Hyperviscosity Syndromes Associated With Immunoglobulin Abnormalities

Kurt J. Bloch and Dennis G. Maki

HYPERVIScosity of Blood may be due to elevated plasma or serum viscosity, to elevated numbers of cells (polycythemia or leukemia) or to increased resistance of cells to the deformation required to accommodate to the varying size and shape of the blood vessels (sickleemia or spherocytosis). This review will be restricted to a consideration of those abnormalities of immunoglobulins which alter the viscosity of serum. While this restriction will greatly facilitate the work of the authors, it is appreciated that the synergistic interaction of serum and cells, for example, may be of critical importance for the production of clinical hyperviscosity syndromes.

Viscosity is the property of fluid to resist flow. For protein solutions this resistance to flow is influenced by both the concentration and intrinsic viscosity of individual proteins in solution. The intrinsic viscosity, a physicochemical property of the protein molecule, is influenced by the molecular size and shape of that protein. γ M molecules have both a high molecular weight and unusual shape—five projections extending outward from a central core. The shape of the molecule may enhance its tendency to aggregate thereby contributing to the high viscosity of serum containing large amounts of γ M molecules. In blood, the interplay of protein molecules, such as γ M, and red cells may further increase viscosity through the formation of a fluid structure, a three dimensional connection of cell-protein-cell bridges, and through the increased attraction of protein-coated cells to adhere to each other in rouleaux groups. These effects are enhanced by any decrease in velocity gradient. The sluggish flow in certain vascular beds with its resulting further enhancement of blood viscosity, may account for the prominence of certain sites, such as the retina and central nervous system, in the symptomatology of the hyperviscosity syndromes.

Hyperviscosity Syndrome Associated with Waldenström's Macroglobulinemia

The association between hyperviscosity of serum and macroglobulinemia was noted in the first two patients whose evaluation permitted Waldenström to delineate, in 1944, the disease entity which bears his name. The high viscosity of the serum of these two patients was attributed to its content of pathological euglobulins of high molecular weight. In subsequent years, knowledge of Waldenström's macroglobulinemia has been expanded and the concept has emerged that many of its clinical features are due to

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hyperviscosity of serum. The combination of symptoms and signs which may be
directly attributed to hyperviscosity of serum and which disappear or ameliorate upon
return of serum viscosity towards normal is referred to as the hyperviscosity syndrome.
Since Waldenström’s initial observations, the signs and symptoms of the hyperviscosity
syndrome have been documented in other disease states characterized by hyper-
gammaglobulinemia including multiple myeloma and connective tissue diseases (see
below).

SIGNS AND SYMPTOMS OF THE HYPERVISCOITY SYNDROME

The following outline is modified after Fahey et al.14 (Table 1).

*Eye Changes:* Symptoms ranging from minor disturbances in vision to almost com-
plete loss of vision, acute in onset, have been described.14 Ophthalmoscopically, the
most constant features include distension and tortuosity of retinal veins, local areas of
beading and dilatation creating a “string-of-sausage” appearance, and flame-shaped
and other hemorrhages. Papilledema and microaneurysms have been reported as
well12,14,21 and retinal vein thrombosis may occur.45 Conjunctival vessels have been
described as dilated and tortuous with marked sludging of the red cells.21 In one
patient with the hyperviscosity syndrome and multiple myeloma, correction of hyper-
viscosity of serum led to rapid improvement in vision, and regression of retinal venous
dilatation and tortuosity, retinal edema, and partially of hemorrhages.21 Other
hemorrhages, exudates, and microaneurysms required weeks to months to improve or
clear completely. Serial fluorescein angiography studies demonstrated a decrease in
retinal circulation time after plasmapheresis.

