MEDICAL GRAND ROUNDS

PARKLAND MEMORIAL HOSPITAL

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MACROGLOBULINEMIA

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I. Introduction: The Nature of Macroglobulinemia

In 1944 Waldenström[1] described 3 patients with a disorder of insidious onset occurring in late adult life and characterized by anemia, bleeding diathesis, variable lymphadenopathy and hepatosplenomegaly, elevated erythrocyte sedimentation rate, infiltration of the marrow by lymphocytoid plasma cells, and hyperglobulinemia. Serum from these patients had a markedly elevated viscosity and contained a globulin of high molecular weight (approximately 1 million) as determined from its sedimentation coefficient of 19-20S in the ultracentrifuge. This serum protein component was, therefore, called a "macroglobulin".

Definition: Macroglobulinemia is a plasma cell dyscrasia (Table 1) specifically involving cells which normally sensitize IgM immunoglobulin.

TABLE 1

PLASMA CELL DYSCRASIAS*

Clinically overt forms, with distinctive clinical and pathologic features:
- Myeloma (IgG, IgA, IgD, IgE, Light Chain Disease, nonsecretory)
- Macroglobulinemia (IgM)
- Primary amyloidosis (usually Bence Jones protein)
- Heavy chain diseases (gamma, alpha, mu)
- Lichen myxedematosus (papular mucinosis)(IgG)

Clinically occult (asymptomatic or presymptomatic) forms:
- Plasma cell dyscrasias of unknown significance (PCDUS)
  - -with chronic infectious or inflammatory processes
  - -with nonreticular neoplasms
  - -with various other disorders
  - -in healthy persons (age-related incidence)
- Transient plasma cell dyscrasias

*Modified from Osserman, ref. 2.

As with other plasma cell dyscrasias, the hallmark is the production of a monoclonal immunoglobulin (M-protein) which appears in the serum and is the result of a disproportionate increase in a single clone of cells (Fig. 1).

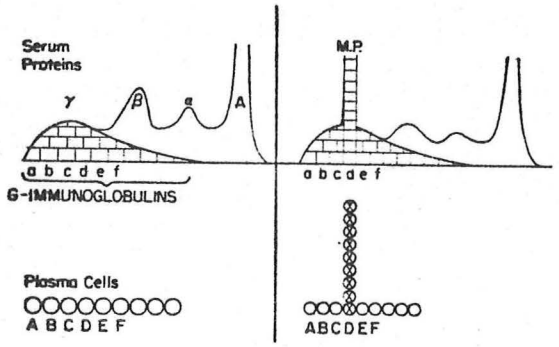

FIG. 1. Schematic diagram of a possible relationship between normal plasma (*left*) cells and normal G immunoglobulins and between a malignant plasma cell (*right*) clone and the corresponding myeloma protein (M.P.).

The homogeneous protein product has a discrete electrophoretic mobility and contains only a single light chain class (κ or λ). Various attempts to establish quantitative criteria for diagnostic IgM levels (5 X normal, 10 X normal, > 15% of the serum proteins) have been unsatisfactory. The term "macroglobulinemia" is usually employed to designate the disorder described by Waldenström; i.e. the clinically overt form. The term should not be used for increases in serum IgM which are of a polyclonal nature.

Macroglobulinemia is a specific clinical entity which significantly differs from multiple myeloma. The IgM disease resembles more a malignant lymphoma of the non-Hodgkins type and, in many respects, is closely related to chronic lymphocytic leukemia (CLL). Macroglobulinemia thus serves as a bridge between plasmacytic disorders on the one hand and lymphoproliferative diseases on the other. It is not surprising, therefore, that the morphology and clinical findings are variable. However, as noted above, the feature common to all cases of macroglobulinemia is the production of a monoclonal IgM protein. As is true of other human plasma cell dyscrasias and malignant lymphomas, the etiology of macroglobulinemia has not been established.

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II. IgM Immunoglobulin

Structure

IgM consists of five subunits which, like other immunoglobulins, are composed of disulfide-linked heavy-light chain pairs (Fig. 2).

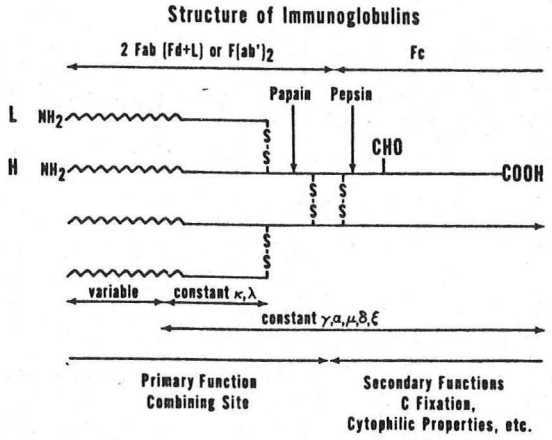

FIG 2. Schematic diagram of immunoglobulin molecules and localization of structures responsible for primary and secondary functions of antibodies. H = heavy chain; L = light chain; CHO = carbohydrate. (Ref. 40)

The heavy chain, designated mu, has a molecular weight in the range of 65-75,000 daltons and is composed of an amino-terminal variable portion and a carboxy terminal common region. The light chains (kappa or lambda) are similar to those

found in other classes of immunoglobulins. IgM contains 10-12% carbohydrate which is covalently linked to the heavy chains. The four-chain subunit has a molecular weight in the range of 180-190,000 daltons and the intact molecule is a circular pentamer (Fig. 3) with evidence of some degree of flexibility.

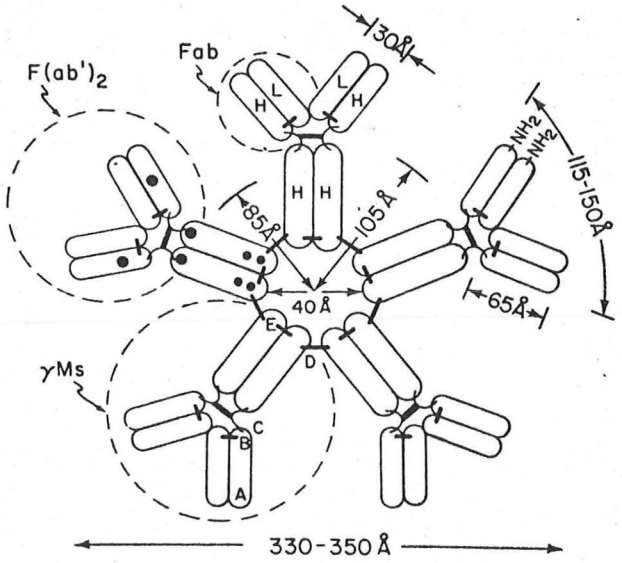

FIG. 3. Schematic representation of pentameric γM. (Ref. 18)

The IgM subunits are themselves disulfide-linked and the molecule also contains a single J (joining) chain per polymer (Fig. 4). The J chain is attached in

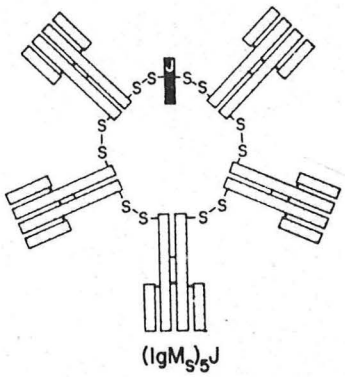

Fig. 4. (Ref. 20)

the region of the Fc fragment and is also present in polymeric IgA. As is true of other immunoglobulins, IgM can be split by proteolytic enzymes (papain, trypsin) into Fabμ and Fcμ fragments. The Fab fragment contains the antibody combining site and the Fc fragments are involved in secondary biologic activities. Since there are ten Fab fragments per mole of IgM, it might be expected that the molecule would be decavalent. This has, in fact, shown to be the case for small antigens. For large protein antigens, however, the valence is usually 5, one of the Fabs on each subunit being unavailable owing to the large size of the antigen.

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Synthesis

IgM immunoglobulin is synthesized and secreted by cells of the B lymphocyte-plasma cell series. Normal, unstimulated (by antigen) B lymphocytes contain cell surface receptor immunoglobulin which has been identified as the 8S IgM subunit (μ_2, L_2). After stimulation by antigen, these B lymphocytes differentiate and proliferate into plasma cells which secrete IgM. In the more differentiated cells the IgM subunit appears to be the main intracellular precursor as determined from cell culture studies. Polymerization into the intact IgM pentamer occurs just before or at the time of secretion. The relationship between intracellular 8S IgM and membrane-bound IgM is incompletely understood.

