

# IgM monoclonal gammopathy

## *Histopathologic and clinical spectrum*

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The differentiation between multiple myeloma and macroglobulinemia is usually not difficult. However, occasionally a patient will have presenting symptoms common to both diseases.<sup>1-8</sup> Furthermore, macroglobulinemia may be associated with lymphocytic lymphoma, chronic lymphocytic leukemia, or an additional monoclonal spike.<sup>9-31</sup> A "benign" IgM monoclonal gammopathy may also occur. The incidence of such intermediate syndromes and their prognostic significance is not well established.

This paper reviews 28 cases of IgM monoclonal gammopathy seen at the Cleveland Clinic; the histopathologic spectrum and clinicopathologic correlates are emphasized.

### **Materials and methods**

The records of 28 patients who had immunochemical studies compatible with IgM monoclonal gammopathy were reviewed. Representative blood smears, bone marrow aspirates or biopsy specimens or both were examined, as well as any other available surgical and necropsy material. Peripheral blood smears were examined for the presence of rouleau and unusual white cell morphology. A 500-cell count differential was done on each marrow aspirate, unless

it was extremely hypocellular. One hundred cell counts or qualitative estimates of dominant cell type were made on hypocellular specimens. The dominant marrow proliferating cell type was identified as plasmacytic, mature lymphocytic, or intermediate ("plasmacytoid lymphocyte" with an eccentric nucleus, clumped chromatin, and absence of a paranuclear halo).

Protein electrophoresis was performed on cellulose acetate using the Beckman microzone system with B-2 buffer (pH 8.6), Beckman fixative-dye solution (Ponseau-S, trichloroacetic acid, sulfosalicylic acid), and was read in the Beckman densitometer at 520 nm. Immunoelectrophoresis was performed in a Buchler electrophoretic chamber with a Heathkit power supply applying 90 volts constantly to serum buffered with barbital to pH 8.2 (ionic strength 0.04), and Behring antisera exposed to the electrophoresed sera. Following overnight (16–18 hour) incubation at room temperature in a moist chamber, zone diameters were measured and compared with curves derived from reference sera.

The material examined histopathologically was provided by seven necropsy and 11 surgical specimens. The surgical specimens were derived from bone marrow, liver, small bowel, kidney, and lymph node biopsies.

The criteria for a favorable response to initial chemotherapy were (1) an increase in the hemoglobin level of  $\geq 3$  g/dl; (2) disappearance of well-documented symptoms (e.g., recurrent epistaxis); decrease in hepatosplenomegaly or lymphadenopathy; (4) decrease in IgM of at least

50% initial level; and (5) sustained improvement for 3 months after initiation of therapy.

## Results

The data on the 28 patients are summarized in the *Table*. Both sexes were affected (13 men, 15 women), and most patients were age 60 or older (range 49 to 76 years, mean 63 years). Symptoms referable to anemia were present in 23 patients. Unusual symptoms included malabsorption, bone pain, lytic bone lesions on roentgenography, and the nephrotic syndrome. One patient (case 16) had Raynaud's phenomenon, and gangrene of a toe. Symptoms referable to the central nervous system were observed in only three patients. Two patients had histories of tuberculous infection or chronic cholecystitis.

Laboratory studies revealed anemia in 23 patients. Three had hypercalcemia and hyperuricemia, one an elevated serum creatinine level, and six had positive direct Coombs' tests. Elevated serum viscosity was present in all but two patients, although only three manifested the stigmata of the hyperviscosity syndrome. Five patients had cryoglobulinemia.

All patients had a "spike" on paper electrophoresis, which on immunoelectrophoresis was shown to be monoclonal IgG (M  $\kappa$  or M  $\lambda$ ). One patient (case 26) is currently undergoing evaluation for a biclonal IgM gammopathy. Four patients had depression of IgG or IgA. Serum albumin was depressed in six patients. There was no statistically significant difference between the patients with an initial serum IgM content  $> 3$  g/dl and those with  $< 3$  g/dl.

The light chain present was kappa type in 18 patients and lambda in 10 patients. Two patients fulfilled the criteria for benign monoclonal gammopathy as outlined by Osserman and Farhangi.<sup>32</sup> Another patient (case 12) had a monoclonal IgM of 4000 mg/dl; however, the marrow aspirate was normal, no anemia was present, and the patient was asymptomatic. She was treated with a short course of chlorambucil and is well with normal serum protein electrophoresis 5 years after treatment.

Examination of the peripheral blood smears demonstrated rouleau in all but six patients. Seven patients had an absolute mature lymphocytosis. Plasmacytoid lymphocytes were frequently identified in the peripheral blood (*Table*). Plasma cells and plasmablasts were seen in the smears of two patients (*Fig. 1*). Initial thrombocytopenia was identified in one patient.

Bone marrow aspirate specimens were hypocellular in 15 patients, but bone marrow biopsy specimens in these patients usually revealed hypercellularity. The dominant proliferating cell type was the mature lymphocyte in 21 cases (*Fig. 2*); however, in most aspirate specimens plasmacytoid lymphocytes and plasma cells were also present. In three patients, plasma cells and their precursors were dominant. Bone lesions were identified in two of the three, lytic humeral lesions associated with a pathological fracture in case 19 (*Fig. 3*), and diffuse osteoporosis in case 28 (*Figs. 4 and 5*). One patient had an equal infiltration of plasma cells, mature lymphocytes, and intermediate forms. Mast cells were prominent in six specimens. In three, the aspirate

was within normal limits. Two of the normal aspirates (cases 15 and 17) were obtained from patients with benign monoclonal gammopathy, and one from a patient with a moderate elevation of IgM which disappeared after a short course of chemotherapy (case 12).

Seventeen surgical and necropsy specimens were reviewed. In 10, mature lymphocytic infiltrates involving heart, gut serosa, spleen, pancreas, liver, lymph nodes, kidney, uterus, thyroid, lungs, and skin of ear in various combinations were present (*Figs. 6 and 7*). The mature lymphocytes were usually accompanied by plasmacytoid lymphocytes and plasma cells. The pattern of organ infiltration was most suggestive of mature lymphocytic lymphoma, and assumed both nodular (two patients) and diffuse (eight patients) patterns. A diffuse immature lymphocytic lymphoma was identified in one patient (case 22).

As illustrated in *Figures 8 and 9*, a pleomorphic infiltrate of large mononuclear cells, immunoblasts, plasma cells, and occasional Sternberg-Reed-like cells effaced the architecture of the node. In three patients, various combinations of plasma cell infiltration of bone marrow, liver, kidney, anterior pituitary, spleen, lymph nodes, leptomeninges, and peripheral nerves were observed. One patient (case 1) who had a marrow plasmacytosis without evidence of lytic bone lesions had persistent hypercalcemia and alveolar septal metastatic calcification of the lung (*Fig. 10*). This patient also had hyaline tubular casts, degenerating tubular epithelial cells, nephrocalcinosis, and a plasmalymphocytic infiltrate of kidney at ne-

Table. IgM monoclonal gammopathy; clinical and histopathologic findings, 28 patients

Case	Sex/ age	Complaints	Physical findings	Associated disease	Peripheral blood morphology					Histopathology	
					Rou- leau	Ane- mia	Plas- ma cells	Dominant marrow proliferating cell			Plasma cells
								Mature lymphocy- tosis	Inter- mediate		
1	M/76	Dyspnea, confu- sion	CRVO, HSM	Multiple mye- loma	+	+	+	*	+	Multiple myeloma involv- ing kidney, spleen, liver, lymph nodes, marrow, anterior pitui- tary	
2	F/58	Diarrhea, weight loss	HS	Malabsorption syndrome	+	-	-	+	*	Intestinal lymphectasia; DMLL with plasmacy- toid differentiation (lung, spleen, marrow, lymph nodes)	
3	M/59	Lymphad- enop- athy	S	CLL	+	+	-	+	*	Pleomorphic lymphoma c/ w Richter's syndrome involving marrow, lymph nodes, spleen, adrenals	
4	F/50	Epistaxis, weak- ness	L, HS SRVD	...	+	+	-	+	*	Pleomorphic lymphoma; ? histiocytic lymphoma	
5	M/67	Angina, dyspnea	L, HS	ASHD	-	-	-	+	*	...	
6	F/49	NV, weak- ness	HS	Chronic chole- cystic disease	+	+	-	+	*	DMLL with plasmacytic differentiation (lymph node)	
7	F/74	LBP, numb- ness	Normal	Multiple mye- loma	+	+	-	+	*	Multiple myeloma involv- ing lymph nodes, spleen, marrow, periph- eral nerves	

