SUBJECT REVIEW

Multiple Myeloma

Review of 869 Cases

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A review of 869 cases of multiple myeloma seen at the Mayo Clinic from 1960 through 1971 revealed that 98% of patients were 40 years of age or older and that 61% of them were males. Initial findings were bone pain in 68% of patients, anemia in 62%, renal insufficiency in 55%, hypercalcemia in 30%, a palpable liver in 21%, and a palpable spleen in 5%. Proteinuria was noted in 88% and Bence Jones proteinuria was identified in 49%. Skeletal roentgenographic abnormalities were seen in 79%. Serum protein electrophoresis showed a spike in 76%, hypogammaglobulinemia in 9%, and minor or no abnormalities in 15%, and a globulin spike was seen in 75% of the urinary electrophoretic patterns. Immunoelectrophoresis of the serum revealed a monoclonal heavy chain in 83% and a monoclonal light chain in the serum in 8% (Bence Jones proteinemia). Three patients had no monoclonal protein in the serum or the urine ("nonsecretory"). Amyloidosis was found in 7% of the patients. Follow-up information was obtained in 99.7%; 82% of the 869 patients have died. Infection and renal insufficiency were the most common specific causes of death. The median survival was 20 months; 66% of the patients were alive at 1 year and 18% at 5 years.

Multiple myeloma (plasmacytic myeloma, plasma cell myeloma, myelomatosis, Kahler's disease) is a malignant disease of plasma cells that typically involves the bone marrow but often involves other tissue as well. A myeloma may be regarded as a neoplastic proliferation of a single line of plasma cells producing a specific protein as if under constant antigenic stimulation. This protein is monoclonal; it comprises one heavy-chain class (γ, IgG; α, IgA; μ, IgM; δ, IgD; or ϵ, IgE) and one light-chain class (κ or λ), and is often referred to as an M or myeloma protein.

The first patient known to have multiple myeloma was Thomas Alexander McBean, who was seen in 1845. McBean had severe recurrences of pain during the 17 months of his illness, and his urine contained unusual "animal matter" that became soluble when boiled and formed again when cooled.[1] Although William MacIntyre recognized the effect of heat on the urine, it was a young physician and chemist, Henry Bence Jones, who described the protein in detail.

The term "multiple myeloma" was introduced by Rustizky in 1873. There was, however, little interest in the disease until 1889, when Kahler described a striking case. The plasma cell was discovered in 1890 by Cajal, who was examining syphilitic condylomas; the term "plasma cell" was applied by Unna in the following year. In 1900, Wright, in presenting a case, recognized that the myeloma tumor consisted of plasma cells. Electrophoretic techniques were applied to the study of multiple myeloma by Longsworth and associates in 1939,[2] and immunoelectrophoresis was described by Grabar and Williams[3] in 1953; these two procedures have facilitated the diagnosis and contributed greatly to the recognition and understanding of this disease.

Multiple myeloma accounts for about 1% of all types of malignant disease and slightly more than 10% of hematologic malignancies. In the United States, the death rate from multiple myeloma has increased from

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0.8 per 100,000 population in 1949 to 1.7/100,000 in 1963, an increase in accord with that reported from most countries. In both Sweden and England the rate is approximately 3/100,000, and in northeast Scotland the rate is 3.4/100,000.[4] In Olmsted County, Minnesota, the rate was 3/100,000 for the decades 1945 through 1954 and 1955 through 1964. It seems probable that the death rate for myeloma has not changed in the last 20 years, and it is likely that the apparent increased rates are related to increased utilization of medical facilities and improved diagnosis rather than increase of actual incidence.[5]

MATERIAL AND METHODS

Method of Study.—The records of all patients with a diagnosis of multiple myeloma, plasmacytic myeloma, plasma cell myeloma, plasmacytoma, myelomatosis, or Kahler's disease seen at the Mayo Clinic from Jan. 1, 1960, through Dec. 31, 1971, were obtained and reviewed. The data were abstracted on sheets suitable for keypunching. The laboratory data for each visit were reviewed, and maximum and minimum values with their dates of occurrence were recorded. Keypunching and abstracting errors were detected by computer. Examples of errors are the following: a record of a serum protein peak on electrophoresis when there was no record of any serum protein value; a record of the cause of death or a death certificate if the patient were living; and any printout showing an unlikely value such as a leukocyte count of 90,000/mm³. The data were tabulated and analyzed with the aid of a computer. Distributions were run for each laboratory test, which thus made it possible to determine the frequency and distribution of any particular laboratory value. Initial values were those derived from laboratory tests performed within 3 months of the original diagnosis of myeloma; values obtained later, even if that particular test had not been performed before, were excluded from the "initial" values. In the review of data, any value that did not appear compatible (e.g., more than 5% immature leukocytes listed or more than 10% plasma cells in the peripheral blood) was reassessed. Character counts of each abstract card provided the number of entries for each value.

Follow-up letters were written to all patients and to each patient's physician when the patient had not been seen or heard from during the previous year. Letters were written to other contacts of the patient such as hospitals or other medical institutions where the patient had been. Death certificates were requested from the Department of Vital Statistics of the state of residence of the patient. Even when the date of death was not known, the death certificate was often obtainable when we provided a 2- to 3-year interval during which time we thought that the patient had died. Retail credit searches produced follow-up information in some instances.