Under certain conditions low molecular weight (7-8S) IgM is secreted. This phenomenon has been described in a variety of disease states including systemic lupus erythematosus, unclassified dysproteinemia, hereditary telangiectasia, Waldenström's macroglobulinemia, various other lymphoproliferative disorders, rheumatoid arthritis, and several infectious diseases. In general, these low molecular weight IgM proteins are indistinguishable from the 7S monomers produced by reduction in alkylation of the intact 19S pentamer. Biosynthetic studies indicate that the low molecular weight IgM is formed directly and at a different rate than 19S IgM. Nevertheless, it is possible that in some instances IgM breakdown products are being detected.

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Metabolism

76-80% of injected radiolabeled IgM remains in the intravascular compartment. This is similar to the findings on the distribution of fibrinogen (80% intravascular) but differs from those of IgG, albumin, and transferrin where only about 40-45% of the body content is intravascular. The IgM synthetic rate of 6.7 mgs/kg of body weight per day is about 1/4 that of IgG (Table II).

TABLE II

BIOLOGICAL PROPERTIES AND ACTIVITIES OF HUMAN IMMUNOGLOBULINS[a]

Characteristics	IgG1	IgG2	IgG3	IgG4	IgA1	IgA2	IgM	IgD	IgE
Serum (mg./ml.)	5–12	2–6	0.5–1	0.2–1	0.5–2	0–0.2	0.5–1.5	0–0.4	0–0.002
Secretion	−	−	−	−	+	+	(+)	−	?
Cerebrospinal fluid (μg./ml.)		2.5–7.5 IgG					not detectable		
Half-life in days	23	23	16	23	6	6	5	3	2
Fractional turnover (%)	7	7	17	7	25		18	37	89
Synthesis (mg./kg./day)	25		3.4		24		7	0.4	0.02
Placental transfer	+	+	+	+	−	−	−	−	−
Classic C	++	+	++	−	−	−	+	−	−
Alternate C	−	−	−	−	+	+	−	±	±
Prausnitz-Küstner	−	−	−	−	−	−	−	−	+
Reverse passive cutaneous anaphylaxis	+	−	+	+	−	−	−	−	−
Macrophages	+	±	+	±	−	−	−	−	−
Neutrophiles	+	+	+	+	+	+	−	−	−
Platelets	+	+	+	+	−	−	−	−	−
Lymphocytes	+	±	+	±	−	−	−	−	−
Staphylococcal A	+	+	−	+	−	−	−	−	−
Cystic fibrosis factor	+	+	−	−	−	−	−	−	
Rheumatoid factor (antigen)	++	+	−	+	(+)		(+)		(+)
Rheumatoid factor (antibody)			IgG+			IgA+	+	−	−

[a] Symbols used: −, negative; (+), occasional positive reaction; ±, weakly positive; +, positive; ++, strongly positive; blank space, not tested.

(Ref. 40)

The mean half-life of survival of IgM is 5.1 days and the fractional catabolic rate is 18% of the intravascular pool per day. Unlike IgG, the catabolic rate of IgM is not affected by its serum level. Thus, the serum IgM level is directly related to rate of synthesis of the protein (in the absence of abnormal gastrointestinal protein loss).

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Function

The serum concentration of IgM is about 1 mg/ml, accounting for approximately 7% of the total serum immunoglobulins. Buckley et al. have reported that increased IgM occurs in 3.2% of apparently healthy subjects. The first antibodies detected after primary antigenic challenge are usually in the IgM class. Isohemagglutinins, cold agglutinins, rheumatoid factors, and antibodies against the somatic O antigen of gram-negative bacteria are typically, but not exclusively, IgM antibodies. The heterophile antibody of infectious mononucleosis is of the IgM type. In addition, Rh antibodies, anti-thyroglobulin, anti-insulin, and antinuclear factors have been detected in the IgM class. Increased IgM serum levels are the principal immunoglobulin abnormality noted in patients with malaria, trypanosomiasis, and endemic or sporadic non-toxic goiter. In addition, IgM has been found in parotid secretions of patients with IgA deficiency. IgM fixes complement via the classical pathway but does not cross the placenta (Table II). Considerable data support the fact that IgM is the first immunoglobulin to appear both phytogenetically and ontogenetically. Suppression of IgM synthesis in chick embryos results in a suppression of IgG synthesis as well, and data from Cooper's group indicate that IgG-producing cells arise exclusively from cells that previously synthesize IgM. These results suggest that primary isolated deficiency of IgM would be unlikely to occur and indeed its existence in humans is questionable.

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III. Cytology and Histopathology

A. Light microscopy

The IgM-producing cells in macroglobulinemia are typically described as "lymphocytoid" plasma cells or "plasmacytoid" lymphocytes, i.e. cells intermediate between a small lymphocyte and a mature, typical plasma cell. In actuality, the cytology is variable and may consist of a population of either predominantly small lymphocytes or typical plasma cells rather than the so-called "intermediate" forms. PAS-positive intranuclear inclusions in the cells are characteristic but not specific for macroglobulinemia. Similar inclusions may be found in the cytoplasm of marrow or peripheral blood lymphocytes; in some cases these assume the appearance of rod-shaped crystals located within the cisternae of the rough endoplasmic reticulum. The histopathology is often described as "pleomorphic lymphoma", but a definitive diagnosis of macroglobulinemia cannot be made by light microscopy. The bone marrow, spleen, lymph nodes, and liver are the major organs involved in this condition. In the marrow there is a focal or diffuse infiltration by lymphoid cells that varies in appearance from case to case and within the same individual. It should be emphasized that such infiltration may be patchy (5-10% of the nucleated cells). In addition, increased mast cells are characteristically seen in the marrow. In lymph nodes there is frequently a lymphocytic infiltration of the capsule and pericapsular adipose tissue and also a blurring of the follicular pattern. In some situations the appearance is that of a diffuse or nodular, well-differentiated lymphocytic lymphoma. Occasionally, the histologic appearance resembles that of histiocytic lymphoma (reticulum cell sarcoma). A similar picture is present in the spleen. In the liver there is frequently a periportal lymphocytic infiltration of variable proportions. Less commonly, this infiltrate extends along the hepatic sinusoids. It should be emphasized that there are cases of Waldenstrom's macroglobulinemia in which the appearance in lymph nodes and other lymphoreticular organs is unremarkable except for modest lymphocytic infiltration of the marrow and moderate peripheral lymphocytosis. In non-reticuloendothelial tissues the lymphocytic infiltration is variable and frequently absent.

In view of the inconstant nature of the histopathology, it is not surprising that IgM peaks occur with increased frequency in patients who have diffuse malignant lymphoma. Thus, Alexanian has found a 4.5% incidence of IgM monoclonal serum spikes in patients with diffuse lymphomas (chronic lymphocytic leukemia, lymphocytic lymphoma, reticulum cell sarcoma). This is an incidence about 100 times greater than that found in apparently normal individuals. No IgM spikes were seen in 218 patients with Hodgkins disease or 292 patients with nodular lymphoma. It is noteworthy that none of the patients with IgM peaks had hyperviscosity, i.e., most of the peaks were at a rather low level (median 2.0 gms%). This entity has been called "macroglobulinemic lymphoma".

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B. Immunofluorescence

Although all peripheral blood small lymphocytes appear similar, the immunofluorescence technique has been of considerable aid in identifying B and T cells in animals and humans. Normally, about 15-30% of peripheral blood lymphocytes carry surface immunoglobulin and are therefore identified as B cells. In most laboratories the majority of these surface immunoglobulin-positive cells stain with anti-μ serum. The surface immunofluorescence and other in vitro methods have been most helpful in classifying patients with lymphoproliferative diseases as to the B or T cell nature of their lymphocyte populations. Most patients with chronic lymphocytic leukemia and the follicular (nodular) lymphomas have monoclonal B cell populations. As noted, the principal cytologic feature of macroglobulinemia is the pleomorphic character of the lymphoid cells in the peripheral blood, bone marrow and lymph nodes. Preud'Homme and Seligmann have studied 34 patients with macroglobulinemia and have found that intracytoplasmic staining for monoclonal IgM was restricted to the plasma cells in the bone marrow and a limited number of lymphocytes in the bone marrow and peripheral blood. In 31 of the patients a large predominance of lymphocytes in the marrow possessed membrane-bound IgM. Double-labeling experiments showed that most lymphocytes bearing IgM on their surface had no detectable intracytoplasmic IgM, whereas those cells with intracytoplasmic IgM (including all plasmacytes) also contained membrane-bound IgM with the same light chain type as the IgM in the serum. In untreated patients, 15-80% (mean 50%) of the blood lymphocytes also had a monoclonal IgM on their surface, despite the absence of lymphocytosis in most cases. When the disease was controlled by therapy, a low percentage of blood lymphocytes (mean 9%) had monoclonal surface IgM. The number, size, and intensity of the membrane fluorescence varied greatly from cell to cell in marrow and peripheral blood samples of a given patient, a finding in marked contrast to the homogeneous fluorescent pattern usually observed in CLL. The data suggest that macroglobulinemia represents a proliferation of a B cell monoclone with continuous maturation from the small lymphocyte to the IgM-secreting plasma cell, whereas CLL, in most cases at least, represents a monoclonal proliferation of B lymphocytes that are blocked in their maturation process. In view of the large number of circulating lymphocytes bearing the monoclonal marker, macroglobulinemia may be considered a leukemic process. Both surface IgD and IgM have recently been detected on the same cell in macroglobulinemia, a finding analogous to that encountered in CLL; the significance of this surface IgD is unknown.