8	F/68	Arthralgia, anemia	L, S	Diabetes mellitus	+	+	-	-	+	*	*	...
9	M/47	Weakness	L, S	CLL	+	+	+	-	+	*	*	...
10	F/49	Dyspnea	Edema	CLL	+	+	+	-	+	*	*	NMLL (marrow)
11	M/68	None	HS	Diverticulitis	-	+	-	-	+	*	*	...
12	F/69	None	None	BMG (?)†	-	-	-	-	Normal	Normal	Normal	...
13	F/52	Dyspnea	CHF	...	+	+	-	-	+	*	*	Anthracotic lymph node (medist)
14	M/52	Neck mass	L, S	Monilia	+	+	-	-	+	*	*	DMLL (heart, spleen, liver, kidney, stomach, marrow, lymph nodes)
15	F/78	Numbness	CTS	BMG	-	-	-	-	Normal	Normal	Normal	...
16	F/67	Raynaud's phenomenon	L	CLL; gangrene (toe)	+	+	+	-	+	*	*	DMLL (heart, liver, kidney, spleen, LN, marrow)
17	M/68	Abdominal pain	None	BMG	-	-	-	-	Normal	Normal	Normal	...
18	M/67	Back pain, numbness	L, HS	Mixed sensory motor neuropathy	+	+	-	-	+	*	*	...
19	M/73	Confusion, weakness	HS, CRVO	...	+	+	-	-	+	*	*	...
20	M/74	Vertigo, epis-taxis	None	...	-	+	-	-	+	*	*	...
21	F/60	Weakness	L	CLL	+	+	+	...	+	...	...	DMLL (marrow)
22	F/61	Dyspnea	L, S	Diverticulitis	+	+	...	...	+	...	...	DILL (LN)
23	F/49	Weakness	S	...	+	+	...	...	+	...	...	DMLL (marrow)

Table — Continued

Case	Sex/ age	Complaints	Physical findings	Associated disease	Rou- leau	Ane- mia	Peripheral blood morphology		Dominant marrow proliferating cell		Histopathology
							Plas- ma cells	Abso- lute lym- pho- cyto- sis	Mature lympho- cytosis	Inter- mediate Plasma cells	
24	F/52	Epistaxis	HS, reti- nal hem- or- rhages	...	+	+	...	...	+	...	...
25	M/68	Weakness	L, HS	...	+	+	...	...	+	...	Lymphoma cutis (ears)
26	M/69	Back pain	Muscle spasm	Squamous cell carcinoma 2° in vertebra	+	+	...	...	+	...	DMLL, NMLL with plas- macytoid differentiation (marrow)
27	M/70	Fatigue	L	Diabetes melli- tus	+	+	...	...	+	...	DMLL with plasmacytoid differentiation
28	F/75	Back pain	Un- known	...	+	+	...	+	...	+	...

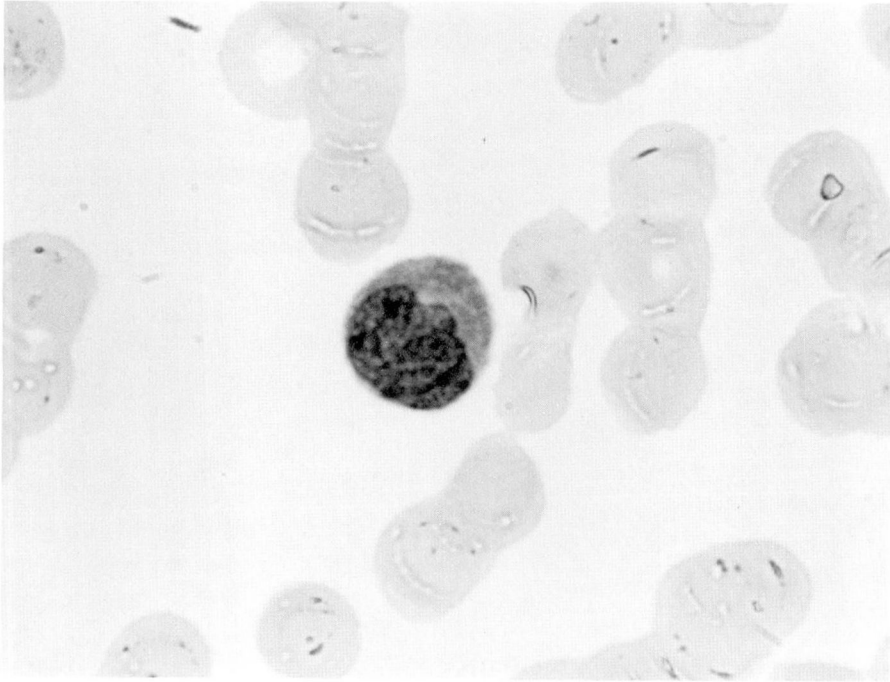
+ = present.

- = absent.

\* = present, but not dominant.

† = This patient had no anemia, was asymptomatic, had a normal bone marrow aspirate; her quantitative IgM was 3000 mg/dl, which reverted to normal following a short course of chlorambucil.

Abbreviations: CRVO = central retinal vein occlusion; HS = hepatosplenomegaly; DMLL = diffuse mature lymphocytic lymphoma; S = splenomegaly; CLL = chronic lymphocytic leukemia; L = lymphadenopathy; SRVD = segmental retinal venous distention; ASHD = atherosclerotic heart disease; NV = nausea and vomiting; LBP = low back pain; LN = lymph node; NMLL = nodular mature lymphocytic lymphoma; BMG = benign monoclonal gammopathy; CHF = congestive heart failure; CTS = carpal tunnel syndrome; DILL = diffuse immature lymphocytic lymphoma.



**Fig. 1.** Peripheral blood smear (case 1) demonstrating circulating plasmablasts (Wright's stain,  $\times 1600$ ).

croscopy compatible with "myeloma kidney" (Fig. 11).

### Discussion

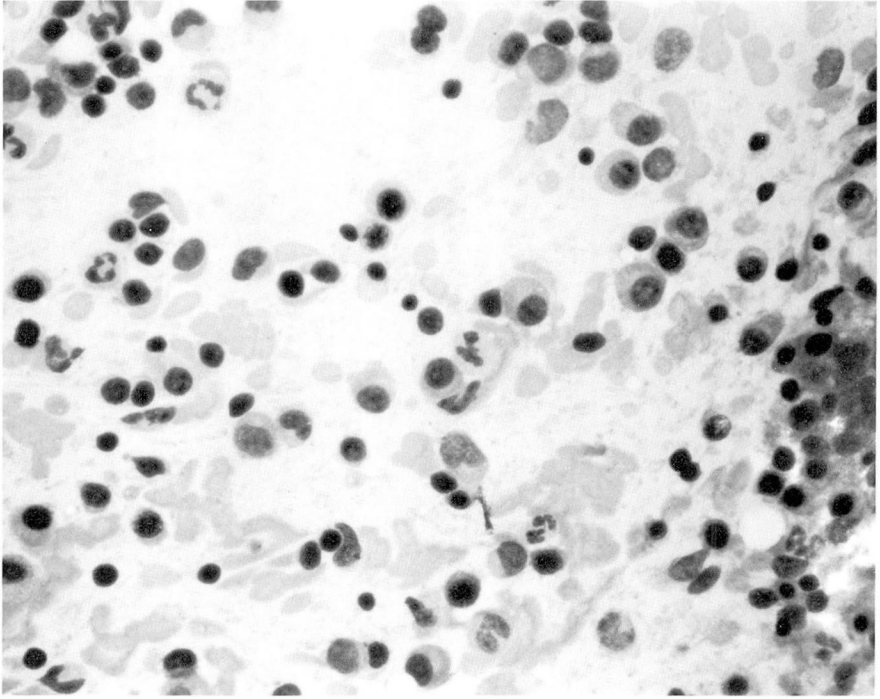
Since the original description of macroglobulinemia by Waldenström in 1944,<sup>33</sup> a large number of cases have been reported. The syndrome is characterized by the presence of a monoclonal immunoglobulin which on immunoelectrophoresis is composed of  $\mu$  heavy chains and one light chain type ( $\kappa$  or  $\lambda$ ) with a variable proliferation of, and infiltration by lymphoid cells demonstrating a plasmacytic differentiation.