Diagnostic Criteria.—The diagnosis of multiple myeloma was based on the following findings: (1) increased numbers of abnormal, atypical, or immature plasma cells in the bone marrow or histologic proof of plasmacytoma; and (2) the presence of a monoclonal protein in the serum or urine; or (3) bone lesions consistent with those of myeloma. Patients with plasma-cell reactions to connective tissue diseases, liver disease, metastatic carcinoma, or chronic infections were excluded. Also excluded were patients with benign monoclonal gammopathy, which is characterized by a monoclonal serum protein concentration of less than 2 g/dl, normal serum

Table 1.—**Age and Sex Distribution of Patients at Diagnosis**

Age, yr	Sex distribution, %	
	Males (N=529)	Females (N=340)
<40	2	2
40-49	8	11
50-59	25	29
60-69	40	37
70-79	22	18
80-89	3	3
% of total	61	39
Mean age, yr	62	61

Table 2.—**Frequency of Various Features in the History**

Feature	Frequency, %
Bone pain, as initial finding	68
Infection, bacterial	12
Herpes zoster	2
Fever (from myeloma)	1
Bleeding, gross	7
Other malignancy	
Family	6
Patient	7

Table 3.—**Initial* Blood Counts**

Variable	Total no. of patients	Mean value	Frequency, %
Hemoglobin, <12 g/dl	741	11.1	62
Leukopenia, <4,000/mm³	737	6,450	16
Thrombocytopenia, <100,000/mm³	543	195,000	13
Thrombocytosis, >300,000/mm³	543	195,000	11

*In this and other tables, the term "initial" refers to the 3-month period following the original diagnosis of multiple myeloma.

Table 4.—**Maximum Erythrocyte Sedimentation Rates (Westergren)**

Rate, mm in 1 hour	Frequency, % (N=841)
<10	6
10-20	4
21-50	14
51-100	38
>100	38
Mean, 82.5	

albumin, fewer than 5% plasma cells in the bone marrow, an absence of myeloma bone lesions, Bence Jones proteinuria, anemia, and observation for at least 3 years without change or development of these abnormalities. Patients presenting with solitary plasmacytomas, extramedullary plasmacytoma, or plasma cell leukemia were also excluded from this study.

The criteria for the diagnosis of multiple myeloma were fulfilled for 869 patients during the period from 1960 through 1971, and their records form the basis of this study.

FINDINGS AND DISCUSSION

Age and Sex Distributions.—Only 2% of the patients were less than 40 years of age at the time of diagnosis; the greatest incidence was in the seventh decade of life (Table 1). Table 1 also shows that 61% of the patients were males.

History.—The frequency of various features of the history is summarized in Table 2. *Bone pain* was present at the time of diagnosis in 68% of the patients. This is to be expected because myeloma is predominantly a disease of the bone marrow, with secondary osteolysis. Bone pain usually involves the back or chest, and the extremities less often. The pain is usually precipitated by movement and does not occur at night except with change of position—in contrast to the pain of metastatic carcinoma, which frequently is worse at night. The pain of myeloma is often sudden in onset and may be extremely severe. It may be protracted or transient and may shift from one location to another for no apparent reason. Persistent localized pain or tenderness of sudden onset usually indicates a pathologic fracture, which often occurs with only minimal trauma. The patient's height may be shortened by several inches because of vertebral collapse and kyphosis.

In contrast to lymphoma, *fever* is uncommon; in only 1% of the patients was fever attributed to myeloma. *Bacterial infections* were recorded in 12% of our patients; six patients each had more than five acute bacterial infections. The infection rate would undoubtedly have been higher if it had been possible to follow the patients closely throughout the duration of their illness. Infection in myeloma is most often caused by *Diplococcus pneumoniae, Staphylococcus aureus,* and *Escherichia coli;*[6] recently, the predominance of gram-negative organisms in myeloma has been emphasized.[7] The impairment of antibody response,[8] deficiency of the uninvolved immunoglobulins, reduction of delayed hypersensitivity in some instances, and depression of activity of the neutrophils[9] all contribute to infection in these patients. This propensity to infection is further increased by chemotherapeutic depression of the immune response and production of neutropenia.

Herpes zoster occurred in 2% of the patients. Opportunistic infections due to organisms such as *Pneumocystis carinii*[10] are undoubtedly more common than reported and must be considered in every patient with myeloma and fever of undetermined cause.

Weakness and *fatigue* are common symptoms and often associated with *anemia,* which was present initially in two-thirds of our patients. *Weight loss* and *night sweats* usually are not prominent until the disease is advanced. Gross *bleeding* was present in 7% of our patients; this most often took the form of epistaxis, but gastrointestinal bleeding was also noted.

A history of another malignancy in addition to the myeloma was reported by 7% of the patients (Table 2). The major symptoms may result from other complications such as renal insufficiency, hypercalcemia, and deposition of amyloid. The latter may produce congestive heart failure, nephrotic syndrome, orthostatic hypotension, peripheral neuropathy, or increased bleeding tendency. A history of malignancy in first-degree relatives was recorded in 6% of our patients.

Table 5.—**Initial Serum Creatinine Concentrations**

	Concentration, range, mg/dl							
Patient group	<1.0	1.0-2.0	<1.3	1.3-2.0	2.1-5.0	5.1-10.0	>10.0	Mean conc.
Males (N=238), %	. . .	. . .	46	22	19	8	5	2.8
Females (N=151), %	44	30	. . .	. . .	19	4	3	2.1

Table 6.—**Initial Serum Calcium Concentrations**

Concentration, mg/dl*	Frequency, % (N=611)
<8.0	1
8.0-10.1	69
10.2-15.0	28
>15.0	2
Mean, 10.1	

*Upper limit of normal serum calcium concentration is 10.1 mg/dl.