*Hematologic Manifestations:* Chronic or recurrent oozing of blood from the mucous
membranes of the mouth and gums, in the absence of thrombocytopenia, is a common
manifestation of the hyperviscosity syndrome; spontaneous bleeding occurs daily in
some patients.14 Epistaxis, often severe and difficult to control, may also accompany
this syndrome. Other manifestations include prolonged local bleeding at sites of minor

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<td>Distension and tortuosity of retinal veins “string-of-sausage”</td>
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<td>appearance</td>
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<td>Oozing of blood from oral mucous membranes</td>
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<td>Bleeding from nose, urinary and gastrointestinal tract</td>
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<td>Prolonged bleeding at sites of minor surgical procedures</td>
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<tr>
<td>Anemia</td>
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<td><strong>Neurologic</strong></td>
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<tr>
<td>Headache, dizziness, vertigo, nystagmus, postural hypotension</td>
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<td>Somnolence, stupor, and coma</td>
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<td>Generalized seizures, EEG changes</td>
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<td>Congestive heart failure</td>
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<td>Expanded plasma volume</td>
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<td><strong>Renal</strong></td>
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<tr>
<td>Glomerular deposits attributable to HVS?</td>
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<td>Diminished concentrating and diluting ability attributable to</td>
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<tr>
<td><strong>Subjective</strong></td>
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<td>Weakness, fatigue, anorexia</td>
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*Modified after Fahey et al.14*
surgical procedures such as skin biopsy or tooth extraction. Bleeding from the urinary and gastrointestinal tract (colonic diverticuli) has been reported. The mechanism by which hyperviscous blood disrupts the microcirculation has not been delineated. Alteration in platelet function probably contributes to the various hemorrhagic accompaniments of the hyperviscosity syndrome. Platelets from patients with macroglobulinemia of Waldenström, coated in vivo with γM immunoglobulin, or normal platelets exposed in vitro to patients' plasma have been shown to function poorly in the release of platelet factor 3.

A relationship between erythrocyte life span and serum viscosity has been noted in some patients with macroglobulinemia. When viscosity was increased, red cell survival was decreased; following plasmapheresis, erythrocyte survival increased. It was suggested that shortened red cell survival might be attributed to the blood loss accompanying the hyperviscosity syndrome. In addition, coating of red cells by macroglobulin might interfere with their function and contribute to their destruction—the highly viscous plasma leading to erythrocyte stasis and sequestration at sites where red cells are removed from circulation.

Neurologic Manifestations: These include headache and dizziness; true vertigo; nystagmus; somnolence, progressing to stupor, and coma; and generalized convulsive seizures. Electroencephalographic abnormalities consisting of slow, diffuse dysrythmias have been noted and found to be most pronounced in patients with high serum viscosity. Reversible postural hypotension has been described. Partial hearing loss, with recovery or improvement on correction of hyperviscosity was noted. Profound, persistent deafness may accompany Waldenström's macroglobulinemia apparently on the basis of thrombosis of the venous system of the inner ear. Whether milder degrees of hearing loss occur regularly in patients with the hyperviscosity syndrome remains to be established by comparison with a control population.

Cardiovascular Manifestations: Although it might be expected that hyperviscosity and its associated hypervolemia (Ref. 22 also see below) would be associated with angina pectoris and congestive heart failure in the elderly patients with Waldenström's macroglobulinemia, cardiac manifestations were rarely reported. In one patient described by Solomon and Fahey, intractable cardiac failure was not ameliorated by digitalis or diuretics, but remitted completely following plasmapheresis. Improved cardiac function after plasmapheresis was also recorded in a patient with multiple myeloma and the hyperviscosity syndrome.

Macroglobulinemic patients with the hyperviscosity syndrome and a relative serum viscosity greater than 4.0 had significantly larger mean total blood volume than predicted for their sex, height, and weight. The increase in blood volume was attributable to an increase in plasma volume. When relative serum viscosity was plotted against plasma volume, a striking correlation was observed; the higher the viscosity, the greater the plasma volume. The plasma volume was determined in six patients before and after relative serum viscosity had been reduced by plasmapheresis; a mean decrease of 45% was reported.

Renal Manifestations: Deposits of IgM on the endothelial aspect of the glomerular basement membrane constitute one aspect of the pathology of Waldenström's macroglobulinemia. Hyperviscosity of serum might have a role in the passive deposition of the protein, but direct tests of blood or serum viscosity levels were not made in the patients described. In agreement with the editorial of Williams, the effect of hyperviscosity on renal functions, such as the countercurrent mechanism, would seem
to be a fruitful area for investigation. Perhaps the impairment of renal acidification observed in Waldenström's macroglobulinemia is also related to hyperviscosity.

Plasmapheresis, presumably accompanied by a reduction in serum viscosity, was followed by a decrease in renal excretion of protein in one patient, and by improvement in concentrating and diluting ability in another.