The validity of classifying macroglobulinemia as either primary or secondary is open to dispute<sup>34</sup> and often difficult to accomplish. A relationship between macroglobulinemia and tuberculosis or chronic inflam-

mation or neoplasia has been previously emphasized.<sup>35-38</sup> In the present series there were five cases that might be considered "secondary." One patient (case 26) had a squamous cell carcinoma metastatic to bone marrow in addition to an IgM monoclonal gammopathy. Both proliferations were present in a vertebral bone marrow biopsy. Migliore and Alexanian,<sup>39</sup> however, have shown that the incidence of a monoclonal spike in approximately 5,000 patients evaluated for neoplasia, excluding myeloma, was similar to a comparable normal adult population. Various studies have suggested a familial basis or predisposition for the disease, describing family clusters of patients with macroglobulinemia.<sup>40, 41</sup>

Other clinical parameters which were evaluated parallel closely the re-





**Fig. 2.** Bone marrow aspirate (case 2); the dominant marrow proliferating cell type is the mature lymphocyte with plasmacytoid lymphocytes and occasional mature plasma cells. This morphology was observed in the majority of aspirate specimens (Wright's stain,  $\times 400$ ).

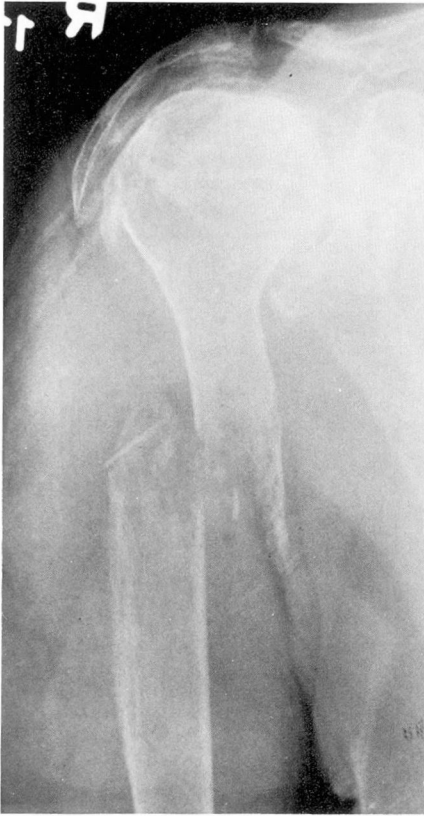
sults of previously reported series.<sup>34, 36</sup> Elderly patients of both sexes were affected equally. Symptoms compatible with the hyperviscosity syndrome developed in only three patients in this series, despite the finding of increased serum viscosity in 26 patients. Five patients had cryoglobulinemia. In MacKenzie and Fudenberg's series<sup>34</sup> of 40 cases, 32% fulfilled their criteria for diagnosis of the hyperviscosity syndrome (epistaxis, cephalgia, tinnitus, weakness). Other stigmata of the syndrome include transient neurological deficits, such as intermittent paresis and disturbances of level of consciousness, deafness, and seizures. The symptoms did not appear until segmental retinal vein distention was present. Segmental retinal vein distention and punctate retinal hemorrhages were

observed in four patients in this series. On physical examination splenomegaly and hepatosplenomegaly or lymphadenopathy or both were present in the majority of patients (*Table*).

Reduced quantities of other immunoglobulin classes (IgG, IgA) were observed in only four patients and were of mild degree, in contrast to patients with myeloma.<sup>42</sup> When quantitative IgM levels were grouped into increments of 1000 mg, no statistically significant correlation with survival could be identified. This may be related to an inherent defect in the radial immunodiffusion technique used to determine quantitative IgM levels; antisera used in this test are prepared from monoclonal proteins and may not react with all IgM present.

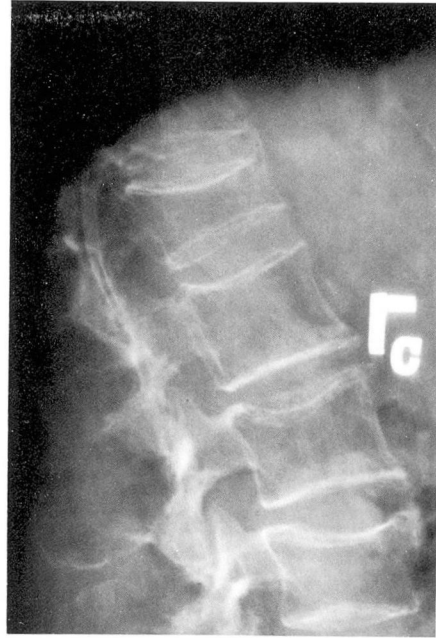
Several cases of two or more coex-





**Fig. 3.** Roentgenogram, right humerus (case 19); lytic metaphyseal lesions associated with a pathological fracture.

istent monoclonal gammopathies (IgM or IgG + IgA) have been reported.<sup>9-31</sup> McNutt and Fudenberg,<sup>19</sup> in describing a patient with a preponderance of IgG, but with a clinical picture resembling macroglobulinemia, demonstrated that the clinical course of patients with multiple M-components was not necessarily related to the M-component present in the highest concentration as suggested by Saunders et al.<sup>23</sup> The presence of two M-components superficially implies biclonal cell proliferation. Rudders et al<sup>43</sup> have described a patient with IgG/IgA monoclonal immunoglobulins (lambda light chain type in each case), in which immuno-



**Fig. 4.** Roentgenogram, lumbar spine (case 28); moderately severe osteoporosis is identified.

fluorescence of the myeloma marrow cells demonstrated cells to which both IgG and IgA were attached (in addition to cells containing only IgG or IgA). Pernis et al<sup>44</sup> have identified both IgM and IgG antibody on the same cell following primary immunization of rabbits. However, present concepts relating to immunoglobulin synthesis include separate genes controlling synthesis of the polypeptides of the constant and variable regions of the molecule. Furthermore, antibody specificity is a function of the variable portion of the heavy and light chains. Wang et al<sup>29, 30</sup> and Levin et al<sup>31</sup> studied the amino acid sequences in the variable regions of IgM and IgG in a patient with biclonal gammopathy, and found the sequence to be identical. The above data are thought to support the existence of a single clone or myeloma cells (or myeloma-macroglobulinemia