Physical Examination.—The liver was palpable in 21% of the patients, but in only 5% was the liver palpable 5 cm or more below the costal margin. The spleen was palpable in 5%, but the extent of *splenomegaly* was not great; in only 0.6% of the patients did the spleen extend more than 5 cm below the costal margin. *Lymphadenopathy* likewise was relatively uncommon and detected in only 4% of patients. In a number of these patients, the lymphadenopathy consisted of submandibular swelling from macroglossia due to amyloidosis.

Pallor is a most common finding and reflects the presence of anemia. *Bone deformity* or *tenderness, pathologic fracture,* and *tumor formation* may also be found. *Extramedullary plasmacytomas* are uncommon but may produce large subcutaneous masses that frequently have a purplish hue. *Purpura* may be prominent.

Congestive heart failure, nephrotic syndrome, peripheral neuropathy, or macroglossia may result from coexistent amyloidosis.

Results of Laboratory Investigations. Blood Counts.—The mean initial values for hemoglobin concentration, leukocyte count, and platelet count are listed in Table 3. *Anemia* was present at the time of diagnosis in 62% of our patients. It may be quite severe; 8% of patients presented with hemoglobin values of less than 8 g/dl. Anemia is normocytic and normochromic and results mainly from the inadequate production of red cells, presumably from displacement by excessive numbers of abnormal plasma cells; shortening of red cell survival, bleeding, and iron deficiency may also be factors. Increased plasma volume, which probably is the result of the osmotic effect of the large amount of monoclonal protein, commonly produces hypervolemia and decreases the hemoglobin and hematocrit concentrations.[11] Thus, significant anemia may be suggested by the hemoglobin or hematocrit value when the red cell mass is only slightly diminished.

Table 7.—**Serum Uric Acid Concentrations**

Males* (N=305)		Females* (N=184)	
Concentration, mg/dl	Frequency, %	Concentration, mg/dl	Frequency, %
≤4.2	6	≤2.2	2
4.3-8.0	55	2.3-6.0	37
8.1-10.0	16	6.1-10.0	49
10.1-15.0	19	10.1-15.0	10
>15.0	4	>15.0	2
Mean, 8.3		Mean, 7.0	

*Upper limits of normal values: for males, 8.0 mg/dl; for females, 6.0 mg/dl.

Table 8.—**Concentrations of Serum Lipids**

	Frequency, %	
Concentration, mg/dl	Cholesterol (N=300)	Triglycerides (N=131)
<50	0	13
50-150	26	71
151-300	68	14
301-500	5	0
>500	1	2
Mean, mg/dl	203	105

Typically an *increased erythrocyte sedimentation rate* (ESR) is found; 76% of our patients had a value greater than 50 mm in 1 hour (Westergren) (Table 4). Since 10% of our patients had a sedimentation rate less than 20 mm in 1 hour, it must be emphasized that a normal sedimentation rate does not exclude the diagnosis of myeloma. *Rouleau formation* of grade 3 or 4 was present in 61% of 772 patients and of grade 1 or 2, in 27%; only 12% showed no increase in rouleau formation. The common blue-gray staining of the background of the peripheral blood smear is attributed to the increased protein content.

A *positive Coombs' test* was recorded in 10 of our patients, but 5 of them were women and several others had had previous transfusions; only 1 of these patients had documented hemolysis.

The initial *leukocyte count* was less than 4,000/mm³ in 16% of patients, and 9% had an initial leukocyte count of greater than 10,000/mm³. Immature leukocytes were recorded in the differential count during the course of their disease in 50% of patients, but usually in only small numbers; their proportion ex-

Table 9.—**Results of Findings of Liver Function**

Finding	No. (and %) of patients
Liver palpable	869 (21)
Serum alkaline phosphatase increased*	336 (25)
BSP elevated (>5% in 1 hour)	202 (39)
Serum albumin (initial) ≤3.0 g/dl†	727 (52)

*Upper limit of normal, 60 U/liter; mean value in these patients, 55 U/liter.
†Mean value for these patients, 3.0 g/dl.

Table 10.—**Results of Miscellaneous Laboratory Investigations**

Test	No. of patients studied	% positive
Rheumatoid factor	74	8
Coombs' test	58	17
LE clot	110	1
Serum viscosity (>1.7)	80	89
Cryoglobulin	325	5
Pyroglobulin	500	1

ceeded 5% in only 6% of the patients. A leukemoid reaction consisting of more than 15% immature leukocytes in the peripheral blood occurred in 10 patients but we were unable to make a diagnosis of leukemia in all of these patients. (Of course, leukemia might have developed if the patients had survived longer.) Plasma cells were recorded in the differential count of 16% of 826 patients during the period of observation but the proportion exceeded 5% in only 16 patients. Undoubtedly, the percentage of plasma cells would have been greater if a buffy coat had been examined.

Thrombocytopenia (<100,000/mm^3) was present initially in 13% of our patients. *Thrombocytosis* (300,000/mm^3), which has been noted in the past,[12,13] was present in 11%; only 1% of patients had an initial platelet count of greater than 500,000/mm^3 (Table 3). Thrombocytopenia is common in far-advanced disease with extensive marrow replacement or after radiation therapy or chemotherapy.

Renal Function.—*Renal insufficiency* is common in myeloma[14] and an *elevated serum creatinine concentration* was an initial finding in 54% of males and 56% of females. Almost one-third of the patients had an initial serum creatinine of greater than 2 mg/dl (Table 5).