Subjective Symptoms: Weakness, fatigue, and anorexia are included among the subjective symptoms which may be corrected by reduction in serum viscosity.

LABORATORY DIAGNOSIS

The viscosity of serum is usually measured in a simple inexpensive device such as the Ostwald viscosimeter (depicted in Ref. 5 and 14). In this instrument, the time required for a constant volume of liquid at a given pressure and temperature to flow through a capillary tube is determined. Clinical laboratories usually determine the relative viscosity of serum, which is obtained by dividing the flow time of serum by the flow time of water in the same instrument at 37°C. Normal serum values of relative viscosity range from 1.4 to 1.8. It is crucial that the instrument used be completely free of adherent proteinaceous debris. Following each use, the instrument is first rinsed in saline in order to avoid precipitation of protein in the capillary tube, and is then further cleansed by immersion in acid chromate solution.

A rapid screening test has been introduced by Wright and Jenkins who found that the red blood cell pipette was a suitable viscosimeter for detection of hyperviscosity. These authors found that there was little difference in relative viscosity values whether serum or plasma was used, and whether the test was performed at room temperature or 37°C. Pipettes with star-shaped beads (Yankee, Clay-Adams, Proper-Trophy) were recommended; cylindrical beads in other pipettes occasionally obstructed the opening in some pipettes.

In the past, attempts were made to employ various modifications of viscometry in order to distinguish hyperviscosity attributable to macroglobulinemia from other causes of hyperviscosity. The temperature-viscosity index (TVI) was introduced by Waldenström. This index depends upon the measurement of relative viscosity at 13°C and 37°C. The TVI was calculated as follows: TVI = (100 × relative viscosity at 13°C)/relative viscosity at 37°C. Values greater than 120 were considered indicative of macroglobulinemia. Based on an extensive examination of this test, Somer concluded that it was of limited clinical usefulness; while only five of 15 sera from patients with macroglobulinemia had TVI values above 120, so did three of 16 cases of γG myeloma. Another procedure introduced by Steel was the “interpolated 7% viscosity.” In this procedure, measurement of serum viscosity was made after diluting the serum to a protein content of 7 g/100 ml of serum; the relative viscosity of myeloma sera was thereby reduced to the normal range, while in macroglobulinemia it remained abnormal.

Direct immunochemical methods employed in clinical laboratories have replaced these indirect procedures for identifying the immunoglobulins involved in the hyperviscosity syndromes. However, recently both procedures, the latter somewhat modified (see below), have been reintroduced for detecting unstable aggregating γG myeloma proteins associated with the hyperviscosity syndrome.

RELATIONSHIP OF VISCOITY LEVEL TO CLINICAL SYMPTOMS

Fahey pointed out that the serum viscosity associated with clinical symptoms differs from one individual to another; the concept of a “symptomatic threshold” was
introduced to indicate the point at which further viscosity increases begin to cause symptoms. It seems likely that a combination of factors including the presence of primary diseases of the microvasculature, level of the hematocrit, cardiac insufficiency, local pH, and ionic strength may account for the specific viscosity level at which symptoms occur. The major target organ affected was also found to differ among patients with the hyperviscosity syndrome. Patients with relative viscosity levels between 2 and 4 are rarely symptomatic; a few patients with levels between 4 and 5 have symptoms. Most individuals with relative viscosity between 5 and 8 have symptoms, and nearly all do at levels between 8 and 10. At relative viscosities of 10 or more, all patients are symptomatic. Lethal levels of hyperviscosity have not been defined; a patient under our care first became comatose with a relative serum viscosity of 26.

TREATMENT OF THE HYPERVISCOSITY SYNDROME

Removal of plasma protein by a simple method of plasmapheresis was first assessed in a patient with multiple myeloma in a study conducted in 1952. Although the patient had hypergammaglobulinemia and a serum M-component, it is unknown whether hyperviscosity was present. The patient tolerated removal of 30 g of plasma protein daily for at least 5 wk without ill effect and without substantial decrease in the concentration of plasma protein. Subsequently, plasmapheresis was employed therapeutically by Skoog and Adams to remove the serum M-component of a patient with Waldenström's macroglobulinemia. (This patient may be presumed to have had the hyperviscosity syndrome since retinal venous dilatation and venous segmentation were less marked at the end of the plasmapheresis period.)