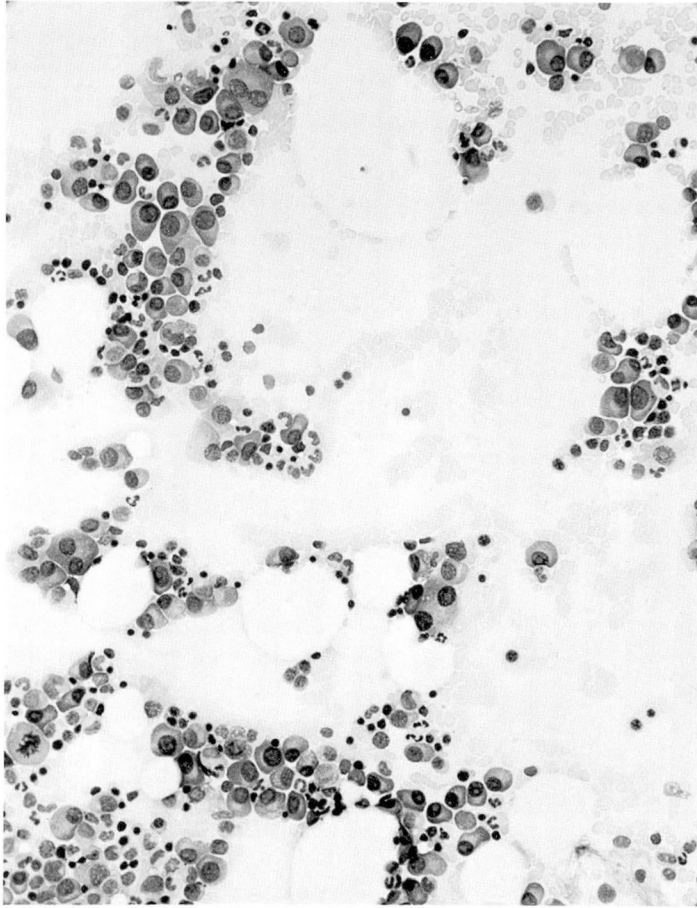


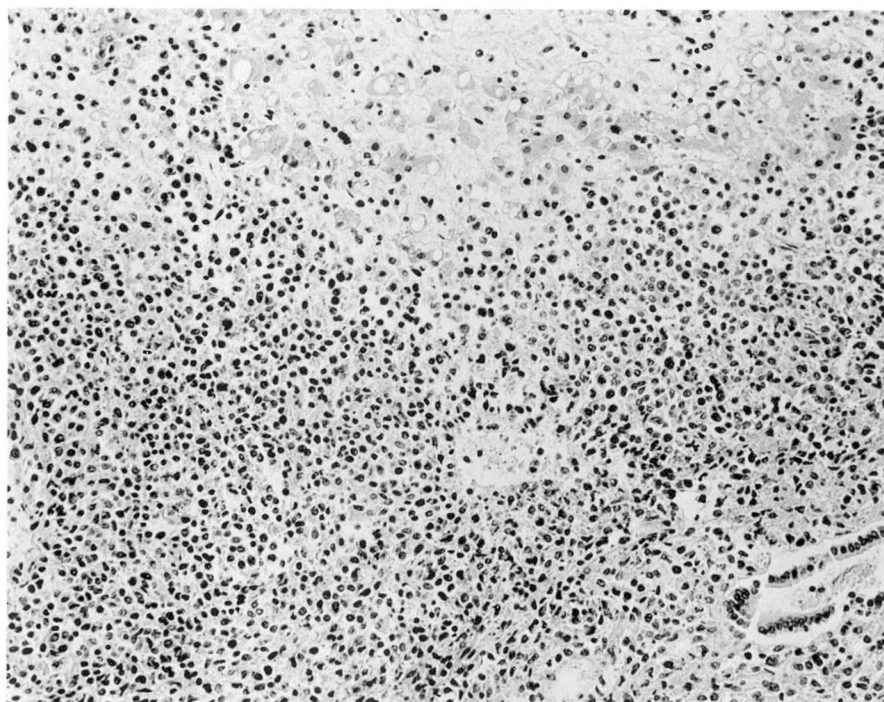
Fig. 5. Dominant marrow plasmacytosis with plasmablasts (case 1) (Wright's stain,  $\times 160$ ).

cells), with a single gene synthesizing the variable regions of both M-components, and separate genes synthesizing the constant regions of the two M-components.

Examination of the peripheral blood smears in our series disclosed rouleau formation of red blood cells in 22 patients, and plasmacytoid lymphocytes or plasma cells in 13 patients. In this series the mature lymphocyte was the dominant marrow cell type (21 patients), but was usually accompanied by plasmacytoid lymphocytes and plasma cells. Rohr,<sup>45</sup> Dutcher and Fahey,<sup>35</sup> and MacKenzie and Fudenberg<sup>34</sup> have indicated that

the proliferating marrow cell type may be dominantly mature lymphocytic, plasmacytic, or intermediate (plasmacytoid lymphocytic). In this series three patients demonstrated a marrow plasmacytosis (cases 1, 7, 28). In a series of 18 patients with macroglobulinemia, Martin<sup>36</sup> found one with a dominant marrow plasmacytosis. Many investigators who have reported "myelomatosis and macroglobulinemia" have relied upon ultracentrifugation to establish the diagnosis of macroglobulinemia.<sup>46-53</sup> However, since Smith et al<sup>54</sup> and others<sup>55, 56</sup> have demonstrated that aggregates of IgG and IgA can be pres-



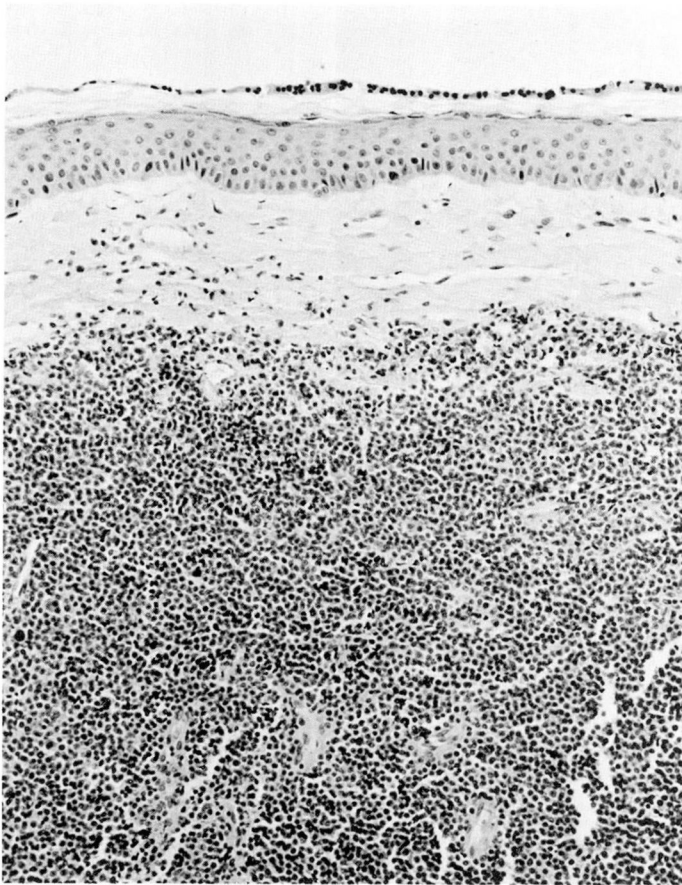


**Fig. 6.** Necropsy section of liver (case 14) demonstrating a diffuse mature lymphocytic lymphoma with plasmacytic differentiation (hematoxylin and eosin stain,  $\times 160$ ).

ent in patients with plasma cell myeloma, and on ultracentrifugation can be shown to have high sedimentation coefficients, the analysis of "macroglobulins" must be based on immunoelectrophoretic identification of the M-component as IgM type. Eight cases of macroglobulinemia and marrow plasmacytosis have been reported; these patients had immunochemical verification that their "macroglobulin" was IgM.<sup>1-8</sup> A mouse plasmacytoma has been described which secreted IgM; the morphology of the tumor was identical to that of IgA/IgG-producing plasmacytomas.<sup>57</sup> Rywlin et al<sup>58</sup> have reviewed the histology of marrow biopsy specimens from 26 patients with monoclonal macroglobulinemia. In 11 patients the lymphoid infiltrate was characteristic of nodular (seven pa-

tients) or diffuse (four patients) lymphocytic lymphoma, and in six a nodular lymphoid hyperplasia was present. Lymphoid nodules were normal or absent in the remaining nine patients.

