr. Mac Intyre, to Dr. Henry Bence Jones, a 31-year-old

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physician at Saint George's Hospital of London, who had already established a reputation as a chemical pathologist. The patient who contributed the urine has been identified by the inventive sleuthing of John Clamp as Thomas Alexander Mac Bean, suffering from emaciation with severe pain in the ribs and other parts of the axial skeleton.

Many of the important clinical features of plasma cell myeloma were described in a series of four paper by Henry Bence Jones[1], John Dalrymple[2], and William Mac Intyre[3] between 1846 and 1850.

Mr. Mac Bean, 44 years of age and a rich highly respectable grocer and tradesman in London, was seen in consultation on October 30th, 1845, by Dr. William MacIntyre[4], a 53-year-old Harley Street consultant and physician to the Western General Dispensary, Saint Marylebone in London. The patient had taken a vacation in the country in September 1844 to regain his strength. While vaulting out of an underground cavern on his vacation, he had *instantly felt as if something had snapped or given way within the chest, and for some minutes he lay in intense agony, unable to stir*[5]. He was subsequently treated by his physician by means of the removal of a pound of blood and the application of leeches on the chest which resulted in considerable weakness but alleviation of his pain. He developed pleuritic pain in the spring of 1845 which did not respond to cupping or therapeutical bleedings. The use of steels and quinine therapy resulted in rapid improvement and by mid summer he was capable to travel to Scotland where *he was capable of taking active exercise on foot during the greater part of the day, bounding over the hills, to use his own expression, as nimbly as any of his companions*[6]. Unfortunately, his pain recurred and he died on January 1, 1846. The final diagnosis was *atrophia by albuminuria,* and at post-mortem examination, the ribs were soft, readily broken, and easily cut by the knife. The anterior of the ribs was filled with a *gelatiniform substance* which consisted mainly of round or oval cells containing one or two nuclei, and larger than the normal peripheral blood cells. Wood engravings made from the drawings of Dr. Dalrymple[7], surgeon at the Royal Ophthalmic Hospital, Morfield, are consistent with the appearance of plasma cells.

As with many *first reported cases*, earlier examples can be found in literature. It is most likely that Sara Newbury, a 39-year-old woman, the second patient described by Solly[8] in 1844, had multiple myeloma. She developed severe back pain four years before her death. She felt excruciating pain *just as if her thighs were being broken into a thousand pieces* [9] while her husband was lifting her from the fireplace to carry her to bed. He felt her thighs give way, and she was unable to walk thereafter. Fractures of the clavicles and right humerus occurred. She was hospitalized at Saint Thomas Hospital of London and was treated with an infusion of orange-peel and a rhubarb pill when necessary as well as an opiate at night for controlling the intense pain. She died on April 20th, 1844, and an autopsy revealed a soft, reddish gelatinous substance in the bones. Solly examined the red matter under the microscope with Mr. Birkett of Guy's Hospital of London who found the cells had a *clear oval outline enclosing one bright central nucleus, rarely two, never more*[10]. Dalrymple[11] stated that the microscope appearance reported by Mr. Birkett *accords very nearly* with his description of Mac Bean's bone marrow.

2. *Bence Jones proteinuria*

The unusual characteristics of the urinary protein, consisting in the precipitation at 40-58°C, but redissolution on further heatings, only to reappear once more on cooling, were confirmed by Dr. Henry Bence Jones who observed also that the addition of nitric acid produced a precipitate which was redissolved by heat and formed again upon cooling. He calculated that the patient excreted more than 60 grams of the protein daily. He concluded erroneously that the proteins was *hydrated deutoxide of albumen*[12], an error not corrected for nearly a century. Bence Jones reported the findings to the Royal College of Physicians in 1847[13] and published a more detailed account of his investigations in 1848[14].