One of the most important causes of renal insufficiency is *hypercalcemia*. Hypercalcemia was noted in 30% of the patients initially (Table 6); *hypocalcemia* was present in only 1%. Hypercalcemia must be suspected in the presence of anorexia, nausea, vomiting, polyuria, increased constipation, weakness, confusion, stupor, or coma. If recognized

Table 11.—**Results of Electrophoresis of Serum**

	No. (and %) of patients
Mobility of peak	
γ	457 (53)
β	182 (21)
α_2	9 (1)
"Polyclonal" peak	8 (1)
Hypogammaglobulinemia	78 (9)
"Normal"	124 (15)
Total	858 (100)

Table 12.—**Results of Immunoelectrophoresis of Serum**

	No. (and %) of patients
Immunoglobulin	
IgG	316 (59)
IgA	126 (23)
IgD	6 (1)
Negative (heavy chain)	89 (17)
Total	537 (100)
Light Chain	
κ	320* (60)
λ	158* (30)
Negative	55 (10)
Total	533 (100)

*Includes Bence Jones proteinemia.

early and if therapy is promptly instituted, the results are good; frequently, renal function is improved. Another common cause of renal insufficiency is the so-called *myeloma kidney*, in which the distal and proximal convoluted tubules become obstructed by large laminated casts surrounded by giant cells. Contrary to the commonly accepted belief that these casts are composed of precipitated Bence Jones protein, they actually consist of albumin, IgG, and light chains of both kappa and lambda types.[15] Atrophy of the renal tubular epithelium rather than the presence of casts has correlated best with renal failure. Bence Jones protein may damage the tubular cells and lead to atrophy and degeneration. However, Bence Jones proteinuria evidently is not always nephrotoxic, for we have seen a number of patients who have excreted large amounts without renal insufficiency developing. *Hyperuricemia*, which was present in 39% of males and 61% of females, may contribute to renal insufficiency (Table 7). These rates are higher than one would expect because the serum uric acid was determined initially in only a little more than one-half of our patients, and it is likely that more of those with hyperuricemia were measured than those with normal values.

Intravenous urography has precipitated acute renal failure,[16] but it appears that the risk of failure is slight if dehydration from water deprivation and laxatives is minimized and if abdominal compression and hypo-

Table 13.—**Results of Electrophoresis of Urine**

	No. (and %) of patients
Mobility of peak	
γ	188 (34)
β	215 (39)
α_2	11 (2)
Protein mainly albumin	54 (10)
"Normal"	83 (15)
Total	551 (100)

tension are avoided during the procedure.[17]

Other factors that may contribute to renal insufficiency are the deposition of *amyloid,* which often produces the nephrotic syndrome, *acute* and *chronic pyelonephritis,* which are not uncommon, and *plasma-cell infiltration* of the kidney.

Proteinuria was present in 88% of 865 patients. Among these patients, 38% had grade 3 or 4 proteinuria and the remainder had either grade 1 or 2 proteinuria, in equal proportions. Bence Jones proteinuria, on the basis of the heat test, was detected in 49% of the 631 patients in whom the test was performed. Excluded from review were 27 in whom tests gave equivocal results.

Serum Lipid and Phosphatase Concentrations and Liver Function.—The *serum cholesterol concentration* was 150 mg/dl or less in 26% of 300 patients (Table 8). Reduction of the serum cholesterol concentration in myeloma has been noted before[18] and may correlate with larger globulin concentrations. Elevation of the serum cholesterol concentration was present in only 6%. The *serum triglyceride concentration* was decreased in 13% of 131 patients (Table 8). The association of myeloma and hyperlipidemia has been reported in 19 cases, often in conjunction with xanthomas.[19] The *serum alkaline phosphatase concentration* was elevated (>60 IU) in 25% of 336 patients (Table 9). Most of these elevations were modest (mean value, 55 IU), but 8 of the 336 patients had serum alkaline phosphatase concentrations exceeding 200 IU. Three of these had amyloidosis, one had chronic ulcerative colitis with hepatomegaly, one had Paget's disease, and one had hepatosplenomegaly of indeterminate etiology; no cause for the increase in alkaline phosphatase could be found in the other two instances.

The *serum acid phosphatase concentration* was elevated (>10 IU) in 14 of 94 patients (all 14 were males). Carcinoma of the prostate was excluded at autopsy in six patients, and tartrate inhibition was less than 20% in three others. In one patient, the acid phosphatase value was normal when repeated, and another had Paget's disease. One patient had a firm prostate on digital examination but further studies were not done. For the remaining two patients, no further information was available.

Evidence of hepatic involvement included the presence of a palpable liver (in 21% of patients), *increased Bromsulphalein (BSP) dye retention* (39%), *elevation of serum alkaline phosphatase concentration* (25%), and *decrease in serum albumin concentration* (52%) (Table 9). The frequency of abnormal results of liver function studies, extensive plasma-cell infiltration of the liver, and jaundice and ascites has been emphasized.[20]

Table 14.—**Results of Immunoelectrophoresis of Urine**

Light chain	No. (and %) of patients
κ	93 (47)
λ	66 (33)
Negative	39 (20)
Total	198 (100)

Cryoglobulinemia and Pyroglobulinemia.—*Cryoglobulins* (proteins that precipitate or gel on cooling and dissolve when heated[21]) were found in 17 (5%) of 325 patients (Table 10). Persons with cryoglobulinemia often have no symptoms, but they may have cold intolerance, as manifested by such symptoms as Raynaud's phenomenon, purpura, cold urticaria, leg ulcers, and gangrene of the extremities.