The most frequently encountered intermediate disease states are represented by the patients with IgM M-components in whom the neoplastic cell, whether it be mature lymphocytic, plasmacytoid lymphocytic, or plasmacytic infiltrates various organs and peripheral blood. The typical picture most closely resembles lymphocytic lymphoma, as noted in the majority of patients (10) in this series from whom surgical or necropsy material was available. Coexistent chronic lymphocytic leukemia (CLL) was seen frequently in this series (seven patients). Approximately 5%



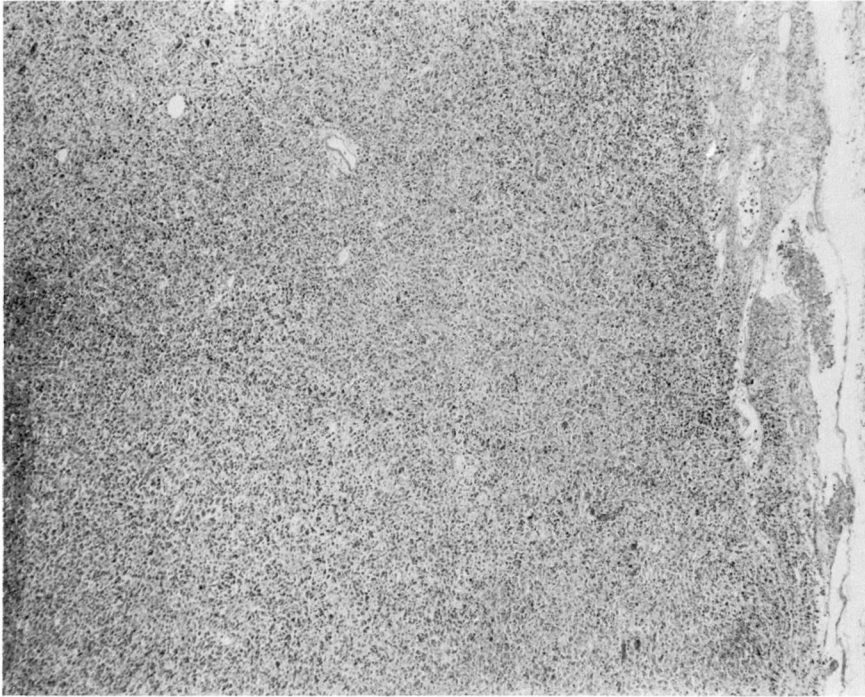
**Fig. 7.** Biopsy specimen from right ear (case 25) demonstrating a diffuse mature lymphocytic lymphoma with plasmacytic differentiation (hematoxylin and eosin stain,  $\times 160$ ).

of patients with CLL have monoclonal gammopathy.<sup>59</sup> Grey et al<sup>60</sup> have shown that monoclonal IgM proteins are present on the majority of lymphocytes from patients with CLL. Although B-cell surface markers are most common, a small number of patients have T-cell surface markers.<sup>61</sup> Furthermore, quantitative alterations in CLL surface markers occur as the disease progresses.<sup>62</sup> Lymphomas can also have similar surface monoclonal globulins.<sup>63</sup> By chronic stimulation of the lymphoreticular system such observations and studies in animals have led to the hypothesis that the M-compo-

nents in plasma cell myeloma and macroglobulinemia are immunoglobulins with antibody activity reflecting induction of globulin synthesis by underlying neoplasia or a chronic inflammatory process.<sup>64-69</sup>

This concept of clone induction of M-component synthesis by an adjuvant is supported by immunofluorescent studies which have shown that plasma cells synthesize only one light chain and one heavy chain type,<sup>70, 71</sup> and that the rate of myeloma protein synthesis parallels the rate of albumin synthesis in normal liver<sup>72</sup> (implying that the quantity of M-component is primarily dependent on cell prolifer-





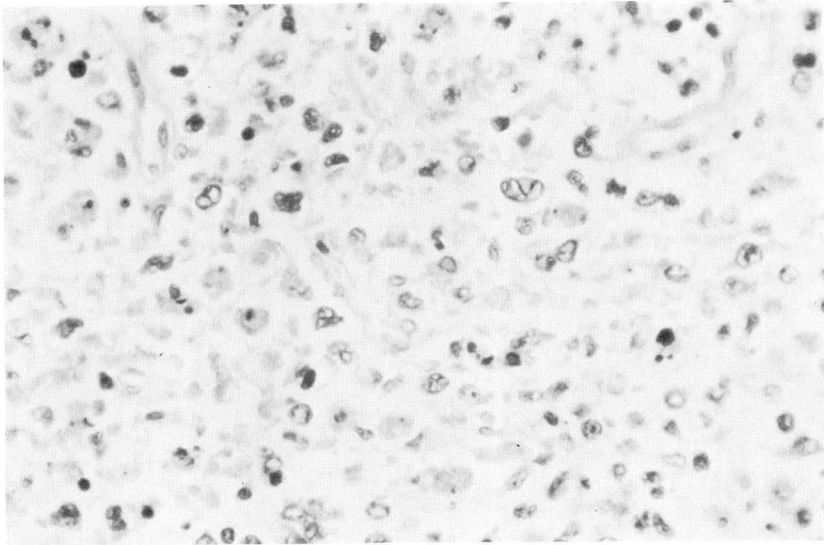
**Fig. 8.** Necropsy section of lymph node (case 3) demonstrating effacement of architecture and fat infiltration by a diffuse infiltrate consisting of large pleomorphic mononuclear cells. In other areas a diffuse mature lymphocytic infiltrate was present (hematoxylin and eosin stain,  $\times 40$ ).

ation). A patient has been described in whom a marrow plasmacytosis and an M-component developed on exposure to sulfisoxazole (Gantrisin), both of which disappeared on withdrawal of the drug.<sup>72</sup>

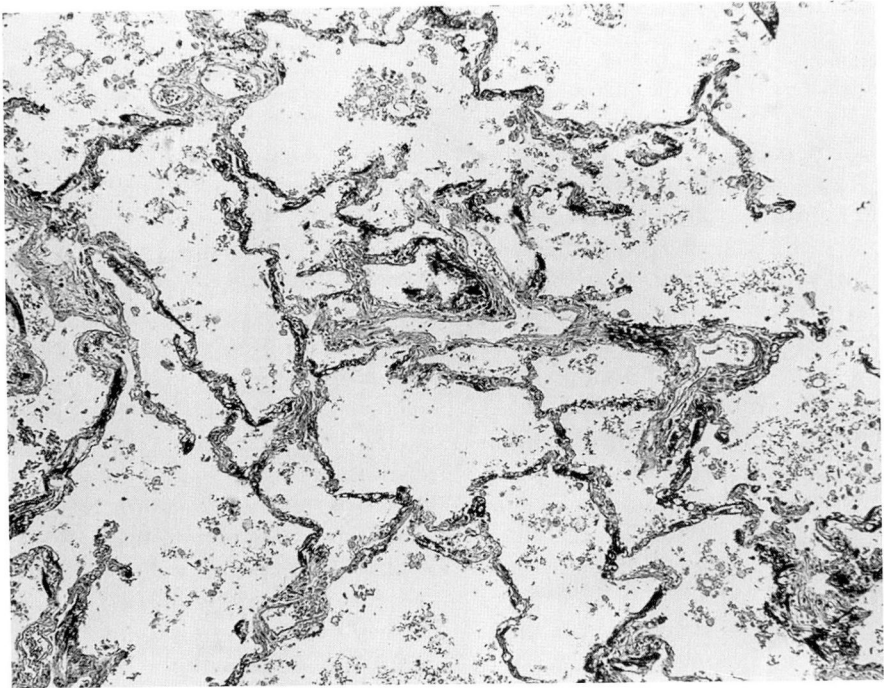
Histopathologic findings on 16 patients were reviewed. Lymph node biopsy specimens demonstrated effacement by sheets of mature lymphocytes, plasmacytoid lymphocytes, and plasma cells. A similar cellular infiltrate was noted in liver, spleen, intestine, thyroid, kidney, and bone marrow (Figs. 6 and 7). A renal lesion characteristic of "myeloma kidney" was present in one patient (case 1) (Fig. 11). Renal disease is not common in patients with macroglobulinemia.<sup>73, 74</sup> When present it may reflect hypercalcemia or uric acid nephropathy,<sup>74, 75</sup> rarely renal amyloidosis,<sup>76</sup> or