At present, plasmapheresis is generally performed as follows: plasmapheresis sets (Fenwal Laboratories, Framingham, Mass.) are used which consist of a 500 ml plastic blood donor pack containing 75 ml of anticoagulant acid citrate dextrose solution, and a 300 ml plasma pack. To start, 500 ml of blood is removed; thereafter the 15-gauge siliconized needle is kept patent with a slow drip of isotonic saline solution, while the blood is centrifuged. Although the conditions of centrifugation are of importance, there appears to be some variation among laboratories.* One group centrifuged the blood at 2000 rpm for 20 min at 22°C, while others have cited conditions of 2500 rpm for 3 min at room temperature in an International PR2 centrifuge or 1500 rpm for 3 min. Under the latter conditions, the plasma contained about 80% of the platelets and about 20% of the white cells. Following centrifugation, the plasma is transferred into the plasma container and discarded; the red cells are suspended in a small amount of saline and reinfused into the patient. For maintenance therapy, we usually repeat the procedure once, removing 2 units of blood at each weekly or bi-weekly session. However, in acute cases with marked hyperviscosity, 3000-4000 ml of blood may have to be processed daily for one or more days. Although the procedure is easiest to perform in the blood bank, it may be carried out at bedside. The plasmapheresis set is a "closed" system, which avoids contamination of blood during the procedure.

Recently, the NCI IBM cell separator has been used to exchange the patient's plasma for reconstituted freeze-dried normal plasma. This procedure allows for rapid removal

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*In our bloodbank, blood is centrifuged for 7.5 min at 5000 rpm in a Sorvall RC3 centrifuge equipped with an HG-4L rotor maintained at 4°C.
of large quantities of M-component with the additional advantage of conserving platelets, and of replacing the patient's deficiencies of albumin and immunoglobulins.\textsuperscript{28} A serious disadvantage of this procedure is the significant risk of viral hepatitis attendant upon use of freeze-dried plasma.

Intensive plasmapheresis to reduce the concentration of serum \(\gamma\)M M-component and to lower serum viscosity levels in the treatment of Waldenström's macroglobulinemia was first intensively studied by Fahey et al.\textsuperscript{14,35,43,36} Daily, repeated plasmapheresis was used to achieve rapid lowering of serum viscosity followed by maintenance treatments consisting of the removal of a few units of plasma weekly. This treatment led to improvement in congestive heart failure and pulmonary hypertension in one patient (who probably had underlying heart disease in addition to serum hyperviscosity), as well as a decrease in severity of retinopathy and cessation of mucous membrane bleeding.\textsuperscript{35,36} Similar treatment in a second patient led to marked symptomatic improvement, retinal veins became less distended and tortuous and most of the retinal hemorrhages and papilledema disappeared.\textsuperscript{35,36} Since in these two patients major clinical symptoms appeared to be due to increased viscosity of serum, it was suggested that beneficial effect of plasmapheresis occurred because of reduction in serum viscosity. Application of plasmapheresis to larger numbers of patients has amply confirmed its beneficial effects. In addition to improvement of retinopathy and vision; resolution of severe oral and other mucous membrane bleeding; improvement in cold tolerance; remission of seizures (with return of EEG to normal); disappearance of vertigo, nystagmus, and postural hypotension; improvement in gait and hearing; lessening of anemia and healing of chronic ulcers have all been observed.\textsuperscript{12,14,20,43} Improvement in appetite, strength, and ability to return to a relatively normal life has also been recorded.\textsuperscript{43}

Reversal of the hyperviscosity syndrome appeared to correct the hypocholesterolemia which may accompany Waldenström's macroglobulinemia; neither the mechanism of its production or correction is understood.\textsuperscript{35} In addition, lowering of serum viscosity has led to an elevation of the paradoxically normal erythrocyte sedimentation rate in a patient with Waldenström's macroglobulinemia.\textsuperscript{35}