Clamp has also analyzed the contributions of the three physicians - Bence Jones, Dalrymple, Mac Intyre - to the discovery of the new entity, named animal matter, in the urine, and con-

cluded that the unique heat-coagulation properties of Mac Bean's urinary protein were discovered by Mac Intyre, and not by Bence Jones. Notwithstanding this, the relevance of Bence Jones consists in the emphasization of the place of proteinuria in the diagnosis of the cases with *mollities ossium* for he said[15] *I need hardly remark on the importance of seeking for this oxide of albumen in other cases of mollities ossium.*

Henry Bence Jones was born on December 31th, 1813 in Yoxford, Suffolk, England, at the home of his maternal grandfather, the Reverend Mr. Bence. He attended Harrow where he excelled in sports and was on the cricket team. Proceeding from Harrow to Cambridge, he entered Trinity College in Dublin, where he was a member of the boating crew. He attended the Divinity Lectures in preparation for ordination but decided against the career of a clergyman[16] after taking his arts degree in January 1836. Instead, he became a pupil of Mr. John Hammerton, apothecary at Saint George's Hospital of London. He enrolled as a full-time medical student after 18 months. During this time, he learned the use of the stethoscope, a relatively new instrument for the physicians. In order to acquire a better knowledge of chemistry[17], he became a private pupil of Professor Thomas Graham at University College of London. As a part of his studies, he was required to examine a renal calculus from the University College Museum; the stone consisted of cystine and its chemical examination led to his first scientific publication. Bence Jones spent six months during 1841 at Giesen, Germany, studying chemistry with Justus Von Liebig, the most famous chemist of the proteins of the time. This fact could explain the interest of Bence Jones for the study of protein and because the urine sample of Mr. Mac Bean was sent to him. He was elected a Fellow of the Royal Society of Physicians in 1846. Dr. Bence Jones was an accomplished physician and acquired a large and remunerative practice, and his profits reached 7,400 pound from April 5, 1864 to April 5, 1865[18]. His patients included the German chemist August Wilhelm Hofman and the English biologist Thomas Huxley, but the most famous of his patients was indoubtly Charles Darwin, the great naturalist, whom he treated with a diet that *half starved him to death*[19]. The inventor of the ophthalmoscope,

Hermann von Helmholtz, had a great deal of respect for Bence Jones. Dr. Bence Jones was well acquainted with Florence Nightingale and had a high opinion of her. He sought her advice about a project that he was considering for reforming the training of the nurses in the hospitals of London. He was also influential in the establishment of the Hospital for Sick Children on Gereat Ormond Street on whose board he served. As a student, Bence Jones attended lectures of the physicist, Michael Faraday, at the Royal Institution. He subsequently became a friend and physician to Faraday and in 1870 published a well-received two-volume biography of the prominent physicist. Dr. Bence Jones was the first to describe xanthine crystals in the urine; he emphasized the frequency of diabetes mellitus in the older population; his publication of a series of lectures on the *application of chemistry and medicine to pathology and therapeutics* was well received; he believed that physicians would be better served if they acquired knowledge about chemistry and physics rather than Latin and Greek studies. In 1861, he noticed frequent heart palpitations and diagnosed rheumatic heart disease with his stethoscope; he had had an episode of rheumatic fever in 1839; he developed a pleural effusion in 1866 and in early 1873 gave up his practice because of hepatomegaly, ascites, and anasarca. He died at his home at 84 Brook Street in London of congestive heart failure on April 20, 1873. Although the two known obituaries[20] of Dr. Bence Jones described his works on renal stones, diabetes mellitus, and malignant and tubercolous involvement of the kidney as well as his emphasis on the value of microscopical analysis of the urine, there was no mention of his paper on the unique urinary protein that will bear his name. Interestingly, Henry Bence Jones did not use the hyphen in his name and it does not appear in any of his more than 40 papers and books. The hyphen appeared and was added by his descendants more than a half century after his death. Therefore, it is correct to omit the hyphen when writing Bence Jones.