interstitial infiltration by lymphocytes or intermediate and plasmacytic forms.<sup>77</sup> The most pronounced changes are in the glomeruli, where PAS positive eosinophilic coagula are noted within the tuft capillaries (IgM by immunofluorescence).<sup>77</sup> A lobular glomerulonephritis has been reported,<sup>78</sup> but renal disease is not usually a dominant feature of macroglobulinemia.

Metastatic calcification of the lung as seen in one patient (case 1) (Fig. 10) has not previously been associated with macroglobulinemia, probably since hypercalcemia is not often present in patients with the disease. Spencer<sup>79</sup> has described diffuse interstitial lymphocytic reticulin-like cellular infiltrate, associated with proteinaceous intraalveolar material and thrombi in small pulmonary arterial

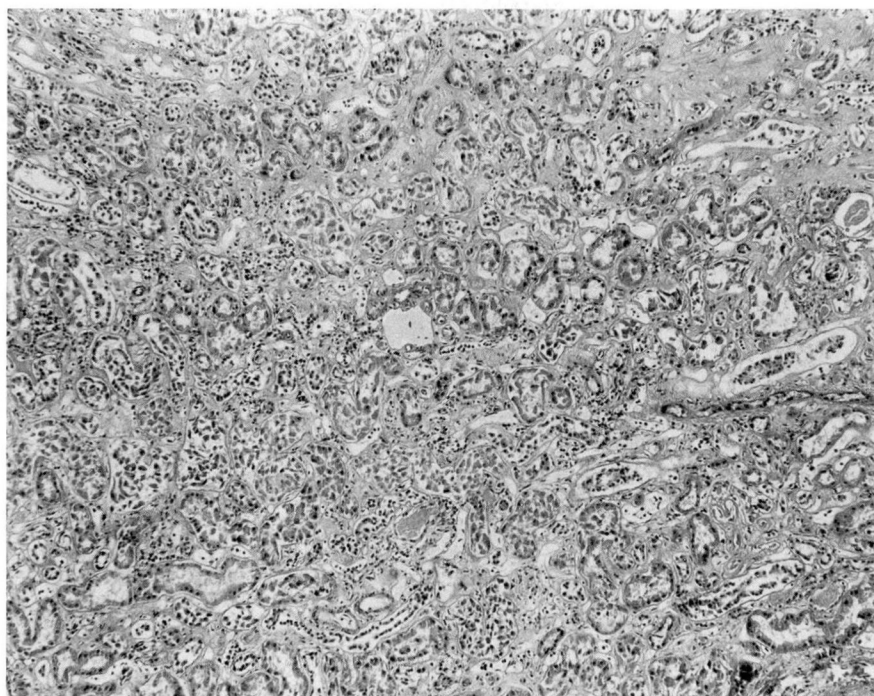


**Fig. 9.** Higher magnification of lymph node section from *Figure 8* above. Occasional Sternberg-Reed-like cells are present (hematoxylin and eosin stain,  $\times 400$ ).



**Fig. 10.** Necropsy section of lung (case 1) demonstrating metastatic alveolar septal calcification. Patient had long-standing hypercalcemia (von Kossa stain,  $\times 64$ ).





**Fig. 11.** Necropsy section of kidney (case 1) demonstrating tubular cell atrophy, lymphoplasmacytic interstitial infiltrate, and hyaline tubular casts. Nephrocalcinosis was present in other sections (hematoxylin and eosin stain,  $\times 64$ ).

branches with or without local deposits of amyloid as most characteristic of the affected lung in macroglobulinemia.<sup>79</sup> A primitive malignant lymphoma compatible with diffuse histiocytic lymphoma developed in two patients (cases 3 and 4) late in the evolution of their illness. Sternberg-Reed-like cells were identified in surgical and necropsy material from these patients. This primitive neoplasm simulating Hodgkin's disease appeared in one patient (case 3) after a diagnosis of chronic lymphocytic leukemia with IgM monoclonal gammopathy had been established. A mature lymphocytic infiltrate was present in segments of bone marrow and lymph node compatible with chronic lymphocytic leukemia/macroglobulinemia. These histopathologic observations together with the accelerated

clinical course are characteristic of Richter's syndrome,<sup>80-83</sup> which probably represents a dedifferentiation of chronic lymphocytic leukemia comparable to a blast transformation of chronic granulocytic leukemia.<sup>81, 82</sup> The histopathology of the lymph node biopsy specimen from one patient (case 4) was similar to that observed in another patient (case 3), including the presence of Sternberg-Reed-like cells, although an absolute lymphocytosis was not shown in the peripheral blood.

We attempted to correlate survival with various parameters. No significant correlation was identified between the initial IgM level and survival. The only significant difference ( $p < 0.01$ ) was found when the mean survival of patients who had an initially favorable response to chemo-

therapy (70 months) was compared with a mean survival for those who had an initially poor response to chemotherapy (27 months). MacKenzie and Fudenburg<sup>34</sup> also found that the prognosis is highly correlated with initial chemotherapeutic response—the length of survival of their responding patients was twice that of those who did not respond. Furthermore, there was no statistically significant differences in survival between patients with CLL and macroglobulinemia and those with macroglobulinemia alone. The mean survival of two patients with a marrow plasmacytosis followed for at least 1 year was 28 months, not significantly different from the mean survival of 41 months for patients with a dominant mature lymphocytic marrow proliferation.

### Summary

The clinical records, peripheral blood smears, marrow aspirates, surgical and necropsy specimens from 28 patients with IgM monoclonal gammopathy were retrospectively reviewed. Disease states intermediate between pure Waldenström's macroglobulinemia and lymphocytic lymphoma, chronic lymphocytic leukemia, and myeloma were observed in 18 patients. Available surgical and necropsy material was compatible in nine instances with diffuse mature lymphocytic lymphoma. Of the three patients who had a marrow plasmacytosis, one had diffuse osteoporosis, one lytic bone lesions, and the third had no demonstrable roentgenographic abnormalities.

There was no correlation between survival and initial IgM levels, between survival and marrow proliferating cell type, nor between initial

IgM level and marrow proliferating cell type. No significant differences in initial IgM levels or survival were identified between patients with coexistent macroglobulinemia and chronic lymphocytic leukemia and patients with macroglobulinemia alone. A statistically significant difference ( $p < 0.01$ ) was found between the mean survival of patients who responded to initial chemotherapy (70 months) and those who did not respond (27 months).

Although 26 patients had increased serum viscosity, only three manifested the hyperviscosity syndrome; all were benefited by plasmaphoresis.