Pyroglobulins (monoclonal proteins that precipitate when serum is heated to 56°C) were found in 5 (1%) of 500 patients[22,23] (Table 10). Unlike cryoglobulins, these proteins precipitate irreversibly and do not dissolve when cooled. Pyroglobulinemia is not associated with a specific clinical syndrome and may be regarded as a laboratory curiosity that is usually recognized when serum is inactivated for the VDRL serologic test. Bence Jones proteinemia should not be confused with pyroglobulinemia; it can be distinguished by immunoelectrophoresis of serum with appropriate antisera.

Fig. 1. Tall, narrow-based monoclonal peak of γ mobility on serum electrophoresis of patient with multiple myeloma. (From Kyle RA, Bieger RC, Gleich GJ: Diagnosis of syndromes associated with hyperglobulinemia. Med Clin North Am 54: 917-938, 1970. By permission of WB Saunders Company.)

Serum Viscosity, Rheumatoid Factor, and LE Clot Test.—The *serum viscosity* was increased in 89% of 80 patients. This, however, does not reflect a true incidence because the test is most likely to be done if a patient has symptoms suggestive of hyperviscosity or a large amount of monoclonal protein in the serum. Only 13% of our patients had a serum viscosity greater than 4; with a viscosity of less than this, symptoms are rare. Symptoms of hyperviscosity include bleeding (particularly of the oronasal areas), decrease of visual acuity, retinopathy, neurologic symptoms, and congestive heart failure.[24-26] Most patients have symptoms when the relative serum viscosity reaches 6 or 7, but the relationship between serum viscosity and clinical manifestations is not precise; we have seen a patient with a serum viscosity of 15 who had no symptoms of the hyperviscosity syndrome. Although this syndrome is most common in macroglobulinemia, it may also be associated with either IgG or IgA myeloma, especially if the IgA protein forms polymers.

A *positive rheumatoid factor* was noted in six patients, and a *positive LE clot test* was noted in one patient. The latter occurred in a patient with rheumatoid arthritis in whom multiple myeloma subsequently developed.

Bone Marrow Aspirate.—Findings on study of the *bone marrow aspirate* were thought to be diagnostic of multiple myeloma in 92% of patients. In 1%, plasma cells appeared lymphoidal and initially suggested the possibility of lymphosarcoma or macroglobulinemia.[27] In 6%, either the increase in the number of plasma cells was insufficient for the diagnosis of myeloma or a nondiagnostic aspirate was obtained. In several of these patients, examination of the bone marrow biopsy indicated myeloma. A bone marrow aspirate was not examined in 1%. The diagnosis of myeloma was established in the remainder of the cases by autopsy, open biopsy of a skeletal lesion, or an extramedullary plasmacytoma. Of the 326 patients in whom the plasma cells were counted or estimated initially, the proportion of plasma cells in 84% of patients was 10% or greater. The mean plasma-cell proportion was 36%. The proportion of plasma cells in a bone marrow aspirate may amount to less than 5% or almost 100% because marrow involvement is usually focal rather than diffuse. Thus, repeated needle aspirations from

Table 15.—**Frequency of Initial Globulin Peak on Serum Electrophoresis in 554 Patients**

Globulin concentration, g/dl	Frequency, %
1.0-2.0	17
2.1-3.0	26
3.1-4.0	21
4.1-5.0	16
5.1-6.0	11
6.1-8.0	8
>8.0	1
Mean, 3.6	

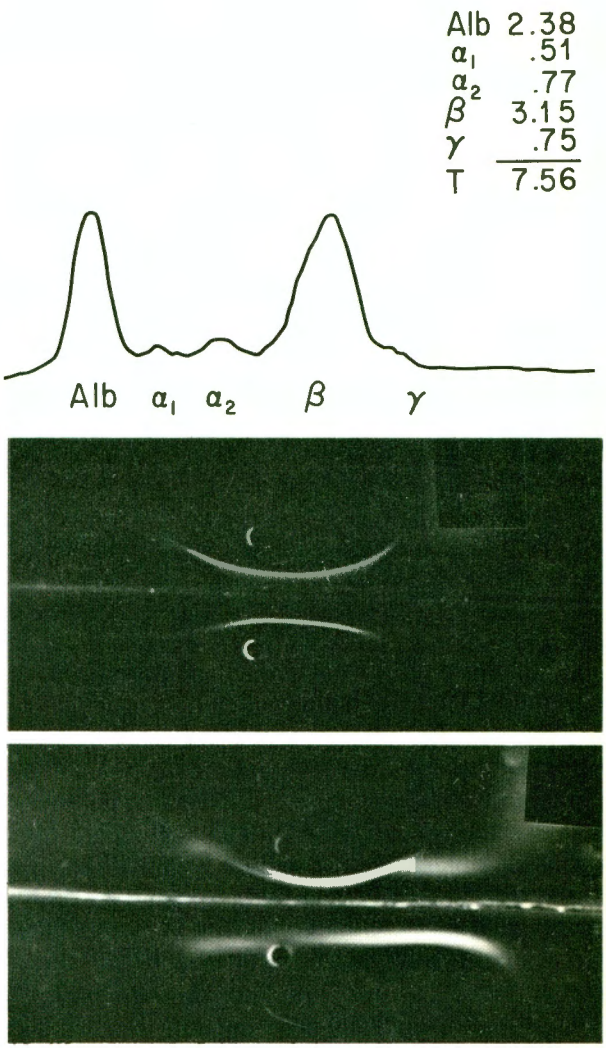


Fig. 2. Results of electrophoresis and immunoelectrophoresis of serum of patient with multiple myeloma. *Upper,* Serum electrophoretic pattern on paper with rather broad β peak appearing polyclonal but consisting of monoclonal IgA κ protein. *Middle,* Result of immunoelectrophoresis of patient's serum (*top well*) and normal serum (*bottom well*) with IgA antiserum in center trough; note patient's thickened IgA arc. *Lower,* Result of immunoelectrophoresis, showing reaction to kappa chain antiserum: prominent band from patient's serum (*upper well*) and elongated band without localized thickening from normal serum (*lower well*). These results confirm the presence of a monoclonal IgA κ protein. (From Kyle RA, Bieger RC, Gleich GJ: Diagnosis of syndromes associated with hyperglobulinemia. Med Clin North Am 54:917-938, 1970. By permission of WB Saunders Company.)