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C. Chromosome Studies

Chromosome aberrations have been reported in a number of cases of macroglobulinemia. The abnormal chromosome, which is present in only a small proportion of dividing lymphocytes may be either a large metacentric, or sub-metacentric, supernumerary chromosome. Indistinguishable chromosomal aberrations have been reported in patients with IgG and IgA monoclonal gammopathies and acute leukemia (myeloblastic and lymphoblastic). Deletions and other structural derangements have also been described. The variety of aberrations in a single patient and variation in morphology between patients make it unlikely that a simple causal relationship between any chromosomal abnormality and the etiology of macroglobulinemia exists.

Several investigators have suggested that genetic factors influence serum IgM levels in both health and disease. A population study of 444 normal individuals belonging to 64 families has indicated that the X chromosome carries genes which affect the serum IgM concentration. There was no correlation demonstrated for IgA or IgG. The familial occurrence of macroglobulinemia has suggested the possibility of a genetic abnormality in the disorder. Two large studies of relatives of patients with macroglobulinemia have demonstrated an increased incidence of both quantitative and qualitative IgM abnormalities. An increased incidence of serum antibodies directed against rabbit or human gamma globulin (rheumatoid factors) was found in first degree relatives of patients. The regulatory mechanisms for immunoglobulin and/or antibody synthesis seem to be disturbed in these families, but whether genetic or environmental factors are responsible is unclear.

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IV. Monoclonal Macroglobulins with Antibody Activity

Although the etiology and pathogenesis of plasma cell dyscrasias are unknown, the possible role of chronic antigenic stimulation leading to an atypical immune response was suggested years ago on clinical grounds alone.

Despite the fact that many investigators considered M-proteins to be abnormal ("paraproteins"), structural data accumulated during the past 15 years have failed to generate convincing evidence of such abnormality. In most instances there is nothing exceptional about M-proteins except their quantity, which reflects the intense proliferation of a monoclone. This concept has been strengthened by the finding of homogeneous M-proteins with antigen-binding activity in both humans and mice with plasma cell dyscrasias. Moreover, there is now abundant evidence to indicate that a homogeneous antibody response can be induced to certain antigens in animals and man. Finally, the transient appearance of serum M-spikes has been well documented in patients with various disorders. There is some basis, therefore, for suggesting that abnormal cells in plasma cell dyscrasias might be derived from cells once involved in immune responses.

A. Anti-IgG (Mixed Cryoglobulins)

Classic rheumatoid factor is a polyclonal IgM antibody to IgG. These anti-gamma globulin factors occur during the course of many chronic disorders of a non-rheumatic nature as well as in rheumatoid arthritis. They are also seen in 2-20% of normal persons. Similar factors arise in hyperimmunized man and rabbits. A monoclonal IgM rheumatoid factor was first described by Kritzman and associates in a patient with macroglobulinemia. Many other reports of patients with macroglobulinemia with IgM proteins which bind IgG are now known and it has been estimated that perhaps 10-20% of Waldenström's patients have proteins with such activity. The characteristic finding in such patients is that they have profound mixed cryoglobulinemia with high-titer rheumatoid factor activity; titers exceeding 1:1,000,000 have been described in several patients. It is noteworthy that except for their cryoglobulinemia, these patients do not differ clinically from other patients with macroglobulinemia. In particular, none of them have had rheumatoid arthritis. Membrane-bound IgM on the cells from such patients has been shown to possess anti-IgG activity. We have had the opportunity to study the antibody nature of two monoclonal macroglobulins from patients with Waldenström's macroglobulinemia in our laboratory. Some of the structural and functional properties of these two antibodies are shown in Table III. They are similar but not identical. Neither of these

TABLE III

Properties of two Waldenström macroglobulin antibodies with anti-IgG activity[a]

Property	IgM_{Lay}	IgM_{Sie}
Euglobulin	No	No
Rheumatoid factor activity	Yes	Yes
Binds native (monomer) IgG	Yes	Yes
K_A for IgG1, κ	$6.8 \times 10^4 M^{-1}$	$4.5 \times 10^4 M^{-1}$
Thermodynamic parameters:		
$\Delta F°$ (kcal $mole^{-1}$)	-5.8 ± 0.2	-5.7 ± 0.1
$\Delta H°$ (kcal $mole^{-1}$)	-7 ± 1	-4.9 ± 1.0
$\Delta S°$ (cal deg^{-1} $mole^{-1}$)	-5 ± 1	2.7 ± 0.3
Antigenic specificity	Fcγ	Fcγ
Antigen-antibody complex	Cryoglobulin	Cryoglobulin
Optimal pH for precipitation of complex	6.0	7.4
Valence:		
Pentamer IgM	5	5 to 10
Isolated Fabμ	10	10
Effective valence of antigen	1	1
Cross-reactivity:		
Lorisiforme IgG	Yes	Not tested
Rabbit IgG	No	Yes
V region subgroups:		
L chain	V_KI	V_KIIIb
H chain	V_HIII	Not known
Cross-idiotypic specificity	Po system	Wa system
Complex fixes complement	No	No

[a] Ref. 97

patients had evidence of immune complex disease despite profound levels of circulating IgM-IgG complexes. In one patient (Sie; see Case I), cryoglobulinemia was constantly present for over 4 years. This contrasts with other patients with monoclonal rheumatoid factor cryoglobulinemia who do not have evidence of a malignant plasma cell dyscrasia but who do manifest a syndrome of purpura, arthralgias and proliferative glomerulonephritis. The absence of immunologically-mediated tissue injury in the Waldenström's patients may relate to the observation that neither of our Waldenström proteins fixed complement. Although cryoglobulinemia has been described in many patients with macroglobulinemia, it would appear that, contrary to previous reports, the cryoglobulin frequently contains multiple components rather than simply the IgM.

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B. Anti-I (Cold Agglutinins)

With rare exceptions, cold agglutinins are IgM antibodies that bind to the I (or i) antigen on red cells at low temperatures and dissociate from the cells on rewarming. Since most normal individuals have low-titer cold agglutinin activity (< 1:64), these cold reactive macroglobulins provide an example of naturally occurring auto-reactive antibodies. Transient rises in titer occur in association with various conditions, especially Mycoplasma pneumonia and infectious mononucleosis; in these instances the IgM molecules are polyclonal and occasionally cause an episode of immunohemolytic anemia (see Table IV).

TABLE IV Differential Diagnostic Features of Cold Agglutinins

		Transient			
			Atypical Pneumonia Hemolytic Anemia		
	Normal	Infectious Mononucleosis	Absent	Present	Chronic Idiopathic
Titer					
Usual	1-2	1-64	64-512	512-4,096	2,048-64,000
Range	0-64	0-1,024	32-1,024	64-16,000	1,024-1,000,000
Antibody specificity	I	i	I	I	I
Temporal course	Stable	Changing	Changing	Changing	Stable
Immunochemical characteristics	Polyclonal	Polyclonal	Polyclonal	Restricted polyclonal or polyclonal	Monoclonal
Cold agglutinin-specific antigenic determinants	†	†	Absent	May be present	Usually present
Thermal maximum	<15°C	†	15°-25°C	>25°C	>25°C
Clinical significance	No	Yes	Yes	Yes	Yes
Hematologic significance	No	Very rarely	No	Yes	Yes
Usual age of patient (yr)	Any	15-30	15-30	15-30	30-70

† Insufficient information available.

(Ref. 114)

By contrast, patients with idiopathic chronic cold agglutinin disease maintain very high-titer cold agglutinins for years; these are invariably monoclonal IgM - nearly always with κ-type light chains. Many patients with idiopathic cold agglutinin disease have been found to have IgM M-components evident on SPE; absorption with red cells in the cold removes both the M-peak and cold agglutinin activity. The levels of monoclonal IgM range from 1.4-24.5 mg/ml in such individuals (Table V). These monoclonal antibodies fix complement, thereby giving rise to a

TABLE V

Protein abnormalities in 18 patients with cold haemagglutinin syndrome

Patients (number or initials)	Agar electrophoresis	γM conc. (mg./ml.)	Remarks
10	one γM peak	3.1–24.5	The peak disappeared after absorption with red cell stromata in all of 8 cases tested
3	no peak	1.4*, 1.6*, 1.9*	Monoclonal γM seen in immuno-electrophoresis
3	no peak	0.9*, 1.2*, 2.6*	No evidence of monoclonal γM-globulin in immunoelectrophoresis
A.V.	two peaks: γG and γM	13.0	The γG peak remained, the γM peak disappeared after absorption with red cell stromata
A.R.	one γG peak	0.7	Very faint γM line before absorption; γG peak remained after absorption with stromata

* The isolated, concentrated cold haemagglutinin behaved as a monoclonal γM-globulin in immuno-electrophoresis.