The relative effectiveness of plasmapheresis in the treatment of the macroglobulinemic hyperviscosity syndrome is related to the largely intravascular distribution of \(\gamma\)M molecules and to the nonlinear relationship of \(\gamma\)M concentration to changes in serum viscosity. Approximately 80\% of \(\gamma\)M is confined to the circulating blood compared to 40\% of \(\gamma\)G; hence considerably more \(\gamma\)M than \(\gamma\)G is readily accessible to plasmapheresis.\textsuperscript{14} Several investigators have shown that the viscosity increment is progressively greater with each unit increase in \(\gamma\)M concentration.\textsuperscript{10,13,46} For this reason, at higher macroglobulin levels, relatively small reductions of serum macroglobulin concentration may greatly reduce the serum viscosity. Removal of 1000 ml of plasma (equivalent to 3 or 4 units of blood) effectively reduces the total \(\gamma\)M by 15\%-20\%,\textsuperscript{43} while reducing relative viscosity by 50\%-100\%.\textsuperscript{5}

No improvement occurred upon reducing the relative serum viscosity from 4 to 2 in one patient with Waldenström's macroglobulinemia and Coombs' positive hemolytic anemia.\textsuperscript{43} nor did plasmapheresis raise the level of blood platelets in a treated patient whose thrombocytopenia was probably attributable to failure of platelet formation.\textsuperscript{43} In the latter case bleeding ceased nevertheless, perhaps because of qualitative improvement in platelet function. In general, plasmapheresis has not influenced hemolytic
anemia, leukopenia, thrombocytopenia, or pancytopenia associated with Waldenström’s macroglobulinemia.\textsuperscript{14}

Since plasmapheresis does not affect the basic disease process, cessation of plasmapheresis, in the absence of other treatment, has resulted in recurrence of the hyperviscosity syndrome after periods of 2–3 wk.\textsuperscript{32} For this reason, maintenance plasmapheresis is necessary, with the removal of two to four units of plasma every 1–2 wk. Primary therapy of the disease process, usually consisting of chemotherapy with chlorambucil, cyclophosphamide, and/or corticosteroids, is also employed and, if effective, may permit reduction in frequency or discontinuance of plasmapheresis.\textsuperscript{14,20,35}

Complications of Plasmapheresis

Plasmapheresis has proven to be a remarkably safe procedure. Immediate complications include hypotension and bradycardia. For these reasons, it has been suggested that patients should be transfused to a hemoglobin level of 9–10 g/100 ml prior to plasmapheresis. In view of the synergistic effects of red cells and macroglobulins on blood viscosity cited above, vigorous transfusion of anemic patients with macroglobulinemia may be hazardous, since the resulting elevation in hematocrits will further increase the blood viscosity.\textsuperscript{31} Initial plasmapheresis in critically ill patients should be directly supervised by a physician.

Intensive plasmapheresis at the rate of 1 liter of plasma per day for five days in normal donors led to a significant fall in concentration of total serum protein, albumin, and \( \gamma \)-globulin, as well as platelets. Serial electrophoretic studies showed that the decrease of \( \gamma \)-globulin was greater than that of other elements. During the recovery period, total protein reached preplasmapheresis levels in 2–4 wk; \( \gamma \)-globulin recovered more slowly and was not back to preplasmapheresis levels for 26–90 days. Recovery of platelet count was prompt.\textsuperscript{18} Patients with the hyperviscosity syndrome may require intensive plasmapheresis for 1–2 days, but seldom is the rate cited above required beyond that time. Since patients may have pre-existing serum protein deficits, serum albumin may have to be replaced soon after the start of intensive plasmapheresis in order to prevent or treat edema.

Chronic plasmapheresis of normal blood donors at rates up to 2.5 liters of plasma per week did not lead to depression of formed blood elements and serum protein levels were only minimally affected.\textsuperscript{18,39} Most patients with Waldenström’s macroglobulinemia tolerate chronic plasmapheresis without difficulty; no major problems were encountered in two patients from whom 114 and 230 units of plasma were removed over a period of 5 and 12 mo, respectively.\textsuperscript{35}

Other Modes of Therapy

Oral administration of DL-penicillamine was associated with a decrease in total serum protein and gamma-globulin concentration in two patients with macroglobulinemia; viscosimetry measurements were not done.\textsuperscript{8} In another patient, administration of DL-penicillamine, 250 mg every 6 hr, produced a marked, sustained decrease of relative viscosity which persisted for several weeks and was accompanied by complete disappearance of the bleeding tendency and cold intolerance. Penicillin G, 10 million units, given intravenously, lowered the relative viscosity by 77\% within 1 hr; this effect was of brief duration, was enhanced by probenecid, and followed by rapid rebound of viscosity. DL-penicillamine, penicillin G, and cysteamine added to the patient’s serum
in vitro also produced a marked decrease in viscosity. The in vitro effect of penicillamine probably does not account for its in vivo action since it is doubtful that the concentration required for depolymerization of γM is achieved in vivo, and because the beneficial affects at times persist long after therapy is stopped. Penicillamine may act as a mild cytotoxic agent to suppress immunoglobulin and M-component synthesis.