Several other scientists have been involved in the history of Bence Jones proteinuria. In 1846, J.F.Heller[21] had described a protein in the urine which precipitated when warmed a little above 50°C and disappeared on further heating; although he did not

recognize the precipitation of the protein when the urine was cooled, it is most likely that this was Bence Jones protein. Acting in advance of his times, Heller distinguished this protein from both albumin and casein, but its original observation was neglected for many years. During the second half of the XIX century, Bence Jones proteinuria was thought to be due to an unrelated malignancy. Therefore, in 1869 Kuhne (cited by Kyle,1991) proposed the term *albumosuria*, and the connection between multiple myeloma and this particular proteinuria was not recognized until 1889, when Kahler[22] established the link between Bence Jones proteinuria and a recently discovered disease called *multiple myeloma*. It is noteworthy that the same material was named *hydrated deutoxide of albumen* by Bence Jones in 1847[23], *animal matter* by MacIntyre three years later[24], and still *almosuria* by Kuhne in 1969 (cited by Kyle,1991). At that time, there was a great confusion on the nature and types of protein, term proposed first by Berzelius in a letter to Mulder in 1838 and used for the first time by Mulder in 1840s, to indicate a material present in both vegetable and animal tissue, sharing the property to be precipitated by heating and redissolved by addition of acids. In 1841, the year in which Bence Jones was in Giesen in his laboratory, the great chemist of proteins Liebig stated that there was only one kind of proteins, being the same substance in all cases, and only in 1845 he changed his opinion. It is possible that his pupil Bence Jones and the others physicians until the beginning of XXth century were still in idea of *only kind of protein* and they believed that the substance present in the urine of Mr. Mac Bean and in the other patients was protein (albumen) modified in some way, perhaps by oxidation. Bence Jones and the others emphasized in their papers the presence of this material in urine, but did not suppose that this material was a new, particular, pathological protein.

The connection between myeloma cells and the unusual Bence Jones protein was further demonstrated by Parkes Weber (cited by Quaglino & Haihoe,1992), who showed in 1910 that material with the characteristic heat precipitation and solubility features of that protein could be extracted from the bone tumors in myeloma. Although similar proteins were also detected by Jacobson in 1917 (cited by Quaglino & Haihoe, 1992) in the serum

of a myeloma patient with renal failure, it was only after the introduction of moving boundary electrophoresis that a clearly abnormal protein appeared sometimes to be present in the urine and appeared invariably in the serum of the patients with multiple myeloma. Two distinct groups of Bence Jones proteins were recognized by Bayne-Jones and Wilson[25] in 1922. In 1956, Korngold and Lipari[26] demonstrated a relationship between Bence Jones protein and the serum proteins of multiple myeloma. It is a tribute to Korngold and Lipari that the two major classes of Bence Jones protein have been designated by the respective Greek letters of their initials, *kappa* and *lambda*. In 1962, Edelman and Gally[27] demonstrated that the light chains prepared from an IgG myeloma protein and the Bence Jones protein from the urine of the same patient were identical.

3. *Multiple myeloma*

In 1867, Herman Weber[28] described a 40-year-old man with severe sternal and lumbar pain. At autopsy, the sternum was almost entirely replaced by a grayish red substance with a microscopical appearance of a *sarcoma*; the skull, the ribs, several vertebrae, and the pelvis were also involved. The term *multiple myeloma* was first introduced by Von Rustisky[29], Russian physician who worked in the laboratory of Von Recklinghausen, in 1873, when, during an autopsy, he found eight separate tumors of the bone marrow. The patient had developed during life paraplegia caused by a tumor involving the sixth and the eighth thoracic vertebrae. The cells of the tumors were described as round with a nucleus located in the peripheral area near the cell membrane. Von Rustisky[30] called this entity *multiple myeloma* to emphasize the observation that the numerous bone marrow tumors - *multiple* - were the main characteristic of the disease, and that the tumors derived from bone marrow - *mielòs* - and not from bone, such as it is erroneously believed before his paper, when the disease was called *mollities* and *fragilitas* ossium, that indoubtly at that time indicated a great bulk of diseases, including osyteomalacia, rickets, multiple tumor metastates and so on.