(Ref. 110)

positive direct Coombs test of the "non-gamma" type. Patients with the idiopathic disorder tend to have a longstanding history of mild to moderate anemia with Raynaud's phenomenon and hemoglobinuria following cold exposure. Severity of the clinical manifestations depend on affinity, concentration and thermal amplitude of the IgM antibody. Many patients have a non-progressive disorder lasting many years, but in others, a picture indistinguishable from macroglobulinemia develops. Rare patients with monoclonal macroglobulins which possessed both cryoglobulin and cold agglutinin properties have been reported; one such protein was shown to have λ-type light chains. Immunochemical and sequence studies have shown marked structural similarities between different IgM cold agglutinins.

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C. Other Specificities

A number of other Waldenström proteins have been demonstrated to have antibody activity (Table VI).

TABLE VI

HUMAN MONOCLONAL MACROGLOBULIN ANTIBODIES:ANTIGENS IDENTIFIED

IgG
Albumin
I blood group
Sp_I blood group
A_I blood group
Aged red cells
Cardiolipin
Phosphoryl choline
Lecithin
Heparin
Klebsiella polysaccharide
Antigen-antibody complexes
Nitrophenyl ligands

Fibrin monomer (?)

In general, three classes of antigens have been identified: Autoantigens, bacterial antigens, and haptens. It should be emphasized that the methodologic problems involved in delineation of antibody activity in homogeneous immunoglobulins are a major limitation. Nevertheless, the finding of human IgM in components with activity for autoantigens and bacterial antigens suggests that an expanded clone of cells is more likely to undergo neoplastic transformation or that certain clones may be more susceptible to such transformation. While normal clones are antigen-regulated and pathologic ones presumably not, antigen can nonetheless be involved in the developmental history of the abnormal clone up to the time when the gross abnormality took place. The virtual inability to induce myeloma in the murine system when germ-free mice are employed also supports the role of an expanded clone as a necessary prerequisite to the development of a malignant plasma cell dyscrasia. The finding of antibody activity to haptenes is also of interest. These activities could represent cross reactions to structurally related determinants. However, the observation that certain myeloma proteins bind multiple structurally unrelated antigens suggests that some antibodies are polyfunctional. The finding that 30% of aged NZB/NZW F_I hybrids develop IgM monoclonal spikes also raises interesting questions of the relationship between autoimmune disease and the subsequent development of malignant lymphoma (see Section VI-B). It should be noted, however, that antibody activity of the monoclonal macroglobulins in these mice has not as yet been identified. In summary, patients with Waldenström's macroglobulinemia who have monoclonal macroglobulins which possess antibody activity may have clinical sequelae related to such antibodies (cryoglobulinemia, cold sensitivity, hemolytic anemia). However, the role of an immune response in the pathogenesis of the plasma cell dyscrasia is unclear.

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V. Clinical and Laboratory Findings

A. The Hyperviscosity Syndrome

As noted, Waldenström described elevated serum viscosity in his original report on macroglobulinemia. Hyperviscosity syndrome occurs in 30-40% of patients; the principal symptoms and signs are listed in Table VII.

Table VII. Signs and Symptoms of the Hyperviscosity Syndrome*

Ocular	Disturbance in vision to complete loss of vision;
	Distension and tortuosity of retinal veins "string-of-sausage" appearance
	Retinal hemorrhage; papilledema
Hematologic	Oozing of blood from oral mucous membranes
	Bleeding from nose, urinary and gastrointestinal tract
	Prolonged bleeding at sites of minor surgical procedures
	Anemia
Neurologic	Headache, dizziness, vertigo, nystagmus, postural hypotension
	Somnolence, stupor, and coma
	Generalized seizures, EEG changes
	Hearing loss
Cardiovascular	Congestive heart failure
	Expanded plasma volume
Renal	Glomerular deposits attributable to HVS?
	Diminished concentrating and diluting ability attributable to HVS?
Subjective	Weakness, fatigue, anorexia

Ref. 149.

Fatigue and generalized weakness are common complaints. Almost all patients have visual disturbances, especially blurred vision. A variety of neurologic problems are also seen and range from headache, ataxia and dizziness to seizures, somnolence and coma. The abrupt onset of deafness has been described. Skin and mucosal bleeding with oozing are frequent. Epistaxis and gingival bleeding are particularly common.

Characteristic findings are apparent on examination of the fundi. The initial and most frequent ocular finding is dilatation and tortuosity of the retinal veins. This abnormality may reach such enormous proportions that the veins appear as large, distended, sausage-shaped loops. This "sausaging" will make the diagnosis. Flame-shaped retinal hemorrhages are common, as are capillary microaneurysms, especially in the periphery. In extreme cases, partial or complete central retinal vein occlusion may occur with widespread retinal hemorrhages, exudates, retinal edema, and papilledema. In addition to the fundus changes, sludging of red cells in the conjunctival vessels may also be present. Sludging of blood, venous stasis, secondary anoxia, and hemorrhages are all explicable on the basis of the increased serum viscosity. Histologic examination of eyes from patients with macroglobulinemia has demonstrated that the changes referable to anoxia (loss of vessel pericytes and and endothelial cells, numerous capillary microaneurysms) are most marked in the retinal periphery where circulation is poorest. As is true of most findings in hyperviscosity syndrome, rapid reversibility of the retinal lesions is demonstrable soon after serum viscosity is reduced. The improvement of the retinopathy is usually seen within a week after plasmapheresis and may be almost complete by 2-3 weeks. However, if actual occlusion of the central retinal vein has occurred visual function may not be completely restored.

Virtually all patients have increased total blood and plasma volumes and hypervolemia correlates with the degree of viscosity. The mechanism for expansion of plasma volume is unknown but appears unrelated to aldosterone-mediated sodium retention. Renal functional impairment and glomerular deposition of IgM may result from hyperviscosity but this has not been clearly established (see Section V-C).

Determination of relative serum viscosity with an Ostwald viscosimeter is simple, rapid and inexpensive. Moreover, this method has been demonstrated to correlate well with clinical findings. The normal value for relative serum viscosity at 37°C is 1.4-1.8 that of water. The high intrinsic viscosity of IgM relative to IgG is depicted in Fig. 5. Note that an IgM concentration in excess of 4 gm% is associated with a steep rise in viscosity.

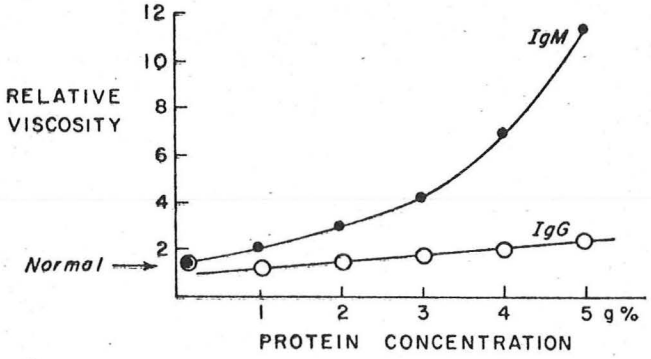

Fig 5. **Relation of serum viscosity to IgM (18 γ_1-macroglobulin) level and to IgG (7S γ_2-globulin) level. In the former, macroglobulinemic serum was diluted with normal serum and in latter, serum from patient with multiple myeloma and IgG myeloma protein was used.** (Ref. 151)

If a cryoglobulin is present, viscosity may be markedly temperature-dependent (Fig. 6).

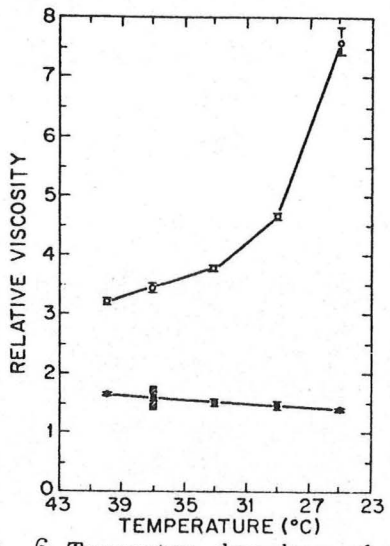

Fig. 6. Temperature dependence of relative serum viscosity. O, Sie serum; ●, normal serum. Brackets indicate the range of duplicate determinations. Bar indicates normal range (1.4-1.8) at 37°C from literature

(Ref. 97)

The hyperviscosity syndrome is rare unless the relative viscosity level rises above 4. Most patients are symptomatic with levels between 5 and 10 and all have symptoms at 10 or more. Although considerable variation between patients occurs, the viscosity level above which symptoms are produced is strikingly reproducible in the same patient. As in polycythemia, recurrence of the same symptom often signals the need for a trip to the Blood Bank. Thus each patient has his own "symptomatic threshold" (Fig. 7); such a concept implies that therapy need only reduce macroglobulin levels sufficiently to bring serum viscosity below this threshold (see Cases 1 and 2 and Section VIII).