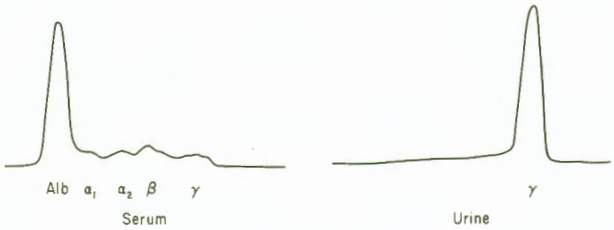


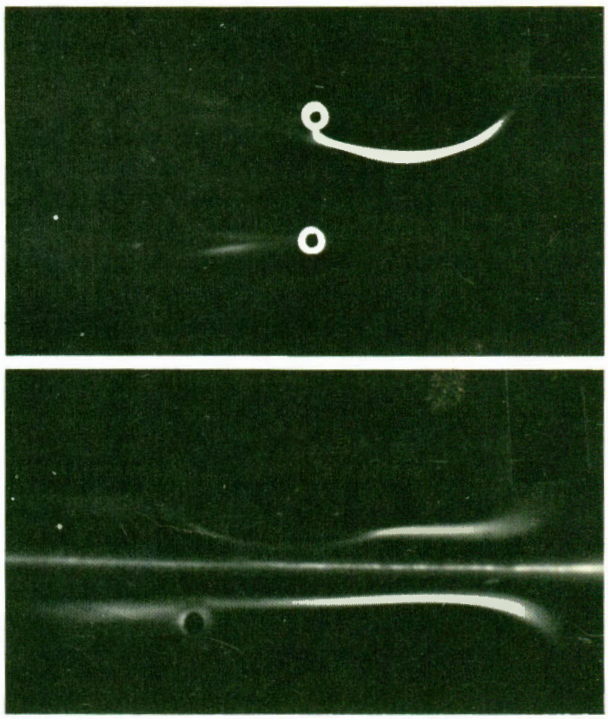
Fig. 3. Multiple myeloma and hypogammaglobulinemia: electrophoretic patterns of serum and urine. Narrow peak in urine was positive for Bence Jones protein. (From Kyle RA, Bieger RC, Gleich GJ: Diagnosis of syndromes associated with hyperglobulinemia. Med Clin North Am 54:917-938, 1970. By permission of WB Saunders Company.)

multiple sites may be necessary to establish the diagnosis of multiple myeloma.

Marrow plasmacytosis is not peculiar to multiple myeloma, and it may occur in cases of carcinoma, connective tissue diseases, liver diseases, hypersensitivity states, and infections. The findings of immaturity, increased pleomorphism, and frequent mitotic figures point toward myeloma rather than a plasma-cell reaction.[28] Rarely, patients with plasma-cell reactions to connective tissue diseases, metastatic carcinoma, liver disease, or viral infections have more than 20% plasma cells in their marrow;[29] one then often sees mature plasma cells in a perivascular distribution, whereas in myeloma the plasma cells are immature and are often nodular in distribution.[30,31] Therefore, the diagnosis of multiple myeloma depends on the appearance as well as the number and distribution of plasma cells. Because of focal marrow involvement, a negative bone marrow aspirate does not exclude the diagnosis. Needle aspirations of tender areas are often productive. Because fractures of the sternum have occurred after sternal punctures in patients with myeloma, we recommend the posterior iliac crest as the preferred site for bone marrow aspiration.

Electrophoresis and Immunoelectrophoresis.—Both serum and urine were studied by electrophoresis and by immunoelectrophoresis. Results for *serum* are summarized in Table 11 and in Table 12; results for *urine* are summarized in Tables 13 and 14. A tall, sharp peak, as seen on the densitometry tracing, or a dense localized band on the cellulose acetate strip migrating in the γ range was seen in 53% of our patients, in the β range in 21%, and in the α_2 range in 1% (Fig. 1) (Table 11). Among the 554 patients with a serum globulin spike, the globulin concentration exceeded 2 g/dl initially in 83% (Table 15). A polyclonal (broad-based) peak was found in 1% (Table 11). This occurs particularly in IgA monoclonal proteins, which have a tendency to form polymers (Fig. 2).