One of the most striking cases of multiple myeloma was that of Dr. Loos, a 46-year-old physician, who developed a chest pain aggravated by breathing in July 1879. Intermittent pain aggravated by exercise occurred in multiple bones. Albuminuria was noticed in September 1881 and pallor was seen in 1883. Two years later he was seen by Dr. Otto Kahler[31]: the physician noted that the lower ribs of the patient touched the iliac crest. His severe kyphosis increased and his chin pressed against the sternum producing a decubitus ulcer. He died on August 26th, 1887, and at autopsy the ribs were soft and contained numerous gray-reddish masses. Microscopical examination revealed the presence of large round cells consistent with multiple myeloma. Kahler[32] recognized that the urinary protein of the patient had the same characteristics as that described by Bence Jones[33]; the conclusive diagnosis was *severe osteoporosis secondary to the proliferation of large round cells*.

Otto Kahler, born in 1849, received his Medical Doctor degree from the University of Prague. He spent a sabbatical year in Paris where he became interested in neurology and anatomy. He contributed to the pathological anatomy of the central nervous system and to tabes dorsalis. Unfortunately, he died of carcinoma of the tongue shortly after his 44th birthday in 1893. Although the work of Kahler, who published a detailed review of multiple myeloma in 1889[34], aroused considerable interest in all Europe, where the disease is still often referred to as *Kahler's disease*, his obituaries and eulogies made no mention of his famous paper.

It is not surprising that the land mark contributions by Bence Jones and Kahler were not recognized during their lifetimes.

In 1897, Bozzolo gave a further detailed description of the disease in a lecture, published in *extenso* the year after[35], at the 2nd National Congress of Italian Society of Internal Medicine, and proposed the name of *Kahler's disease*; his name was added, at least in Italy, to that of Kahler in the eponym of myeloma.

The term *plasma cell was* coined by Waldayer[36] in 1875, describing first very large, basophilic, round or oval bone marrow cell with eccentric large nucleus, but it is most likely that he was describing tissue mast cells and not plasma cells. Ramòn y

Cajal[37] in 1890 and Unna[38] in 1891, working independently, described accurately the morphology of the plasma cells. Ramòn y Cajal, during the study on syphilitic condylomas[39], and Unna during the study on cutaneous lupus[40], recognized that the cells under observation were quite different from those known and that the unstained perinuclear area - *hof* -, successively identified containing the Golgi apparatus. In 1895, Marschalko[41] described the essential characteristics of plasma cells; still to day the mature, well-differentiated plasma cells are called Marschalk cells. Since the tumor cells of myeloma are not commonly conspicuous in the peripheral blood and since the techniques for aspirating bone marrow were not developed until the 1920s, it is not surprising that the origin and the nature of the myeloma cells remained in doubt for many years after the disease itself had been recognized, evidence being largely obtained from autopsy specimens with variable degenerative changes. More than 60 well-defined cases of the disease were known, when in 1900 Wright, in two identical papers[42], reported a patient with multiple myeloma and, observing the close resemblance of the tumoral cells with those of bone marrow, stated that the tumor consisted of plasma cells; he proposed the term *plasmacytoma*[43] to emphasize the neoplastic proliferation of this cellular lineage. On the other hand, for many years after this elegant demonstration, there was still confusion, with supposed examples of erythroblastic or myeloblastic myelomas as well as plasmacytic ones being reported. In 1903 Foà (cited by Di Guglielmo,1954) reported the first case of myeloma with the presence of plasma cells in the peripheral blood; there are several evidences that this is the first case of plasma cell leukemia. In 1904 Ribbert (cited by Di Guglielmo,1954) published a case in which the tumoral cells were identified as *erythroblasts* and the term erythroblastoma was proposed. In 1906 Lumbarsch (cited by Di Guglielmo,1954), on the basis of cytological and histological appearance of bone marrow, proposed to separate the myeloma into *lymphocytoma, erythroblastoma, plasmacytoma* and *leukocytoma*. This was the first attempt of classifying morphologically the disease. Successively, with the introduction of the bone marrow cytoaspirate for the diagnosis of the hematological

disorders[44], only the plasma cells were considered the tumoral cells from which myeloma arises. The mistake was probably due to the lack of adequate preparation by apposition or by smear of the histological and cytological material, or to *post-mortem* changes in the cells. The first cases of myeloma diagnosed in vivo only on the features of the bone marrow cytoaspirate[45] were in 1931. An useful cytological classification, based only on the plasma cell morphology, has been proposed by Bayrd[46] in 1948, and it is still widespreadly used.