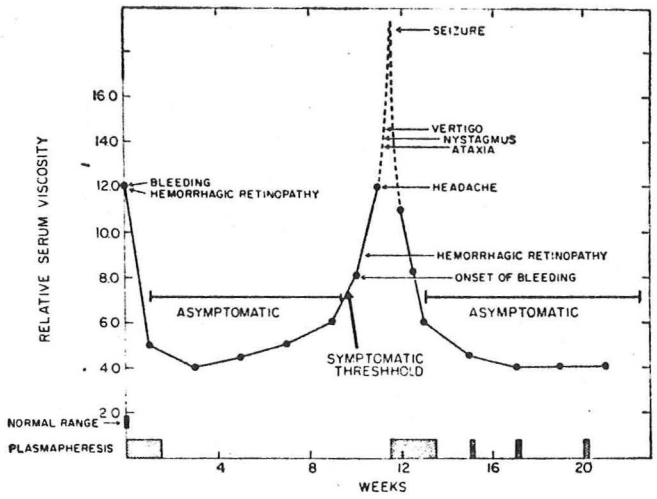

Fig. 7. **Correlation of clinical findings and serum viscosity level in a patient with macroglobulinemia.**

(Ref. 151).

Macroglobulinemia accounts for 85-90% of cases of hyperviscosity syndrome. The differential diagnosis includes multiple myeloma, rheumatoid arthritis and polycythemia. The two most important features of this syndrome are that 1) it can be diagnosed by physical examination and 2) most of the symptoms and findings are readily reversible by prompt removal of plasma.

The blood and plasma of patients with macroglobulinemia behave as non-Newtonian fluids, i.e. viscosity increases with decrease in shear rate. If red cells are added to viscous, macroglobulinemic serum, the viscosity of the resultant mixture may approach that of a rigid gel. Thus, rheologic synergism between plasma and red cells causes the viscosity of whole blood to be greater than the sum of the individual viscosity values of plasma and red cells in protein-free saline. Studies in macroglobulinemic mice have shown that plasma or serum viscosity are only partial determinants of whole blood viscosity, and the effect of the macroglobulin in causing aggregation of erythrocytes <u>in vitro</u> may have a role in elevating total blood viscosity. Total blood viscosity was elevated and found to be a function of both plasma concentration of macroglobulin as well as the hematocrit. These data indicate that measurement of total blood viscosity using sophisticated instruments such as a cone plate viscosimeter may be theoretically advantageous. However, this equipment is not

widely available and the results of viscosity determinations on such instruments have not been demonstrated to correlate with clinical findings. Despite the fact that capillary viscosimeters such as the Ostwald measure only relative viscosity of serum without controlling shear rate, these seem to be much more practical and the results can be meaningfully utilized in patient management. In some patients, the molecular shape of IgM as well as its concentration appears to be an important factor in the production of the hyperviscosity syndrome. Other factors include protein-protein interactions between IgM and other plasma constituents (see Case 4).

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B. Initial Presentation

Macroglobulinemia accounts for 8-15% of all plasma cell dyscrasias. It is a disease of the elderly, with highest incidence during the sixth and seventh decades, and is rare under the age of 40. It occurs somewhat more commonly in males than in females. The disorder, which is frequently mild and compatible with prolonged survival, is occasionally discovered in asymptomatic individuals (Sec. VI-A). Many of the initial signs and symptoms relate to elevated serum viscosity, as noted previously. The most common presenting symptoms are listed in Table VIII,

TABLE VIII

INCIDENCE OF PRESENTING SYMPTOMS (227 Cases)

Symptom	No. of Cases
Hemorrhage	104
Fatigue, weakness	99
Weight loss	52
Neurologic disturbance	24
Visual disturbance	20
Dyspnea	19
Infection	15
None	13
Adenopathy	11
Raynaud's phenomenon	8
Arthralgias	6
Abdominal pains	4
Pruritus	3
Anorexia	2
Edema	2
Mandibular swelling	1
Psychosis	1
Mouth ulcer	1

McCallister et al. (Ref. 15)

and the incidence of various physical findings are shown in Table IX.

TABLE IX

INCIDENCE OF PHYSICAL FINDINGS (227 Cases)

Finding	No. of Cases
Ocular changes	84
Hepatomegaly	84
Splenomegaly	79
Lymphadenopathy	62
Neurologic (CNS &/or peripheral)	36
Petechiae, purpura	35
None	23
Pneumonia, pleural effusion	19
Edema	13
Congestive heart failure	9
Mikulicz's syndrome	7
Sjögren's syndrome	4
Cutaneous lesions	4
Mouth ulcer	1

McCallister et al. (Ref. 15)

Fatigue, weakness, anemia, lymphadenopathy, hepatosplenomegaly, and hemorrhagic tendency are the most common presenting manifestations. Other frequent findings include Raynaud's phenomenon (in patients with cold agglutinins or cryoglobulins), visual disturbances, recurring infections, and various neurologic disorders. It should be noted that symptoms referable to bone pain are invariably absent.

Laboratory Studies: Anemia is present in approximately 80% of patients and results from multiple etiologies, including decreased bone marrow production, mild shortening of red cell survival, and bleeding with superimposed iron deficiency. Marked rouleaux is evident on peripheral smear and a very high erythrocyte sedimentation rate - usually above 100 mm/hr is seen. The white cell and platelet counts are normal or low. Variable degrees of lymphocytosis are present in the peripheral blood. The bone marrow and lymph node morphology has been discussed (see Section III).

Serum protein electrophoresis discloses the typical M-spike (Fig. 8),

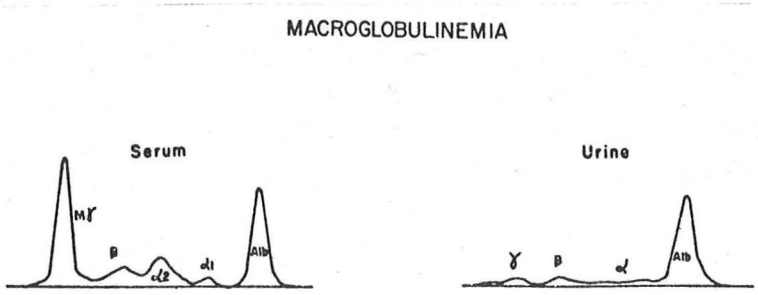

Fig. 8

(Ref. 2)

which is demonstrable as IgM with κ light chains in 80% of cases by immunoelectrophoresis. Ultracentrifugation is not necessary to make the diagnosis. Gross Bence Jones proteinuria occurs in only 10-20% of cases with macroglobulinemia (cf. with 60-70% in myeloma). In Bence Jones positive cases, an M-spike will be present on urine protein electrophoresis and the light chain will be of the same class as that present in the serum. Since 50% of IgM's are euglobulins, the Sia test is frequently positive. However, this procedure is nonspecific and its value overemphasized. Cryoglobulins and cold agglutinins are common (Section IV) and rheumatoid factor or Coombs testing may be positive. Serum uric acid may be elevated but calcium and BUN are usually normal. Bone x-rays may show osteoporosis but lytic lesions are very rare and should make one question the diagnosis.

Multiple hemostatic defects have been described (Table X).

Table X. **Hemostatic Abnormalities Associated with Dysproteinemias**

I. Hemorrhagic Abnormalities
  (A) Abnormalities of Platelets
    (1) Thrombocytopenia
    (2) Impaired Function
  (B) Abnormalities of Plasma Coagulation Factors
    (1) Inhibitors of Coagulation
      (a) Fibrin monomer aggregation
      (b) Factor VIII
      (c) nonspecific—usually detected by thromboplastin generation test
      (d) other coagulation factors
      (e) Factor X deficiency due to in vivo inactivation
    (2) Depression of Clotting Factors
  (C) Hyperviscosity Syndrome
  (D) Miscellaneous
II. Thrombotic Abnormalities

(Ref. 190)

Defective platelet factor 3 availability, as well as reduced adhesion and aggregation are common and signify a platelet functional defect with associated prolonged bleeding time and poor clot retraction. These platelet abnormalities are more likely to be present with high concentrations (> 5 gm%) of M-protein. Coagulation abnormalities seem to be of two kinds: first, the monoclonal protein may act as a coagulation inhibitor (circulating anticoagulant) which prolongs the clotting time of normal plasma. Interference with fibrin monomer aggregation with prolonged thrombin time is especially common. Second, the protein may simply complex with the patient's own clotting factors, leading to reduced coagulant activity but no inhibitory effect on normal plasma. Thus the bleeding tendency in these patients results from multiple mechanisms: coating of formed elements by the macroglobulin, high serum viscosity, and other protein-protein interactions, particularly with coagulation factors (see Case 4). The hemostatic abnormalities tend to be partially or totally correctible by plasmapheresis.