### References

1. Adner PL, Wallenius G, Werner I: Macroglobulinemia and myelomatosis. *Acta Med Scand* **168**: 431-437, 1960.
2. Welton J, Walker SR, Sharp GC, et al: Macroglobulinemia with bone destruction. *Am J Med* **44**: 280-288, 1968.
3. Wanner J, Siebenmann R: Über eine subakut verlaufende osteolytische Form der Makroglobulinämie Waldenström mit plasmazellenleukämie. *Schweiz Med Wochenschr* **87**: 1243-1246, 1957.
4. Bachmann R: The diagnostic significance of the serum concentration of pathological proteins (m-components). *Acta Med Scand* **178**: 801-808, 1965.
5. Castleman B., Scully RE, McNeely BU: Case records Massachusetts General Hospital (case 31-1972). *N Engl J Med* **287**: 243-248, 1972.
6. Waldenström J: Hypergammaglobulinemia as a clinical hematological problem; a study in the gammopathies. *Prog Hematol* **3**: 266-293, 1962.
7. Schwarz J: Subleukämischer Verlauf einer Makroglobulinämie Waldenström mit Osteolysen: IgM-kappa-kryoglobulin mit antinuklearer Aktivität und Kettenfragment. *Klin Wochenschrift* **51**: 900-906, 1973.
8. Berman HH: Waldenström's macroglobulinemia with lytic osseous lesions to plasma-cell morphology. Report of case. *Am J Clin Pathol* **63**: 397-402, 1975.
9. Imhof JW, Ballieux RE, Mul NAJ, et al:

- Monoclonal and diclonal gammopathies. *Acta Med Scand* **179**: Suppl 445: 102-115, 1966.
10. Fateh-Moghadam A, Beil E, Borchers H, et al: Plasmozytom, Makroglobulinämie Waldenström und Morbus Paget bei einem Patienten mit IgAK+IgMK-Doppelparaproteinämie und Bence-Jones-Protein (Typ K). *Blut* **21**: 146-154, 1970.
  11. Harboe M, Hannestad K, Sletten K: Oligoclonal macroglobulinemia. *Scand J Immunol* **1**: 13-26, 1972.
  12. Hopper JE: Immunofluorescent evidence for a common clonal origin of IgM- $\lambda$  and IgG- $\kappa$  paraproteins. (Abstr) *Clin Res* **21**: 557, 1973.
  13. Hopper JE, Noyes C, Heinrickson RL, et al: Idiotypic antigenic analysis and n-terminal heavy chain sequences of monotypic IgM- $\lambda$  and IgG- $\kappa$  from a single patient. (Abstr) *Clin Res* **21**: 581, 1973.
  14. Bjerrum O, Wecke B: Two M-components ( $\gamma$ GK and  $\gamma$ ML) in different cells of the same patient. *Scand J Haematol* **5**: 215-234, 1968.
  15. Jensen K, Jensen KB, Olesen H: Three M-components in serum from an apparently healthy person. *Scand J Haematol* **4**: 485-488, 1967.
  16. Josephson AS, Nicastrì A, Price E, et al: H $\mu$  chain fragment and monoclonal IgA in a lymphoproliferative disorder. *Am J Med* **54**: 127-135, 1973.
  17. Keller H, Spengler G, Skvaril F, et al: Zur Frage der Heavy chain disease. Ein Fall von IgG-heavy chain Fragment und IgM-Typ K-Paraproteinämie mit Plasmazellenleukämie. *Schweiz Med Wochenschr* **100**: 1012-1022, 1970.
  18. Koraglod L: Plasma proteins: methods of study and changes in disease, *in* *Prog Clin Pathol*, Stefanini M, ed. New York, Grune and Stratton, 1966, p 340.
  19. McNutt DR, Fudenberg HH: IgG myeloma and Waldenström macroglobulinemia. Coexistence and clinical manifestations in one patient. *Arch Intern Med* **131**: 731-736, 1973.
  20. Natvig JB, Kunkel HG: Human immunoglobulins: classes, subclasses, genetic variants, and idiotypes. *Adv Immunol* **16**: 1-59, 1973.
  21. Penn GM, Kunkel HG, Grey HM: Sharing of individual antigenic determinants between a  $\gamma$ G and a  $\gamma$ M protein in the same myeloma serum. *Proc Soc Exp Biol Med* **135**: 660-665, 1970.
  22. Preud'homme JL, Seligmann M: Surface bound immunoglobulins as a cell marker in human lymphoproliferative diseases. *Blood* **40**: 777-794, 1972.
  23. Sanders JH, Fahey JL, Finegold I, et al: Multiple anomalous immunoglobulins. Clinical, structural and cellular studies in three patients. *Am J Med* **47**: 43-59, 1969.
  24. Seon BK, Yagi Y, Pressman D: Monoclonal IgA and IgM in the serum of a single patient (SC). II. Identity of light chains from IgA( $\kappa$ ) and IgM( $\kappa$ ). *J Immunol* **110**: 345-349, 1973.
  25. Pruzanski W, Underdown B, Silver EH, et al: Macroglobulinemia-myeloma double gammopathy; a study of four cases and a review of the literature. *Am J Med* **57**: 259-266, 1974.
  26. Silverman AY, Yagi Y, Pressman D, et al: Monoclonal IgA and IgM in the serum of a single patient (SC). III. Immunofluorescent identification of cells producing IgA and IgM. *J Immunol* **110**: 350-353, 1973.
  27. Tischendorf FW, Heckner F: Atypisches Plasmozytom mit gG<sub>3</sub>K-gMk-doppelparaproteinämie. Bence Jones Protein (Typ k) und Lysozymurie. *Dtsch Ges Hematol* **8**: 162-168, 1969.
  28. Curtain CC: Immuno-cytochemical localization of two abnormal serum globulins in the one bone-marrow smear. *Aust Ann Med* **13**: 136-138, 1964.
  29. Wang AC, Wang IY, McCormick JN, et al: The identity of the light chains of monoclonal IgG and monoclonal IgM in one patient. *Immunochemistry* **6**: 451-459, 1969.
  30. Wang AC, Wilson KS, Hopper JE, et al: Evidence for the control of synthesis of the variable regions of light and heavy chains of immunoglobulins G and M by the same gene. *Proc Natl Acad Sci USA* **66**: 337-343, 1970.
  31. Levin AS, Fudenberg HH, Hopper JE, et al: Immunofluorescent evidence for cellular control of synthesis of variable regions of light and heavy chains of immunoglobulins G and M by the same gene. *Proc Natl Acad Sci USA* **68**: 169-171, 1971.
  32. Osserman E, Farhangi M: *in* *Hematology*, Williams WJ, ed. New York, McGraw-Hill, 1972, p 963.
  33. Waldenström J: Incipient myelomatosis or "essential" hyperglobulinemia with fibrinogenopenia; A new syndrome? *Acta Med Scand* **117**: 216-247, 1944.
  34. MacKenzie MR, Fudenberg HH: Macro-