4. Paraproteinemias

The increased erythrocyte sedimentation rate in multiple myeloma was noted by Ellinger[47] in 1899; he emphasized also the elevated urinary excretion of protein and proposed the eponym *Bence Jones proteinuria,* in honor of the first author who described this particular aspect of the disease. In 1928, Perlzweig and collegues[48] reported hyperproteinemia when they described a patient with multiple myeloma who had 9.0 to 11.0 grams of globulin in his serum. Five years later, Wintrobe and Buell[49] observed that the proteins of some patients with multiple myeloma precipitated when exposed to cold, and called this unusual serum proteins *cryoglobulins*. After the introduction of the studies of the serum proteins by means of ultracentrifugation, in 1937 Tiselius[50] used an electrophoretic technique to separate serum globulins into three components which he designated *alpha, beta* and *gamma*. Two year later, Longsworth and collegues[51] demonstrated the tall, narrow-based *church-spire* peak in the serum of patients with multiple myeloma. Subsequently, filter paper and then cellulose acetate and agarose have been used as the supporting medium (zone electrophoresis). In 1953, Grabar and Williams[52] described immunoelectrophoresis which has facilitated the diagnosis of multiple myeloma. In 1980 was tested first the immunofixation[53]; this technique is more sensitive than immunoelectrophoresis and is very helpful in the recognition of small monoclonal light chains when none are found with immunoelectrophoresis.

With the introduction in the 1940s of the term *paraproteins* and *paraproteinemias* by Apitz[54] to indicate the presence of a monoclonal proteic component in the serum and in the urine, and the diseases characterized by the presence of such proteins, respectively, and the subsequent widespread use of electrophoresis techniques in the analysis of clinical specimens, it soon became apparent that paraproteins were gamma-globulins, manifest on electrophoresis as a sharply concentrated narrow band and thus contrasting with the normal broad gamma-globulin band, established around the same time to be constituted chiefly of the proteins with specific antibody activity, the immunoglobulins. In fact, Bing and Plum[55] in 1937 have correlated the plasma cells with the production of the circulating serum globulins. At that time there were many controversies on the nature of antibodies; it must be remembered that even in 1938 Marrack[56] stated in a report to the Medical Research Council: *controversy concerning the nature of antibodies centres round the question whether they are protein or not*. This relationship had been clearly demonstrated in 1948[57], and confirmed by others successively, but it was only in the 1960s that it was definitely demonstrated by the identification of antibodies into plasma cells by electron microscopy[58].

These observations suggested that each paraprotein represented a neoplastic monoclonal expansion of production of a single immunoglobulin, and raised the possibility that plasma cells might have a special role in antibody formation. The availability of such monoclonal immunoglobulins in large quantities from the serum of myeloma patients greatly facilitated the analytical researches which led, in the 1950s and later, to the elucidation of the molecular structure of the immunoglobulins in relation to their function, their separation into different subclasses, and in due course to an understanding of the genetic mechanisms operating in their production. In a real sense, the study of myeloma proteins provided the single most important key to immunological advances during the 20 years from 1950 to onwards.

Only in the 1970s, a definitive nosological systematization of plasma cell dyscrasias, especially multiple myeloma, was achieved.

Hobbs[59] proposed for these diseases the term *immunocytoma*, in order to indicate a tumoral expression of the immunocompetent cells. Salmon and Seligmann[60] established definitively that multiple myeloma and related diseases are neoplasias of a cell of the B-lymphocyte lineage evolved to the final stage of plasma cell; this cell proliferates until forming a large population of similar cells; this population is believed to be monoclonal, that is, derived from a single cell, because the cell itself produce a homogeneous immunoglobulin composed of a single class of heavy chain and one type of light chain, or their fragments; the proliferation occurs in three different phases: the first or polyclonal phase is characterized by an expansion of all immunocompetent cell lineages, the second or premonoclonal phase by a controlled and benign expansion of a single cellular clone, the third or monoclonal phase by an uncontrolled and malignant proliferation of the same cellular clone.

