Paraproteinemia

BLOOD HYPERVISCOSITY AND CLINICAL MANIFESTATIONS

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ABSTRACT Many of the clinical features of paraproteinemia result from impairment of blood flow through the vascular tree because of blood hyperviscosity. Studies were carried out in 65 patients with serum paraproteins (31 with IgG, 25 with IgM, and 9 with IgA) to examine the relationship between the blood viscosity and the frequency of selected clinical features. The blood and plasma viscosities were measured at low rates of shear. Blood hyperviscosity was present in 91% of the patients and plasma hyperviscosity in 75% of the patients. In each of the three immunoglobulin classes both the blood and plasma viscosities increased logarithmically with the paraprotein concentration being greatest in the case of IgM. In addition, the relationship between the hematocrit and the logarithm of blood viscosity tended to be linear at any given protein concentration. In patients with very high levels of paraprotein the blood viscosity was modified by low hematocrits; the latter was below 30 in 70% of patients in whom the concentration of paraprotein was above 4 g/100 ml. The prevalence of clinical complications involving the retinal circulation, the peripheral vascular system, and the central nervous system increased markedly with increasing blood viscosity, measured at 0.18 s^{-1}. One or more of these regions was affected in greater than 80% of patients with blood viscosity above 60 centipoise and in less than 23% of patients with blood viscosity below 40 centipoise. These observations illustrate the complex relationship between blood viscosity, concentration of paraprotein, immunoglobulin class and hematocrit, and emphasize the importance of measuring the whole blood viscosity at low rates of shear in determining the risk of vascular complications.

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INTRODUCTION

Many of the clinical features of paraproteinemia are considered to result from the increased resistance to blood flow associated with blood hyperviscosity. The documentation of such changes in viscosity has been reported, and in addition a number of studies have attempted to define the relationship between the viscosity and the frequency of vascular complications (1–5). However, the results have been variable and inconclusive. This could be attributed to the measurement of the serum viscosity alone thereby neglecting the important contributions of erythrocytes to the viscosity of whole blood.

The blood viscosity is also a function of the rate of shear. The strength of interaction between the plasma proteins (especially immunoglobulin and fibrinogen) and the erythrocytes, which is a major determinant of the blood viscosity, can best be assessed at low rates of shear (6). Actual shear rates in the micro circulation vary both spatially and temporally and are difficult to determine. Blood flow in the micro circulation is intermittent and hence conditions near or at zero shear rate may exist normally (7). The thesis of the present study is that clinical complications of blood hyperviscosity in paraproteinemia result from impedence of the micro circulation by increased erythrocyte aggregation induced by the paraprotein. This argument is supported by the studies of Rosenblum and Asofsky (8) which demonstrated that the blood flow in the micro circulation of macroglobulinemic mice is inversely related to the blood viscosity. In addition profound intravascular erythrocyte aggregation was found to be dependent

on the level of blood viscosity measured in vitro (9). Since the degree of erythrocyte aggregation can best be assessed in vitro by measuring the whole blood viscosity at low shear rates (6, 10, 11), a shear rate was selected for whole blood (0.18 s^{-1}) and plasma (1.5 s^{-1}) which was low and yet within the technical limitations of the instrument used.

From the variety of viscometers available, the rotational viscometer fulfilled the requirement for accurate control of shear rate, whereas the capillary tube viscometer did not. In particular, the capillary tube viscometer was quite unsuitable for measurement of whole blood viscosity, one of the principal aims of this paper.

The purpose of the present study was to measure the whole blood and plasma viscosity in paraproteinemia at low rates of shear and to correlate this with the incidence of clinical features of the hyperviscosity syndrome for each of the three major immunoglobulin classes.

METHODS

Patients. 65 patients were studied. The paraprotein belonged to the IgG class in 31 patients, IgA in 9 patients, and IgM in 25 patients.

Protein studies. Paraproteins were identified by serum protein electrophoresis on cellulose acetate strips by using the Beckman Microzone system. (Beckman Instruments, Inc., Fullerton, Calif.) Quantification was determined by using the total serum protein level combined with the integrated densitometer recording of the serum protein electrophoresis (Beckman microzone densitometer R-110). Confirmation and further characterization of protein abnormalities were determined by immunoelectrophoresis of the serum against polyvalent and specific antisera (12).

Hematocrit. The hematocrit was determined by using heparinized micro-hematocrit tubes (Sherwood Medical Industries Inc., St. Louis, Mo.). Premixed blood was drawn into the capillary tubes which were then centrifuged at 14,000 *g* for 5 min (Clements micro-hematocrit centrifuge). The hematocrit was read to the nearest 0.5% from the top of the cell volume by using the Micro hematocrit capillary tube reader (Sherwood).