OTHER CAUSES OF HYPERVISCOITY SYNDROMES: MULTIPLE MYELOMA ASSOCIATED WITH γA M-COMPONENTS

Macroglobulinemia of Waldenström is the most common cause of the hyperviscosity syndrome, approximately 85%-90% of cases arising on this basis. Next in frequency is multiple myeloma; during the past 5 yr, multiple myeloma associated with γA M-components has been the second most common cause of the hyperviscosity syndrome at the Massachusetts General Hospital (Table 2). The routine performance of viscosimetry in patients with γA myeloma, particularly those with multiple M-component bands on electrophoresis, probably account for the frequent detection of these cases. The finding of an increased viscosity frequently permitted correct interpretation of symptoms and signs as due to hyperviscosity, rather than the basic disease process.

Individual instances of the hyperviscosity syndrome associated with γA myeloma have been reported; in virtually every instance, polymerization of γA monomers has been implicated. Vaerman et al.49 reported a patient with multiple myeloma who had two serum M-components, which on analysis proved to be monomer–polymer forms of γA. The relative serum viscosity was 5.6; it seems likely that the polymer of γA was primarily responsible for the increase. Of further interest was the demonstration of an expanded blood and plasma volume in this patient. The tendency of γA molecules to polymerize was probably responsible for the hyperviscosity syndrome in two additional patients who appear to have had polymer forms of γA with sedimentation coefficients of 8.5, 10, and 1229 and 15.5, 17, and 20 Svedberg units;48 in a third patient only a single abnormal protein with a sedimentation coefficient of 8.9 was detected, suggesting that polymerization had occurred to the dimer form only.56 Polymer formation appears to depend at least in part on the formation of disulfide linkages among γA monomers.

MULTIPLE MYELOMA ASSOCIATED WITH γG M-COMPONENTS

Hyperviscosity in multiple myeloma of the γG type has been ascribed to the presence in serum of very large quantities of γG globulin,9,23 the presence of γG molecules with unusual molecular configuration (asymmetry),23 or the presence of circulating aggregates of the γG M-components.6,9,42 In one series of six patients reported in

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HYPERVERSCOSITY SYNDROMES

detail, extreme protein concentration appeared essential for the development of clinical symptoms in those cases with \( \gamma G1 \) M-components, while aggregation of M-component molecules appeared to be responsible for hyperviscosity in three with \( \gamma G3 \) myeloma.\(^9\) In the latter cases, aggregation was markedly dependent upon concentration and temperature. Protein complexes were demonstrated by analytical ultracentrifugation of undiluted \( \gamma G3 \) myeloma sera, whereas following 1:1 dilution with phosphate-buffered saline, these complexes were no longer seen.\(^9\) The dilution test proved useful in differentiating hyperviscosity due to macroglobulins and \( \gamma G1 \) myeloma proteins from that due to \( \gamma G3 \) proteins; 1:1 dilution of serum markedly reduced the serum viscosity of the latter, while the relative viscosity of sera from patients with Waldenström's macroglobulinemia and \( \gamma G1 \) myeloma was less affected.\(^9\) Similarly, viscosity determination at two different temperatures also appeared to be useful in distinguishing between these causes of the hyperviscosity syndrome. The relative viscosity of \( \gamma G3 \) sera was markedly elevated at 22°C and 4°C compared to 37°C, while macroglobulinemic sera and \( \gamma G1 \) myeloma sera from patients with hyperviscosity, were barely affected. The portion of the \( \gamma G3 \) molecule responsible for the unstable aggregation observed appeared to be in the Fd region of the heavy chain. Based on these findings, Capra and Kunkel suggested that failure to document aggregation of the M-component in some patients with the hyperviscosity syndrome and \( \gamma G \) myeloma\(^7,19,23\) might be related to the dependence of aggregation upon the concentration of protein involved; presence of aggregates in serum could have been missed because ultracentrifugation was performed with diluted serum only.