5. *Amyloidosis*

Of some interest is also the history of an important complication of multiple myeloma, amyloidosis, that occurs in about 15% of the patients. The name *amyloidosis* was introduced by Virchow in 1854 (cited by Cohen,1992) in the belief that the deposited material, which reacted with iodine, was a starch. Autopsy data consistent with the findings of amyloid were reported by Fontanus as early as 1639. Enlargement and induration of the liver, which may be have represented stigmata of amyloidosis, were mentioned in the 17th and 18th centuries by illustrious authors such as Glisson, Portal and Malpighi. One of the early problems was that enlarged livers were referred to as waxy or lardaceous, and there was semantic arguments about the meaning of these terms. Virchow focused on the cerebral corpora amylacea, and named them *amyloid*; he also noted the cellulose-like nature of the *sago grains* in the *sago spleens* described by Christensen, but he did not at first observe *cellulose* in lardaceous livers. Meckel, Virchow's successor at Charite Hospital in Berlin, applied the iodine sulphuric acid test to lardaceous organs and preferred the term *cholesterin* when the results were positive.

The substantial enlargement and lard-like waxing of the infiltrated liver and kidneys in the systemic disease, and particularly the globular white deposits against the red background of the characteristic sago spleen, had already been described by Rokitansky in 1842[61], but at this time the disorder appeared always to be a secondary manifestation of chronic infections, notably osteomyelitis, syphilis or tuberculosis. Wilks in 1856[62], first recognized that amyloid deposition might occur in the absence of predisposing chronic infection. A case of amyloidosis associated with multiple myeloma was casually noted in 1867, but the first clear report of primary amyloidosis has been attributed to Wild and to Soyka. Some years elapsed before the intimate association with myeloma was noted by Adams and Dowse in 1872 (cited by Cohen,1992). Although the iodine sulphuric stain was useful, it was replaced in 1875 by the metachromatic stain methyl violet, but the histopathology of amyloid were significantly clarified in 1922, when Benhold (cited by Cohen,1992) introduced Congo red, first as a diagnostic test and then as a histological stain. It remains the most useful diagnostic test for the presence of amyloid when used in combination with polarization microscopy.

The disagreements in literature about the terms *fatty, lardaceous, cholesterin*, and then *starch, cellulose,* and *amyloid* prolonged centuries-old debates. Although Freidreich and Kekule[63] demonstrated an absence of carbohydrate in amyloid deposits and they established, as long ago as 1859, that the pathological deposits were of protein - *albuminous* - rather than starch, 70 years passed before a connection with Bence Jones protein was suggested by Magnus-Levy[64] in 1931, and a century before the fibrillary nature of amyloid and the involvement of the immunoglobulins and their light chains in its pathogenesis were determined, and methods devised for its isolation in relatively pure form, suitable for more detailed chemical analysis[65]. By 1964, the amyloid material sometimes occurring in multiple myeloma had been shown to consist of monoclonal immunoglobulin light chains or fragments thereof[66], and a similar constitution was later established for the amyloid of the paraproteinemic plasma cell dyscrasias, including macroglobulinemia and lymphopla-

smacytoid immunocytoma, and that develops in some case of monoclonal gammopathy of undetermined significance[67].

Moreover, although Zenoni[68] in the beginning of this century postulated already the possibility of the existence of two forms of amyloids, either primary or secondary, and Apitz[69] in 1940 described the increased bone marrow plasma cell in primary amyloidosis and suggested the term para-amyloidosis to indicate the form secondary to *paraproteinemias*, only in the recent ten years the deposit in reactive amyloid, secondary to recurrent or chronic infection or to certain neoplastic diseases, was shown to differ in constitution, as did the material of the uncommon heredofamilial systemic amyloidoses, and amyloidosis in which the deposited material was of immunoglobulins light chain derivation was recognized as a separate entity.