Viscosity measurements. The blood and plasma viscosities were measured with a rotational viscometer, the coaxial members of which have a rhombospheroid geometry. Detailed considerations relating to choice of this type of viscometer are presented elsewhere (13, 14), but in brief the machine offered accuracy and adequate range of shear rate, constancy of temperatures, and ability to analyse whole blood that allows interpretation of interaction of plasma proteins with erythrocytes such as may occur in the micro circulation. The speed of rotation-shear rate conversion factor was calculated from the geometry of the rhombosperoids by using the mathematical expression derived by Oka (15). The instrument was calibrated by using viscosity certified oils (Commonwealth Scientific and Industrial Research Organization, National Standards Laboratory, Sydney, Australia). Temperature control was obtained by means of a water jacket enclosing the rhombospheroids. All studies were carried out at 35°C and on blood anticoagulated with dry EDTA (1 mg/ml). The studies were completed within 3 h of collection. The temperature (35°C) was selected for analysis as this was the maximum temperature which could be maintained throughout the sample during the recording. Higher rates-jacket temperatures resulted in a temperature gradient (measured by a thermocouple probe) between the blood closest to the water jacket (outer surface) and that closest to the inner surface of its annulus. The maintenance of uniform temperature throughout the sample was considered to be particularly important at low shear rates because of the reduced mixing at low rates of revolution. The absolute blood viscosity at 35°C may be slightly higher than at 37°C although as both normal and paraproteinemia blood were measured at 35°C, the comparison and interpretation of results remain valid.

The blood viscosity was measured at rates of shear of 0.18 s^{-1}, thus being selected for reporting because, after lengthy analysis, this low shear rate was most discriminating in the detection of hyperviscosity, and was considered more relevant in terms of the shear rates operative in the micro circulation (6, 7, 16, 17). The plasma viscosity was measured at 1.5 s^{-1}. Technical limitations for low viscosity materials prevented the measurement of the plasma viscosity at lower rates of shear.

The blood viscosity of 37 normal subjects was measured to determine the normal viscosity range for this instrument. In addition the hematocrit was varied in 14 cases by the addition or removal of autologous plasma to enable a valid statistical analysis of the blood viscosity for hematocrits from 30 to 50. The linear regression line and tolerance limits for $P = 0.05$ were then calculated on logarithmic transformed viscosity data. Blood hyperviscosity is defined as a blood viscosity value which is above these tolerance limits at the given hematocrit. Linear regression lines were used for analysis of the logarithmic transformation of normal blood viscosity (Hematocrit 30–50) because it was found that this form of analysis gave a satisfactory solution of the viscosity-hematocrit relationship. An examination of data provided by Chien et al. (18) indicates that although the relationship is sometimes expressed as a power polynomial function, the latter includes the solution for hematocrits from 0 to 95. Close inspection of the data plots, with respect to whole blood viscosity in man (18, 19) indicates that over the hematocrit range 30–50 the relationship between log viscosity and hematocrit is closely linear, although there was an important deviation from this simple relationship at higher hematocrits (i.e. >50).

The plasma viscosity of 22 normal subjects was also measured. Plasma hyperviscosity is defined as a value above the mean + 2SD limit determined for normal plasma.

Plasma volume. The plasma volume was computed by using I^{125} albumin dilution (Volemetron, Ames Co., Elkhart, Ind.). Body hematocrit was accepted as 91% of the venous hematocrit (8) and the normal plasma volume range was taken as 38–48 ml/kg (20).

Clinical features. Complete clinical details were available in 57 patients with paraproteinemia. In each patient the following data were collated: (*1*) paraprotein class; (*2*) blood viscosity; and (*3*) clinical features of the hyperviscosity syndrome.

The clinical manifestations selected for analysis were those indicating involvement of the central nervous system (e.g. severe headaches, tinnitus, vertigo, ataxia and coma); the retinal circulation (e.g. venous distension, tortuosity and "trucking", multiple hemorrhages, venous occlusion); the peripheral vascular system (e.g. Raynaud's phenomenon, digital gangrene); and the cardiovascular system (e.g. cardiac failure). These vascular regions were selected be-

cause of their frequent involvement in blood hyperviscosity (21). Clinical evaluation was aided by electrocardiography, chest radiography and where indicated, by electroencephalography, and retinal angiography. Specific clinical features were attributed to blood hyperviscosity according to the following criteria: (*1*) The absence of clinical or laboratory evidence of other disease processes which may be causally related; (2) The temporal association with other clinical features attributable to paraproteinemia such as the tendency to infection (21); (3) Modification of the severity of clinical features after a reduction in protein concentration and blood viscosity (e.g. by plasmapheresis), or an exacerbation of the clinical features concomitant with an increase in protein concentration and blood viscosity.