Hypogammaglobulinemia was present in 78 (9%) patients (Table 11); this is usually associated with a



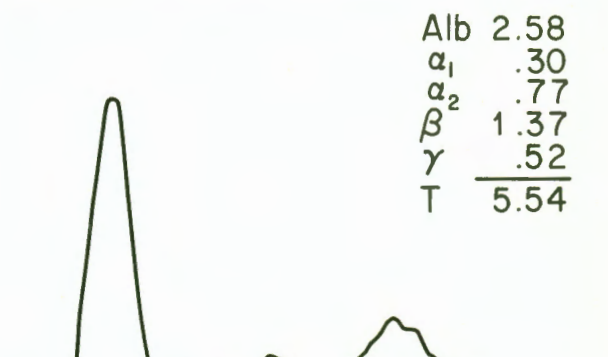


Fig. 4. Myeloma and amyloidosis. *Upper,* Immunoelectrophoretic response to IgD antiserum is sharp band from patient's serum *(upper well)* and absence of band from normal serum *(lower well). Middle,* Immunoelectrophoretic responses to lambda chain antiserum by same patient's serum *(upper well)* and by normal serum *(lower well),* confirming the presence of an IgD lambda type monoclonal protein, in patient. *Lower,* Electrophoretic pattern on paper of serum from same patient, showing only modestly increased β-globulins. (From Kyle RA, Bieger RC, Gleich GJ: Diagnosis of syndromes associated with hyperglobulinemia. Med Clin North Am 54:917-938, 1970. By permission of WB Saunders Company.)

large monoclonal globulin peak in the urine (Bence Jones proteinuria) (Fig. 3). Urine electrophoresis also was performed in 66 of these 78 patients; 56 (85%) had a globulin spike on urine electrophoresis. Of the remaining 10 patients, 5 had amyloidosis in addition to myeloma, 4 of them excreting 4 g or more of albumin daily; 3 of the 10 patients had a small monoclonal protein in the serum or urine. In none of these patients was immunoelectrophoresis of both the serum and the urine negative. The presence of hypogammaglobulinemia in myeloma needs emphasis because myeloma should be considered in all adults with hypogammaglobulinemia and proteinuria.

In 124 (15%) patients, the serum electrophoretic pattern appeared normal or contained only a very small spike or band (Table 11). Urine electrophoresis was performed in 102 of these 124 patients; a globulin spike was noted in 83 (81%) of them. Of the remaining 19 patients, 7 had a monoclonal protein in either the serum or the urine. Immunoelectrophoresis failed to show a monoclonal protein in both the serum and urine in three patients.

Looking at it from another aspect, 23 of the patients with hypogammaglobulinemia or a normal serum electrophoretic pattern had a monoclonal heavy chain in the serum on immunoelectrophoresis. This illustrates the need for immunoelectrophoresis, even when the serum protein electrophoretic pattern is not suggestive of a spike. One of our patients had a very modest serum electrophoretic spike (Fig. 4), but his marrow contained more than 30% abnormal plasma cells and he had extensive amyloidosis. Thus, minimal abnormalities on the electrophoretic pattern may be seen in overt multiple myeloma. Furthermore, if the cellulose acetate membrane had been used throughout this study, more bands or spikes would have been seen because it is more sensitive than filter paper for use as a supporting medium.[32] Innes and Newall[33] reported that 38% of 62 cases of myeloma had normal or minor abnormalities in their serum electrophoretic pattern.

Immunoelectrophoresis of serum was performed in 537 instances (Table 12). In 17%, there was no evidence of a monoclonal heavy chain in the serum but in 38 (8% of the total) of these there was a monoclonal light chain (Bence Jones proteinemia); thus, a monoclonal serum protein was detected in 91%. It is of interest that in 22 of the 38 (58%) patients a lambda class of light chain was found, whereas one would expect this class in only one-third. Of patients with a monoclonal heavy chain in the serum, 71% had IgG, 28% had IgA, and 1% had IgD. The ratio of kappa to lambda chains was 2:1. In 10% of the patients, the monoclonal light-chain type was not detected. In many of these instances, immunoelectrophoresis was done when our antisera were not as satisfactory as at present, and no serum from the patients remains, so it cannot be repeated. The light-chain class of some IgA monoclonal proteins may be difficult to classify. This is particularly true for the lambda class. Immunoelectrophoresis was done in four instances when light-chain antisera were not available. Ninety percent of IgG but only 18% of IgA monoclonal proteins were of γ mobility in the electrophoretic pattern.

Table 16.—**Size of Initial Globulin and Albumin Peaks on Urine Electrophoresis**

Excretion, g/24 h	Frequency of peak, %	
	Globulin (N=171)	Albumin (N=41)
<1.0	16	54
1.0-3.0	45	24
3.1-5.0	13	7
5.1-10.0	17	13
>10.0	9	2
Mean, g/24 h	3.9	2.2

Electrophoresis of urine was done in 551 cases (Table 13). In 75% there was a globulin peak, in 10% the peak had the mobility of albumin, and in 15% no albumin or globulin spike was seen. The incidence of globulin peaks in the urine is higher than expected, and would be lower if urine electrophoresis had been performed in all 869 patients—for, in those patients with little or no proteinuria on routine urine analysis, electrophoresis would have been less likely. The sizes of the urinary globulin and albumin spikes at the time of diagnosis in a smaller number of patients are indicated in Table 16.

Immunoelectrophoresis of concentrated urine and

Table 17.—**Quantitation of Serum Immunoglobulins in 340 Patients**

Immunoglobulin concentration, mg/ml	Frequency, %
IgG	
<6.4	29
6.4-14.3	15
>14.3	56
Mean, 28.2	
IgA	
<0.3	51
0.3-3.0	30
>3.0	19
Mean, 4.6	
IgM	
<0.2	73
0.2-2.0	26
>2.0	1
Mean, 0.3	

Table 18.—**Summary of Roentgenographic Findings**

Finding	No. (and %) of patients
Lytic only	108 (13)
Osteoporosis only	50 (6)
Fractures only	22 (3)
Osteoporosis, lytic, and fractures	473 (57)
Negative	171 (21)
Total	824 (100)

immunodiffusion[34] *of neat urine* showed a monoclonal light chain in 80% of 198 cases (Table 14). Of those patients with a monoclonal protein in the urine, 58% had kappa light chains. There was no monoclonal protein in the urine in 20% of patients.