- globulinemia; an analysis of forty patients. *Blood* **39**: 874-889, 1972.
35. Dutcher TF, Fahey JL: The histopathology of the macroglobulinemia of Waldenström. *J Natl Cancer Inst* **22**: 887-917, 1959.
  36. Martin NH: Macroglobulinaemia; a clinical and pathological study. *Q J Med* **29**: 179-197, 1960.
  37. Weinberg AG, McCracken GH Jr, Lo-Spalluto J, et al: Monoclonal macroglobulinemia and cytomegalic inclusion disease. *Pediatrics* **51**: 518-524, 1973.
  38. Osserman E, Takatsuki K: Considerations regarding the pathogenesis of the plasmacytic dyscrasias. *Scand J Hematol Suppl* **4**: 28-33, 1964.
  39. Migliore PJ, Alexanian R: Monoclonal gammopathy in human neoplasia. *Cancer* **21**: 1127-1131, 1968.
  40. Seligmann M: A genetic predisposition to Waldenström's macroglobulinemia. *Acta Med Scand* **179**: Suppl 445: 140-146, 1966.
  41. Massari R, Fine J, Metais R: Waldenström's macroglobulinaemia observed in two brothers. *Nature* **196**: 176-178, 1962.
  42. McKelvey EM, Fahey JL: Immunoglobulin changes in disease; quantitation on the basis of heavy polypeptide chains, IgG ( $\gamma$ G), IgA ( $\gamma$ A), and IgM ( $\gamma$ M), and of light polypeptide chains, type K (I) and type L (II). *J Clin Invest* **44**: 1778-1787, 1965.
  43. Rudders RA, Yakulis V, Heller P: Double myeloma; production of both IgG type lambda and Ig A type lambda myeloma proteins by a single plasma cell line. *Am J Med* **55**: 215-221, 1973.
  44. Pernis B, Forni L, Amante L: Immunoglobulins as cell receptors. *Ann NY Acad Sci* **190**: 420-431, 1971.
  45. Rohr K: Reaktive Retikulosen des Knochenmarkes. *Acta Haematol* **7**: 321-323, 1953.
  46. Wunderly C, Piller S: Die Färbung der im Blutsrum enthaltenen Proteine, Lipide und Kohlenhydrate nach Papier-Elektrophorese eine chemische Trias. *Klin Wchnschr* **32**: 425-432, 1954.
  47. Droste R: Histiomonozytäre Retikulose mit Makroglobulinämie und Knochendestruktion. *Medizinische No.* 19, 792-794, 1958.
  48. Lennert K: Die pathologische Anatomie der Makroglobulinämie Waldenström. *Frankfurt Ztschr Path* **66**: 201-226, 1955.
  49. Motulsky A, Eriksen N, Volwiler W, et al: *in Transactions of the European Society of hematology. Sixth Congress, Copenhagen, 1957. Basel, Karger, 44, 1958.*
  50. Riva C, Dialer K, Hassig A: Untersuchungen zur forge der Bence-Joneshen proteinurie und proteinemie. *Helv Med Acta* **18**: 401-404, 1958.
  51. Bichel J, Bing J, Harboe N: Cited by Adner PL, Wallenius G, Werner I: Macroglobulinemia and myelomatosis. *Acta Med Scand* **168**: 431-437, 1960.
  52. Creyscel R, Charvillat L, Morel P, et al: Cited by Adner PL, Wallenius G, Werner I: Macroglobulinemia and myelomatosis. *Acta Med Scand* **168**: 431-437, 1960.
  53. Grisolia FT, Cohen PP: Amino acid analysis of serum proteins in multiple myeloma. *Cancer Res* **13**: 851-854, 1953.
  54. Smith E, Kochwa S, Wasserman LR: Aggregation of IgG globulin *in vivo*. I. The hyperviscosity syndrome in multiple myeloma. *Am J Med* **39**: 35-48, 1965.
  55. Levin WC, Ritzmann SE, Seeuwen JP, et al: Some properties of beta-2A-myeloma proteins. *Clin Chim Acta* **10**: 12-20, 1964.
  56. Vaerman JP, Johnson LB, Mandy WS, et al: Multiple myeloma with two paraprotein peaks; an instructive case. *J Lab Clin Med* **65**: 18-25, 1965.
  57. McIntire KR, Asofsky RM, Potter M, et al: Macroglobulin-producing plasma-cell tumor in mice; identification of a new light chain. *Science* **150**: 361-363, 1965.
  58. Rywlin AM, Civantos F, Ortega RS, et al: Bone marrow histology in monoclonal macroglobulinemia. *Am J Clin Pathol* **63**: 769-778, 1975.
  59. Azar HA, Hill WT, Osserman EF: Malignant lymphoma and lymphatic leukemia associated with myeloma-type serum proteins. *Am J Med* **23**: 239-249, 1957.
  60. Grey HM, Rabellino E, Pirofsky B: Immunoglobulins on the surface of lymphocytes. IV. Distribution in hypogammaglobulinemia, cellular immune deficiency, and chronic lymphatic leukemia. *J Clin Invest* **50**: 2368-2375, 1971.
  61. Yodoi J, Takatsuki K, Masuda T: Two cases of T-cell chronic lymphocytic leukemia in Japan. *N Engl J Med* **290**: 572-573, 1974.
  62. Davis S: The variable pattern of circulating lymphocyte subpopulations in chronic lymphocytic leukemia. *N Engl J Med* **294**: 1150-1153, 1976.
  63. Klein G, Clifford P, Klein E, et al: Membrane immunofluorescence reactions of Burkitt lymphoma cells from biopsy speci-



- mens and tissue cultures. *J Natl Cancer Inst* **39**: 1027-1044, 1967.
64. Farhangi M, Osserman EF: Myeloma with xanthoderma due to an IgG monoclonal anti-flavin antibody. *N Engl J Med* **294**: 177-183, 1976.
  65. Seligmann M, Brouet J: Antibody activity of human myeloma globulins. *Semin Haematol* **10**: 163-177, 1973.
  66. Potter M: Myeloma proteins (M-components) with antibody-like activity. *N Engl J Med* **284**: 831-838, 1971.
  67. Metzger H: Characterization of a human macroglobulin. V. A. Waldenström macroglobulin with antibody activity. *Proc Natl Acad Sci USA* **57**: 1490-1497, 1967.
  68. Ashman RF, Metzger H: A Waldenström macroglobulin which binds nitrophenyl ligands. *J Biol Chem* **244**: 3405-3414, 1969.
  69. Mackenzie MR, Goldberg LS, Barnett EV, et al: Serological heterogeneity of the IgM components of mixed (monoclonal IgM-polyclonal IgG) cryoglobulins. *Clin Exper Immunol* **3**: 931-941, 1968.
  70. Chiappino G, Pernis B: Demonstration with immunofluorescence of 19S macroglobulins and 7S gamma globulins in different cells of the human spleen. *Path Microbiol* **27**: 8-15, 1964.
  71. Bernier GM, Cebra JJ: Frequency distribution of alpha, gamma, kappa, and lambda polypeptide chains in human lymphoid tissues. *J Immunol* **95**: 246-253, 1965.
  72. Ballieux RE, Imhof JW, Mul NA, et al: Pathology of immunoglobulins; some aspects of monoclonal gammopathy. *Clin Chim Acta* **22**: 7-13, 1968.
  73. Waldenström J: Macroglobulinemia. *Advances Metab Dis* **2**: 116-158, 1965.
  74. Zollinger H: Die pathologische Anatomie der Macroglobulinämie Waldenström. *Helv Med Acta* **25**: 153-157, 1958.
  75. Morel-Maroger L, Basch A, Danon F, et al: Pathology of the kidney in Waldenström's macroglobulinemia. Study of 16 cases. *N Engl J Med* **283**: 123-129, 1970.
  76. Forget BG, Squires JW, Sheldon H: Waldenström's macroglobulinemia with generalized amyloidosis. *Arch Intern Med* **118**: 363-375, 1966.
  77. Heptinstall R: *Pathology of the Kidney*. Boston, Little Brown and Co, 1974, p 767.
  78. Zlotnick A, Rosenmann E: Renal pathologic findings associated with monoclonal gammopathies. *Arch Intern Med* **135**: 40-45, 1975.
  79. Spencer H: *Pathology of the Lung*, ed. 2. Edinburgh, Pergamon Press, 1968.
  80. Richter M: Generalized reticular cell sarcoma of lymph nodes associated with lymphatic leukemia. *Am J Pathol* **4**: 285-299, 1928.
  81. Long JC, Aisenberg AC: Richter's syndrome; a terminal complication of chronic lymphocytic leukemia with distinct clinicopathologic features. *Am J Clin Pathol* **63**: 786-795, 1975.
  82. Galton D: Management of the chronic leukemias, in *Symposium in Current Concepts in the Management of Leukemia and Lymphoma*. Ultmann JE, Griem ML, eds. New York, Springer-Verlag, 1971, p 158.
  83. Lortholary P, Boiron M, Ripault P, et al: Leucémie lymphoïde chronique secondairement associée à une réticulopathie maligne, syndrome de Richter. *Nouv Rev Fr Hematol* **4**: 621-644, 1964.