In common with myeloma patients, individuals with macroglobulinemia tend to have reduced levels of the normal immunoglobulins and defective antibody response on primary immunization. Infections in patients with macroglobulinemia are increased but said to be not as common as in patients with myeloma. In addition to humoral deficiency, lymphocyte transformation studies suggest that cellular immunity is reduced in patients with macroglobulinemia. However, no systematic investigation of cellular immunity has been performed.

Amyloidosis occurs in patients with macroglobulinemia (see Case 3); it tends to be less common than in myeloma probably because of the better balance between heavy and light chain synthesis in the IgM disease. A number of cases of biclonal gammopathies have been described in which patients produce both a myeloma protein and a Waldenström macroglobulin. The clinical findings in these patients have been variable, in some resembling more myeloma and in others, the picture being more like macroglobulinemia. Oligoclonal macroglobulinemia has also been reported, as have triclonal abnormalities consisting of the simultaneous production of monoclonal IgA, IgM, and IgG in a single individual.

See Refs. 1-17.

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C. Specific Organ System Involvement

1. Renal

Renal function studies in patients with macroglobulinemia are limited. The suggestion that elevated serum viscosity might interfere with the countercurrent mechanism has been supported by the documentation of improved renal concentrating and diluting ability following reduction in serum M-protein concentration by plasmapheresis in one patient with IgG myeloma. Similarly, lowering of serum viscosity by plasmapheresis has resulted in reduced urinary excretion of protein and sodium in a patient with macroglobulinemia. Impaired renal acidification has been demonstrated in various hyperglobulinemic states including macroglobulinemia; the mechanism is unknown. The most prominent anatomic renal lesion in macroglobulinemia has been the finding of intraglomerular non-amyloid thrombus-like deposits along the endothelial aspect of the basement membrane which may occlude the capillary lumen. Immunofluorescent studies of these deposits have demonstrated IgM without evidence of other immunoglobulins, fibrinogen, or complement. Although their functional significance is unclear, these subendothelial IgM deposits may constitute the renal manifestation of hyperviscosity syndrome. As noted, heavy Bence Jones proteinuria and tubular cast formation are most uncommon in macroglobulinemia. The rarity of marked light chain excretion and hypercalciuria probably account for the infrequency of severe renal failure (see Case 4). Glomerular involvement with amyloid may be seen (see Case 3); interstitial infiltration with lymphoid cells and uric acid nephropathy occasionally occur. Immune complex glomerulonephritis with production of the nephrotic syndrome has been recently described in a patient with macroglobulinemia. However, the patient did not have a cryoglobulin and the role of the monoclonal macroglobulin in the pathogenesis of the glomerulonephritis was unclear.

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2. Nervous System

A variety of central and peripheral nervous system involvement has been described. Undoubtedly, some of these relate to hyperviscosity syndrome (see Sect V-A) since they are reversible with plasmapheresis. However, macroglobulinemia with central nervous system manifestations (Bing-Neel syndrome) also has been associated with central nervous system hemorrhage as well as meningeal and parenchymal infiltrations of lymphoid cells. Occasionally, these may assume major proportions and form intracerebral tumors. The monoclonal macroglobulin has been demonstrated in cerebrospinal fluid in several patients. A patient with the clinical picture of progressive spinal muscular atrophy which was reversible after chemotherapy has also been reported. Peripheral neuropathy, predominantly sensory, occurs in 10-20% of patients and has been ascribed to cellular infiltrates and hyperviscosity with chronic ischemia. Demyelination of peripheral nerve also has been documented.

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3. Gastrointestinal

Malabsorption and steatorrhea have been reported in two patients with monoclonal macroglobulin. In the case reported by Pruzanski et al, homogeneous extracellular material was present in the intestinal mucosa; immunofluorescent and histochemical analysis revealed this material to be composed of the monoclonal IgM, lambda protein with an admixture of phospholipid. There is a single report of remission of macroglobulinemia in a patient with Australia antigen-positive hepatitis. Hepatitis has developed in two of our patients with longstanding macroglobulinemia (Cases I and 2). In both instances these were hepatitis B negative and liver biopsies showed the lesion of chronic active hepatitis. The hepatic disease ultimately led to the death of both of these patients.

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4. Pulmonary

Both diffuse interstitial pneumonitis due to plasma cell infiltration as well as localized pulmonary parenchymal mass disease composed of similar cells have been reported in occasional patients. Similar pulmonary involvement has been described in some patients with Sjögren's syndrome and macroglobulinemia (see below).

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VI. Special Considerations

A. Non-progressive ("Benign") Macroglobulinemia.

As is true of other plasma cell dyscrasias, apparently stable and non-progressive forms of macroglobulinemia have been described. The exact incidence of such cases is unknown but they appear to be rather uncommon as compared with analogous instances of IgG "benign" monoclonal gammopathies. The natural history of patients with fortuitously discovered IgM serum spikes is unclear and, as noted previously, the situation is complicated by the lack of clear demarcation between aggressive and non-aggressive disease. Unless there is clear evidence of malignancy or clinically overt disease, therapy should be withheld. Features indicating progressive disease include 1) marked infiltration of bone marrow or other organs with the lymphoid cells, 2) a rising serum spike or a serum spike in excess of 3 gm%, 3) the presence of Bence Jones proteinuria, 4) development of hyperviscosity syndrome, and 5) the development of amyloidosis. It should be emphasized that some monoclonal IgM spikes may signify homogeneous antibody responses in individuals with chronic infections, inflammation or immunodeficiency. In support of such a thesis are the previously noted findings of antibody activity in Waldenström's macroglobulins as well as reports of IgM M-spikes in patients with cytomegalic inclusion disease, leptospirosis and apparently healthy individuals. Moreover, it should be noted that in some of these instances the monoclonal immunoglobulin has been present only transiently.

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B. Association with Connective Tissue Diseases.

Talal and other authors have described 30 patients with coexisting Sjögren's syndrome and lymphoid malignancy, usually macroglobulinemia or histiocytic lymphoma (reticulum cell sarcoma).

In the patients with macroglobulinemia and Sjögren's syndrome, it is unclear which disorder developed first. The association between lymphoproliferative disease of B cells and autoimmunity also occurs in New Zealand black mice; development of monoclonal macroglobulinemia in 30% of such animals who survive to eleven months of age may be an experimental counterpart to that described in certain patients with Sjögren's syndrome. It is perhaps surprising that the individuals with Sjögren's who develop lymphoproliferative disease are patients who usually do not have rheumatoid arthritis. Macroglobulinemia has been described in patients with classic rheumatoid arthritis, however. In these individuals the monoclonal macroglobulin usually does not have rheumatoid factor activity. A survey of 382 patients with rheumatoid arthritis disclosed monoclonal serum immunoglobulins in 7.6%, the highest frequency rate occurring in individuals whose duration of disease exceeded ten years. The development of macroglobulinemia in a patient with discoid lupus erythematosus has recently been reported.

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C. Association with Non-lymphoreticular Neoplasms.

The presence of IgM serum spikes has been reported in occasional patients with carcinomas of various types by many investigators. Thus Osserman reported 70 cases of plasma cell dyscrasias associated with nonreticular neoplasms, five of whom had IgM. Three of the five IgM cases had carcinoma of the tongue. Migliore and Alexanian studied 5066 cancer patients and found a 0.65% incidence of monoclonal gammopathy. The incidence, age, and sex distributions were similar to those of the normal adult population suggesting that the association of monoclonal gammopathy with nonreticuloendothelial neoplasms was fortuitous.

Waldenström emphasized the apparently high frequency of carcinoma in patients with established macroglobulinemia in his early studies. More recently, a 20% incidence of carcinoma was noted in 40 patients with macroglobulinemia studied by Mackenzie and Fudenberg. Three of the eight patients with carcinoma had carcinoma of the lung and three had basal cell carcinomas. Tumors from two of these patients were studied by immunofluorescent techniques for antigens reactive with the respective patient macroglobulin, but the results were negative. Although the presence of macroglobulinemia may indicate an underlying disorder of the immune apparatus which predisposes to the development of carcinoma, it seems as likely that the increased incidence of nonreticular neoplasms in these patients may relate to their advanced age and prolonged course.