6. Other plasma cell dyscrasias

Before reporting some notices of the developmental history of treatment, it is not possible to conclude the history of multiple myeloma and paraproteinemias without recalling Prof. Jan G. Waldenström. He was born in Stockholm, Sweden, the son of Prof. Henning Waldenström, and educated at the University of Uppsala. He was appointed Professor of Theoretical Medicine at Uppsala in 1947. Three years later he became Professor of Practical Medicine at the University of Lund and served as Physician in Chief at the General Hospital of Malmö, Although his earliest work was in acute porphyria, his major contributions have been in the area of the plasma cell proliferative diseases. In 1943, he described a new entity[70] - *purpura hyperglobulinemica* - which is now recognized as benign hyper-gammaglobulinemic purpura of Waldenström. He noted the recurrence of purpura of the lower extremities in young women, the presence of high erythrocyte sedimentation rate, and large amount of gamma-globulin in the form of a broad-based or polyclonal increase in this condition. He postulated that the *derangement in globulin metabolism* was responsible for the syndrome. He also recognized a combination of cirrhosis, elevated erythrocyte sedimentation rate, and hyper-

globulinemia, which was subsequently described by Henry Kunkel. The next year, Waldenström[71] described two patients with oronasal bleeding, severe normochromic anemia, low serum albumin, and an excess of high molecular weight plasma protein. In collaboration with K.O.Petersen, he demonstrated that these gamma-globulins had a molecular weight of approximately 1,000,000 daltons. He believed that these represented a *giant molecule* and were not simply the result of the aggregation of smaller proteins. This new entity is widely recognized as *Waldenström's macroglobulinemia*. His most important contribution was the concept of monoclonal and polyclonal gammopathies which was lucidly presented in his Harvey Lecture of 1961[72]. This differentiation is of great practical importance, since patients with a monoclonal proliferation of plasma cells have either a neoplastic process or a potentially malignant proliferation, whereas the patients with a polyclonal increase in immunoglobulins have an inflammatory or reactive, rarely a neoplastic, process.

The same Author[73] had applied in 1952 the name *essential hyperglobulinemia* to an abnormality characterized by the presence of a monoclonal spike in the gamma region detected through routine electrophoretic analysis of sera, and unaccompanied by related symptoms, and noted that the spike generally remained of constant size over long periods, suggesting a static, relatively benign process. Indeed, alternative names commonly used for this relatively frequent abnormality included *benign, idiopathic, non-myelomatous, lanthanic*, and *asymptomatic monoclonal gammopathy*. Later studies and longer follow-up revealed that this condition sometimes progressed to florid myeloma, macroglobulinemia or amyloidosis, and this development could not be predicted in advance at the time of first diagnosis. Therefore, Kyle[74] considered the term *benign* as a misnomer, and suggested in 1984 that a more appropriate name would be *monoclonal gammopathy of undetermined significance,* and this term became widely adopted.

Finally, the last group of diseases generally considered among the primary paraproteinemias includes the B-cell lymphoproliferative disorders associated with the production of defective immunoglobulin molecules consisting of incomple-

te heavy chains without the normal light chain component. These heavy chain diseases, which may involve any of the immunoglobulin classes. were first recognized within the last thirty years, *gamma heavy chain disease* in 1964 by Franklin et al.[75], *alpha heavy chain disease* in 1968 by Seligmann et al.[76], and the uncommon *mu heavy chain disease* in 1970 by Forte et al.[77] In 1974 the possibility of a plasma cell dyscrasia characterized by the presence in the serum of incomplete molecules of immunoglobulins, such as free heavy chains and free light chain, was also demonstrated.[78]