Three of our patients with myeloma had no detectable monoclonal protein in either the serum or the urine, which is similar to the finding of no abnormalities in 3 of 262 cases by Osserman and Takatsuki.[35] This entity has been designated "nonsecretory" myeloma.[36,37] In these instances, monoclonal proteins may be identified within the cytoplasm of the plasma cell by immunofluorescent staining.

Quantitation of the serum immunoglobulins in 340 patients is summarized in Table 17. The value for IgG was elevated in 56% and the IgA value was elevated in 19%.

Roentgenographic Features.—Skeletal roentgenograms showed abnormal appearances in 79% of our patients, but this proportion would undoubtedly have been higher if roentgenography had been more extensive throughout each patient's illness (Table 18). Over one-half of our patients had a combination of osteoporosis, lytic lesions, and fractures. The characteristic skeletal lesions of myeloma are the so-called punched-out lytic areas without associated osteoblastic changes. They may be sharply circumscribed or, when seen against a background of diffuse bone demineralization, poorly defined. It is particularly difficult to distinguish venous lakes from lytic lesions in the skull. It must be emphasized that multiple lytic lesions are not diagnostic of myeloma and cannot be distinguished roentgenographically from those caused by metastatic carcinoma. The vertebrae, skull, thoracic cage, pelvis, and proximal portions of humerus and femur are the most common sites of involvement. Lesions in the distal portions of the extremities generally are rare, but the incidence would become greater if more roentgenograms were taken. Pathologic fractures, especially vertebral, are common and should always suggest the possibility of myeloma. The vertebral pedicles are rarely involved in myeloma, whereas they are frequently the site of metastatic carcinoma. The bony lesions of myeloma frequently extend into soft tissues, particularly in the ribs and vertebral column, and this finding should alert the clinician to the possibility of myeloma. Osteosclerosis, resembling that associated with metastases, is rarely seen in multiple myeloma.[38] In our experience, ^{99m}Tc-Sn-EHDP (diphosphonate) bone scans are inferior to conventional roentgenography—in contrast to their value in cases of carcinoma of the prostate, in which the scan is superior.[39] However, we have seen positive bone scans in patients with myeloma who have had severe pain almost certainly from multiple myeloma but who have had no roentgenographic abnormalities.

Incidence of Amyloidosis.—Amyloid was documented histologically in 61 (7%) patients with myeloma. This low incidence is explained by the fact that biopsy for amyloid was not generally done unless the patient had suggestive symptoms or findings. Also, there were a number of patients in whom amyloid was suspected on the basis of such conditions as congestive heart failure and carpal tunnel syndrome, but histologic proof was not obtained because it would not have altered the course or therapy of the patient.

Incidence of Appendectomy.—Appendectomy was performed in 33% of our patients with myeloma. It is not possible to evaluate this figure because of the lack of controls. The incidence of appendectomy in a population depends on race, sex, place of birth, and socioeconomic status.[40] Bierman,[41] in an autopsy study, reported that 35% of patients in his series with cancer had had an appendectomy and that 24% in his control series had not. In contrast, Cassimos and associates[42] noted that 25.6% of the control population had had an appendectomy whereas only 16% of the cancer patients had. Kessler[43] could find no evidence that prior appendectomy significantly affected the subsequent risk of cancer.

Treatment and Course.—Therapy was difficult to evaluate in this study because my colleagues and I were not responsible for the continuing care of all the patients. A combination of chemotherapeutic agent, prednisone, and irradiation was used in 55%

Table 19.—**Summary of Therapeutic Measures in 790 Patients**

Therapy	Frequency, %
Chemotherapeutic agents, steroids, and irradiation	55
Chemotherapeutic agents only	16
Prednisone only	2
Urethan	3
Irradiation only	12
None	12

Table 20.—**Current Status and Follow-up Information on 869 Patients**

Status	No. (and %) of patients
Alive	152 (17.5)
Follow-up period, yr	
<1	4 (0.5)
1-2	38 (4.4)
2-3	24 (2.8)
3-5	44 (5.0)
>5	39 (4.5)
No follow-up	3 (0.3)
Dead	717 (82.5)
Total	869 (100.0)

of the patients, and 16% had chemotherapy alone (Table 19). In 12% of patients, no specific therapy was given; most often, this was because the patient was terminal or the diagnosis was made at autopsy.

Follow-up information was obtained in 866 (99.7%) of the 869 patients. In only 4 patients who are still living was the period of follow-up less than 1 year; in 83 of those still living, the period of follow-up exceeded 3 years (Table 20). Of the 866 patients, 717 (82.5%) have died. The median survival period was 20 months. At 1 year, 66% were alive; at 3 years, 32%; and at 5 years, 18%.

Table 21.—**Causes of Death in 535 Cases of Multiple Myeloma**

Cause	No. (and %) of patients
"Myeloma"	232 (44)
Infection	105 (20)
Renal	77 (14)
Cardiac	45 (8)
Stroke	18 (3)
Cachexia	17 (3)
Other malignancy	8 (2)
Miscellaneous	33 (6)
Total	535*(100)

*Cause was unknown in 182 cases.

The causes of death are listed in Table 21. Infection was the most common specific cause of death, followed by renal insufficiency; in this regard, elevation of BUN is the most significant factor affecting prognosis.[44] In 44% of patients, only myeloma was recorded as a cause of death. Replies to letters and even death certificates listed the only cause of death as myeloma. In the miscellaneous group, hemorrhage (13 cases), pulmonary embolus (6), and suicide (3) accounted for 66% of the deaths. Autopsy was performed in 54% of patients.

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