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VII. IgM Heavy Chain (Mu-chain) Disease.

Mu-chain disease is probably the rarest of the heavy-chain disorders, only 7 cases having been described (Table X).

TABLE X

Summary of 7 Cases of μ-Heavy-Chain Disease*

Case/Sex/ Age, yr	CLL Duration, yr	Vacuolated Plasma Cells	Serum		Urine		Hepatosplenomegaly	Marked PL	Bone Lesions	Amyloid
			Hypo γ	μ-Chain Band†	BJP	μ-Chain				
1/M/58[2]	6	+++	+	...	κ	...	+	...	+	++
2/M/6‡	9	+++	+	...	...	...	+	...	...	...
3/F/52[4]	20	++	+	...	κ	...	+	...	...?	...
4/M/43[5]	1	++	(−)	...	κ	...	+	...	...	...
5/M/79[6]	9	+	+	...	κ	...	+	+	...	...
6/M/45[7]	(−)	(−)	(−)	α_2	...	0.4 gm/liter	+	...	...	...
7/F/48[8]	1	?	+	...	κ	...	+	...	...	...

* CLL indicates chronic lymphocytic leukemia; BJP, Bence Jones protein; PL, peripheral lymphadenopathy.
† μ-Chain reactive protein devoid of light chains detected in all sera on immunoelectrophoresis.
‡ From unpublished data.

(Ref. 270).

The clinical picture has been that of long-standing chronic lymphocytic leukemia. Affected patients have primarily visceral organ involvement (spleen, liver, abdominal lymph nodes) with little peripheral lymphadenopathy. Vacuolated plasma cells are present in the bone marrow. Bence Jones proteinuria, type kappa, has been documented in five of the patients. Pathologic fractures and amyloidosis were seen in the initial patient. Routine serum protein electrophoresis usually shows hypogammaglobulinemia. The diagnosis is made by the finding of a rapidly-migrating serum component which reacts with antiserum to mu chains but not with antisera to light chains. With one exception, free IgM heavy chains have not been found in the urine of such patients. There is good evidence to indicate that the mu chain protein is a synthetic, not degradative, product of the immunoglobulin-producing cell. In most of the cases the cell appears to synthesize an incomplete mu chain and a light chain that are not assembled into a complete IgM molecule. It is likely that this failure of assembly is related to a mutation giving rise to an internal deletion of the mu chain in the area where the light chain would normally be covalently attached. Mu chain fragments have been rarely identified in patients with other plasma cell dyscrasias but their origin is unclear.

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VIII. Therapy and Prognosis.

In the initial stages, the disorder may be stable or only slowly progressive and no treatment is necessary. The onset of anemia, bleeding manifestations, massive organomegaly and symptoms related to the hyperviscosity syndrome constitute the major indications for therapy.

A. Plasmapheresis. It is important to emphasize that essentially all of the manifestations of hyperviscosity syndrome respond quickly and dramatically to plasmapheresis (see Section V-A). The effectiveness of this procedure relates to two factors: 1) the fact that nearly 80% of all IgM is confined to the intravascular space and 2) the dependence of relative serum viscosity on IgM concentration. Thus, at higher macroglobulin levels, i.e. more than 4 gms%, relatively small reductions of serum macroglobulin concentrations (15-20%) may reduce relative viscosity by 50-100%. Plasmapheresis should be undertaken in any patient with evidence of the hyperviscosity syndrome and is often necessary as an emergency procedure. It can be performed at the bedside or in the blood bank and as many as three to five units of plasma can be removed daily until the viscosity is lowered below the patient's symptomatic threshold. Measurements of relative serum viscosity should be made before and after plasmapheresis. During the procedure, vital signs must be monitored and fluid replaced. Since all patients have hypervolemia, only about two-thirds of the volume of plasma removed is replaced with normal saline. Most patients with macroglobulinemia tolerate plasmapheresis without difficulty even when anemic. The return of symptoms suggestive of hyperviscosity (e.g. dizzy headaches) indicates the need to repeat the procedure. Some patients are carried on a long-term basis by intermittent removal of plasma to maintain the viscosity at a level below that individual's symptomatic threshold, much as patients with polycythemia vera are intermittently phlebotomized. As much as 300 liters of plasma has been removed from a single patient over a two and a half year period without any indication of adverse effect. In patients with cryoglobulins or cold agglutinins centrifugation should be performed 37°C in order to prevent the macroglobulin from coming down with the cells which will be returned to the patient.

B. Cytotoxic Chemotherapy. Chlorambucil (Leukeran) is the drug of choice and is usually administered in doses of 2 to 6 mg per day p.o. Other alkylating agents including cyclophosphamide and melphalan appear to be equally effective. Patients have been treated with continuous oral alkylating agent therapy for periods as long as nine years with good control of the disease. However, discontinuance of medication has led to relapse in almost all instances (see Case 4). In such cases, the response to reinstitution of treatment has been disappointing. Other agents including corticosteroids have been reported to produce good responses in occasional patients. Scattered reports of treatment with various mercaptanes (e.g. penicillamine) have not been encouraging. Although penicillamine can depolymerize IgM *in vitro* its action probably depends on a mild cytotoxic effect to suppress immunoglobulin synthesis, since it is doubtful that the concentration required for depolymerization is achieved *in vivo*.

C. Other Measures. Recurrent infections tend to occur in some patients and should be treated vigorously after inappropriate cultures are obtained. The presence of hyperuricemia should be treated by the administration of allopurinol. In those few patients who have evidence of Bence Jones proteinuria, dehydration must be avoided so that severe renal functional impairment does not occur.

The course of macroglobulinemia is variable but tends to be more benign than that of multiple myeloma. Overall prognosis appears to be closely related to response to therapy and median survival appears to be in the range of three to five years. Much individual variation is seen, however, the process being quite malignant in some patients and comparatively benign in others. Survivals of a decade or longer have been well documented.

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IX. Case Protocols

Case I R.S. PMH #37-38-71

This 55-year-old white male machinist was in good health until August, 1968, when he noted "cold feet" and hemorrhagic areas over the lower extremities. One month later, he developed severe generalized headaches, blurred vision, gingival bleeding, and epistaxis. At another hospital he was found to have modest generalized lymphadenopathy, hepatosplenomegaly, ataxia, purpura, marked engorgement of the retinal veins, and a mild anemia. Bone marrow aspiration disclosed 21 per cent "lymphoid elements". Serum protein electrophoresis revealed a 6.5 gm per 100 ml monoclonal spike which consisted of IgM; IgG and IgA levels were reduced. The diagnosis of Waldenström's macroglobulinemia with hyperviscosity syndrome was made and the patient was treated with intermittent courses of chlorambucil over the ensuing 15 months. During this interval his hyperviscosity symptoms improved somewhat and the splenomegaly receded.

The patient was referred to this institution in January, 1970. He still complained of headaches, visual disturbances, skin and mucosal bleeding, cold lower extremities and a "blotchy" color of the skin over the legs. He denied Raynaud's phenomenon and acrocyanosis. There was no history of arthralgias, arthritis or morning stiffness, dry eyes, xerostomia, paresthesias, bone pain, weight loss, or increased susceptibility to infections.

An attack of recurrent rheumatic fever led to a medical discharge from the military in 1943. The patient gave a history of longstanding allergic rhinitis but had never received hyposensitization therapy. He denied other allergies, asthma, and previous transfusions. The family history was noncontributory.

On physical examination the patient was obese with normal vital signs, petechiae over the left upper arm and livido reticularis over the lower legs. There was no significant lymphadenopathy. Funduscopic examination disclosed severe venous engorgement with typical sausaging. Marked sheathing of the retinal veins was evident; no hemorrhages were present and the optic discs were flat. Cardiac examination revealed an atrial gallop but no murmur. The liver edge was palpable 2 cm under the right costal margin and the spleen was palpable 2 cm below the left costal margin. The joints were normal except for the presence of Heberden's nodes. Neurologic examination was unremarkable except for mild tandem-gait ataxia. The remainder of the physical examination was within normal limits.