7. *Treatment*

The first proposal for an effective treatment of multiple myeloma was that of whole *body irradiation*, reported by Medniger and Craver[79] in 1942. These Authors obtained a complete or partial remission of the bone pain in seven of eleven treated patients; 4 patients survived 2-5 years after radiation treatment. Medical therapy of myeloma was almost totally ineffective until 1947, when Alwall[80] reported dramatic improvement in one of two patients treated with stilbamadine and urethane. Further study showed that the antimyeloma effect was produced only by urethane. This drug, however, did not prove useful, for it caused considerable nausea and vomiting, and objective improvements occurred in fewer than 15% of patients[81]. Many other agents[82], including pentamidine, nitrogen mustard, 6-mercaptopurine, and 5-fluorouracil, were tried without success. In 1958, Blokhin and colleagues[83] reported to the *New York Academy of Sciences* that D,L-phenylalanine mustard (sarcolysine) produced significant improvement in three of six myeloma patients, including healing of skull lesions in one. Because of this report, the effectiveness of the L-isomer - *L-phenylalanine mustard or melphalan* - was tested[84], and objective improvement occurred in one third of myeloma patients. Cyclophosphamide was soon shown to be equally effective[85], and the value of adrenocortical steroids was also demonstrated[86]. These three drugs - melphalan, cyclophosphamide and corticosteroids - are still fundamental in the therapy of multiple myeloma and are still used alone or in combination in each chemotherapeutical protocol. The first attempt of allogeneic bone marrow transplantation in myeloma[87] was in 1982, utilizing as donor an identical twin, but the disease relapsed after seventeen months.

Also today, the therapy of myeloma is still an enigma[88], but the researches in this field continue[89], especially in the use of new chemotherapeutical agents and interferons.

8. *Conclusion*

The studies on the past two decades have clarified many aspects of the disease, also by means of the experimental animal model for the study of plasma cell dyscrasias in humans, that is the intraperitoneal implantation of plastics and mineral oil in the *BALB/c mice*, plasmocytomas developing within peritoneal and mesenteric granulomas. The studies have identified many predisposing and risk factors, such as chronic antigenic stimulation, viral infections, occupational exposure to pesticides and fertilizers, and radiations. They have clarified the tumor biology of plasma cell myeloma, with the possible involvement of *ras* and *myc* oncogenes. They have established the role of lymphokines in the differentiation and activation of normal B-cell as well as of neoplastic plasma cells, especially IL-6, but also IL-3 and GM-CSF and perhaps all types of cytokines. They have established that the myeloma cells present a Gompertzian growth, disease manifesting clinically when the myelomatous cell mass is more than $0.6 \times 10^{12}/m^2$. They have codified the diagnostic criteria with the recognition of several different clinical forms of myeloma, including *frank myeloma, indolent myeloma, smoldering myeloma, senile myeloma, extraskeletal myeloma, solitary myeloma, non-secretory myeloma, osteosclerotic myeloma*, and *lymphoma-like myeloma*. They have also identified the prognostic factors, mainly the plasma cell labeling index and the serum levels of β_2-microglobulin, proposing several clinical and morphological staging systems.

After 150 years, the odyssey of discovery goes on.

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Bibliography has been subdivided into two parts: the first list - *General Lectures* - indicates, in alphabetical order, several fundamental papers on the hisory and on the developmental concepts of paraproteinemias and plasma cell dyscrasias; the second one consists of the specific studies numbered as they appear during the text.

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Articoli/*Articles*

CURRENT HISTORIOGRAPHY OF MEDICINE. LIBRARY SECTIONS AND MUSEUMS

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SUMMARY

Medical discoveries and increasing number of specialities have restricted space of interests in humanities in the last decades. The European Union in order to ensure a general standard for personnel exchange has issued instructions about the objectives of medical curricula.
Now researches of the humanities are very actively involved and interaction of history of medicine with allied sciences appears to be an essential requirement for the linkage for the medical profession.

The last decades have seen a strong decrease in the number of physicians dedicated to the study of the history of medicine. And prospects seem to be discouraging:

> *There is reason to surmise that the next few decades will witness a reduction in the number of [American] physicians who will contribute to the history of medicine, either as writers or as teachers ... Future physician teachers of medical history may have to be sought in Europe or elsewhere*[1].

In the XIXth century a physician was frequently also devoted to humanities. Both undergraduate and postgraduate medical curricula have now been filled with a progressively increasing

Key words: Historiography of Medicine - Library - Museum