Although in one series of nine cases of myeloma associated with hyperviscosity, five had \( \gamma G3 \) M-components,\(^9\) in a larger group (18 cases), there did not appear to be a predominance of \( \gamma G3 \) proteins among cases with the hyperviscosity syndrome.\(^50\)

The symptoms and signs of the hyperviscosity syndrome associated with \( \gamma G \) or \( \gamma A \) myeloma do not differ from those observed in Waldenström's macroglobulinemia. The expansion of plasma volume accompanying hyperviscosity due to \( \gamma G \) myeloma has been cited by several investigators\(^19,42\) and may have contributed to congestive heart failure in one patient.\(^55\)

A beneficial response to plasmapheresis has been well documented in the hyperviscosity syndrome associated with \( \gamma G \) myeloma.\(^6,19,55\) For example, life-threatening manifestations of serum hyperviscosity, hemorrhage in one patient, and bizarre neurological dysfunction in another, responded to vigorous plasmapheresis.\(^55\)

**HYPERVERSCOSITY SYNDROMES IN THE CONNECTIVE TISSUE DISEASES**

The serum viscosity in patients with high titer of rheumatoid factor was greater than two standard deviations from the mean of a normal population\(^37,38\); however, none of these patients exceeded a relative viscosity of 2.0 (the normal range is 1.08 to 1.22 in this laboratory). The overt hyperviscosity syndrome has been observed in the rheumatic diseases on the basis of unusual serum aggregates. Jason, LoSpalluto, and Ziff reported two patients with nodular rheumatoid arthritis, weakness, and dyspnea, bleeding from the mucous membranes, marked palmar erythema and serum hyperviscosity.\(^17\) The high serum viscosity was attributed to the interaction of rheumatoid factor with intermediate complexes (presumably consisting of \( \gamma G \) anti-\( \gamma G \)-\( \gamma G \) complexes\(^34\)) resulting in the formation of large molecular aggregates. Treatment with corticosteroid and plasmapheresis were accompanied by rapid clinical improvement in
one patient. In another patient, an unusual 13S serum component composed mainly of γG1 immunoglobulins and possessing rheumatoid factor-like activity was responsible for the hyperviscosity syndrome. The 13S component appeared to arise through protein–protein interaction involving the Fc fragment region of the γG monomers, rather than an antigen–antibody interaction. A striking correlation was noted between the intensity of synovitis, myositis, and the concentration of serum γG and 13S serum component; both the protein component levels and the clinical symptoms were favorably influenced by administration of prednisone. A similar patient whose IgG polymer had, in addition, cryoprecipitable properties was reported earlier; this patient, who had been diagnosed as having rheumatoid arthritis, died of bilateral cerebral thromboses possibly secondary to the marked hyperviscosity produced by the polymerized protein.

Finally, it should be mentioned that elevation of serum viscosity measured at 37°C may occur in patients with the mixed (IgG-IgM) cryoglobulinemia syndrome.

HYPERVERSICOSITY SYNDROME IN MACROGLOBULINEMIC MICE

Mice bearing the plasma cell tumor MOPC-104E, which secretes a γM M-component, were found to have an elevated blood and plasma viscosity. Blood viscosity was a function of the hematocrit and of the concentration of macroglobulin. Erythrocytes from macroglobulinemic animals and normal erythrocytes exposed to media rich in macroglobulin formed large complex aggregates in vitro. Aggregation of erythrocytes was observed in vivo in the pial vessels of the brain of macroglobulinemic mice; erythrocyte aggregation and impaired flow were found to be most marked in a mouse with the highest blood viscosity. The duration of an experimentally produced vasoconstriction of the pial arterial bed was markedly prolonged in macroglobulinemic mice; the duration of constriction was a function of the blood viscosity of the mice. It was suggested that the presence of erythrocyte aggregates and abnormally viscous blood impeded reentry of blood into narrowed channels. If hyperviscosity also retards recovery from physiologic cerebral vasoconstriction, then these findings may account for the transient neurologic symptoms found in some human patients with Waldenström's macroglobulinemia. These animal studies stress, once again, the important interrelationship of serum immunoglobulin and red cells in contributing to the viscosity of the blood.

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