Initial laboratory data included hemoglobin 13.2 gm per 100 ml, hematocrit 39 per cent, white blood cell count 4,200 per cubic mm and platelets 150,000 per cubic mm. Rouleaux and occasional plasmacytoid lymphocytes were noted on peripheral smear. The erythrocyte sedimentation rate (Westergren) was 135 mm per hour at 37°C and the Sia test was 4+. Relative serum viscosity was 6.5 at 37°C; large amounts of cryoglobulin were present which caused a marked increase in viscosity below 30°C and opaque serum at 25°C. After 1 hour at 4°C, the serum solidified completely. Serum protein electrophoresis demonstrated a 3.8 gm per 100 ml homogeneous component in the gamma region. Urinary protein excretion was

360 mg per 24 hours and creatinine clearance was 117 ml per minute. A concentrated urine specimen contained kappa but no evidence of lambda light chains by immunoelectrophoresis. Bone marrow aspiration disclosed a hypercellular marrow with 10 per cent plasma cells and focal clusters of lymphocytes. Intranuclear periodic acid-Schiff positive inclusions were present in the latter. The patient's red cells were type A; his serum anti-B titer was 1:64. Direct Coombs and cold agglutinin tests were negative. Clot retraction was decreased but other coagulation studies as well as routine chemistries, chest film, bone survey, and electrocardiogram were within normal limits. The patient underwent plasmapheresis with the removal of 3,300 ml of plasma over a 4 day period with reduction in relative serum viscosity to 3.5 and improvement in symptoms of hyperviscosity syndrome. Daily chlorambucil therapy was begun in the dosage of 2 to 4 mg per day which produced modest granulocytopenia and maintained the relative serum viscosity between 3.0 and 3.5. Serum C3 levels were uniformly reduced (79 to 89 mg per 100 ml) on 6 different occasions. The serum monoclonal component decreased to 2.3 gm per 100 ml by September 1971. The patient remained asymptomatic (although his cryoglobulinemia persisted) until September 1972, when he abruptly developed ascites and jaundice. His subsequent course was one of progressive hepatic failure terminating in death in November 1972. Autopsy disclosed chronic hepatitis with postnecrotic cirrhosis and systemic cryptococcosis.

Case 2 I.H. PMH #43 00 66

This 61 year old mechanic was well until early 1972 when he developed lassitude, postural dizziness and a "tired feeling" in his chest. His local physician referred him to PMH because of anemia and weakness. The patient had a notable family history of cancer.

Physical exam: elderly WM with normal vital signs. Multiple nodular lesions were present over the face, arms and back. Enlarged nodes were present bilaterally in the supraclavicular, axillary and inguinal regions. The fundi showed marked venous engorgement with sausaging and hemorrhages O.S. The spleen was palpable 5 cm below the left costal margin and petechiae and ecchymoses were present over the lower extremities.

Lab data: Hgb 7.3, Hct 22, WBC 2500 (26 polys, 74 lymphs), platelets 40,500. Peripheral smear demonstrated marked rouleaux. ESR 157. SPE disclosed TSP 11.5 with alb 3.1 and 6.2 gm% M-spike in fast-γ region. IEP: IgM, κ with $\downarrow$ IgG and IgA. Urine contained no protein. Uric acid 10.6, Ca 9.6, serum viscosity 6.0. Coagulation studies and x-rays were negative.

Course: Lymph node biopsy showed loss of normal architecture with sheets of lymphocytes, plasma cells and histiocytes (pleomorphic lymphoma). PAS-positive inclusions were present in many cells. Bone marrow specimen was inadequate. Skin lesions were excised and found to be squamous cell carcinoma (on back) and multiple basal cell carcinomas. The patient was plasmapheresed 30 units with a fall in viscosity to 2.8. Chemotherapy with Cytoxan, Prednisone and Allopurinol was begun. He was transfused with packed red cells in December 1972 because of symptomatic anemia. In March 1973 he was readmitted because of icterus and

hepatosplenomegaly. Bilirubin was 5.9, SGOT 2524 and alk phos 27 (KA). Serum M-spike had decreased to 3.1 gm% and viscosity was 2.5. Hematologic values were stable. Liver biopsy disclosed "acute hepatitis consistent with viral etiology". HB antigen was negative. The Cytoxan was stopped and the patient never again received alkylating agents. His peripheral counts, M-spike size and serum viscosity remained essentially unchanged. By August 1973 a liver battery was totally normal and the patient felt well. Late in 1973, the jaundice returned. Repeat liver biopsy in January 1974 showed periportal fibrosis with some bridging and a diagnosis of "chronic aggressive hepatitis" was made. He was begun on Prednisone 30 mg/day with only minimal improvement in liver function studies subsequently. In March 1974 he was admitted in coma and febrile. He was treated for Listeria meningitis but did not improve and expired 9 days later. Autopsy disclosed chronic aggressive hepatitis with early postnecrotic cirrhosis, and systemic Candidiasis.

Case 3 D.F. BUMC 130-248

This 55 year old Italian chef was in good health until May 1971 when he noted peripheral edema, dyspnea on exertion and paroxysmal nocturnal dyspnea. He was treated by his private physician for congestive heart failure and admitted one month later because of gross hematuria. Past history: known gallstones for 20 years with long history of cholecystitis. Physical exam disclosed BP of 94/70 and right-sided abdominal tenderness. There were no other positive findings. Lab data: Hct 44, WBC 11,300 with normal diff, platelets 347,000. Urinalysis: 4+ protein and 75-100 RBC's/HPF. TSP was 5.6 gm% with alb 1.3 and 2.0 gm% M-spike in fast gamma region, shown to be IgM,λ by IEP. Cholesterol 480, uric acid 10.2; other blood chemistries were normal.

Because of persistent abdominal pain, vomiting and the appearance of a palpable mass in the RUQ, the patient underwent cholecystostomy. Cystoscopy disclosed hemorrhagic cystitis. He developed overt congestive heart failure in the hospital; EKG showed good voltage and non-specific ST-T changes. He was discharged with plans for readmission for cholecystectomy at a future date.

He was readmitted in September 1971 because of a 2-week history of progressive weakness and anasarca. Serum M-spike was now 3.1 gm% with marked hypoalbuminemia as before. Protein excretion was 4.7 gm/24 hr without evidence of Bence Jones protein. Amyloidosis was found on renal biopsy. Bone marrow revealed increased cellularity with 20% lymphocytes and marked rouleaux was evident on peripheral smear. Bone films were negative. The patient's edema was refractory to diuretics. He developed cardiac conduction defects and expired on 11/9/71 after a cardiac arrest. Autopsy revealed amyloidosis involving the liver, spleen, lymph nodes, kidneys and heart. Cholelithiasis was also present.

Case 4 W.L. PMH #38-85-95

This 64 year old BM former construction worker was initially seen here in October 1970. He had been followed at USC Medical Center since 1960 when the diagnosis of lymphosarcoma had been made on the basis of a bone marrow study. In 1961 he had received irradiation therapy to the mediastinum, left chest and left axilla. He was found to have macroglobulinemia in 1962. During 1962 and '63 he was treated with daily chlorambucil and since 1964, he had been on daily oral Cytoxan (100 mg/day). SPE in March 1968 disclosed TSP of 9.2 gm% with a fast-gamma M-spike of 3.9 gm%.

When first seen here in 1970, the patient was totally asymptomatic and physical exam was within normal limits. CBC, ESR, UA, blood chemistries and bone films were negative. TSP was 7.6 gm% with no evidence of M-spike on SPE. However, an IgM,κ protein was identified on IEP. Because of the patient's excellent status and long history of continuous Rx with alkylating agents, the Cytoxan was stopped. He did well for the next 15 months but in December 1971, he developed severe headache and epistaxis. SPE revealed a 2.6 gm% M-spike in the β-region.

In January 1972 he was admitted to the hospital after an episode of hematemesis and melena. Physical exam disclosed sausaging and tortuosity of the retinal veins, bleeding gums and hepatosplenomegaly. Lab data: Hgb 10.1, Hct 30, WBC 8500 and platelets 207,000. Rouleaux was evident on peripheral smear. BUN, creatinine and other blood chemistries were normal. Direct Coombs, cold agglutinins and rheumatoid factor were negative. The prothrombin time and PTT were normal but the thrombin time was persistently $>$ 60 secs. Fibrinogen was 350 mg%. Relative serum viscosity was 1.8 but plasma viscosity was found to be 7.5, suggesting an interaction between the patient's macroglobulin and fibrinogen. A cryoprotein was present in both plasma and serum; analysis disclosed the presence of IgM and fibrinogen. Bone marrow exam showed a hypercellular marrow with marked infiltration by plasma cells and lymphocytes. An upper GI x-ray was negative. The urine was negative for Bence Jones protein.

The patient underwent a 12-unit plasmapheresis, following which his mucosal bleeding stopped. However, the thrombin time remained prolonged. Treatment with chlorambucil and prednisone was instituted. During the 3rd week of hospitalization, he developed gram-positive sepsis which responded to vigorous antibiotic therapy. During the fifth hospital week, he was discovered to have hematuria and oliguric azotemia (BUN 60, creatinine 10). Cystoscopy and retrograde pyelography were negative. Renal venography disclosed no abnormalities. Urine IEP showed clear-cut kappa Bence Jones proteinuria. Peritoneal dialysis and plasmapheresis were instituted but the patient again became septic and expired in March 1972. An autopsy was not performed.