RESULTS

Control subjects

Whole blood. There was a linear correlation between log viscosity and hematocrit for the range of hematocrits 30–50. The tolerance limits for $P = 0.05$ are illustrated in Fig. 1. The extrapolation of the regression line to zero hematocrit (i.e. plasma) gives a viscosity of 3.03 centipoise (cp)[1] which is in good agreement with the normal plasma viscosity results obtained at 1.5 s^{-1} (see below). The relationship observed between viscosity and hematocrit is similar to that reported in other studies by using different viscometers (18, 22–26).

Plasma. The plasma viscosity at 1.5 s^{-1} was 2.60 ±0.35 cp (mean±SD).

Paraproteinemia

Whole blood. Blood hyperviscosity was found in 59 (91%) of the 65 patients analysed. The data relating the blood viscosity to the paraprotein concentration and hematocrit of each sample are presented in Fig. 1. Superimposed on these data are the normal blood viscosity limits as defined above.

Effect of paraprotein concentration on blood viscosity. The results were analysed in three groups according to the paraprotein concentration in the blood sample: 0–2 g/100 ml; 2–4 g/100 ml; and >4 g/100 ml. The results of effects of paraprotein concentration on whole blood viscosity were analysed in three protein concentrations. The division 0–2 g/100 ml was considered appropriate because it approximates the total upper limit immunoglobulin concentration in normal blood. The division at 4 g/100 ml divides the remaining patients into two approximately equal groups. There were marked differences in the distribution of the paraprotein concentrations between the three immunoglobulin classes. For example, 66% of patients in the IgA class had a paraprotein concentration greater than

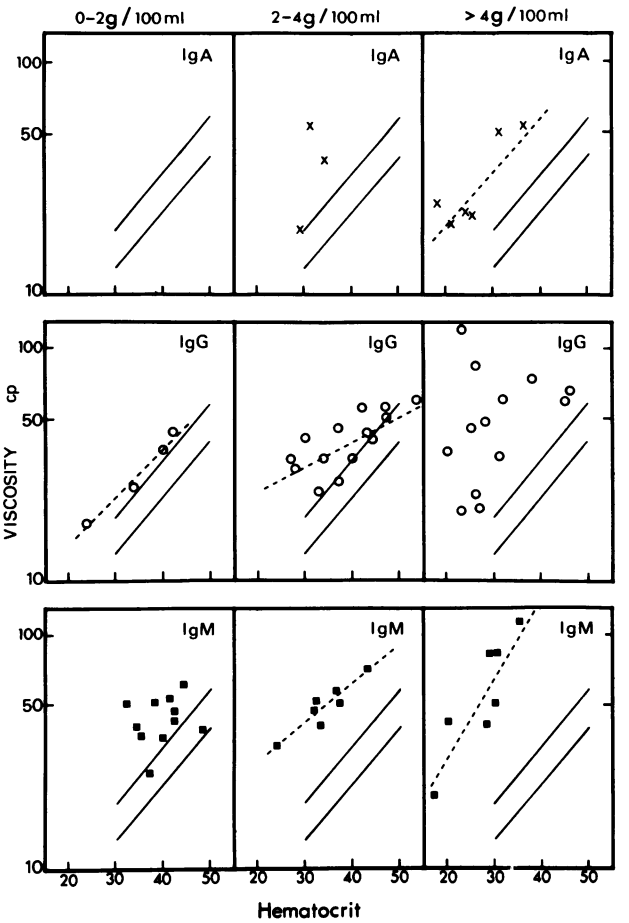

FIGURE 1 Blood viscosity in paraproteinemia. Rate of shear 0.18 s^{-1}. The results are presented in three groups (0–2 g/100 ml, 2–4 g/100 ml, and >4 g/100 ml) according to the concentration of paraprotein. The tolerance limits for $P = 0.05$ are indicated by the pairs of continuous lines. The regression analyses with regression coefficients >0.72 are illustrated (interrupted lines). Paraprotein class identification, IgG, ○; IgA, ×; IgM, ■.

4 g/100 ml whereas 41% of patients in the IgG class and only 28% of patients in the IgM class had a paraprotein concentration above this level.

Fig. 1 shows that the whole blood viscosity is dependent on the concentration of paraprotein—an increase in concentration being associated with a disproportionate increase in blood viscosity measured at the same hematocrit. This dependence is illustrated by the progressive increase in the viscosity above from the normal range with increasing concentration of paraprotein.

Effect of hematocrit on blood viscosity. Fig. 1 also indicates the important influence of hematocrit on viscosity in paraproteinemia. The relationship between blood viscosity and hematocrit follows approximately a log-normal distribution.

[1] *Abbreviation used in this paper*: cp, centipoise.

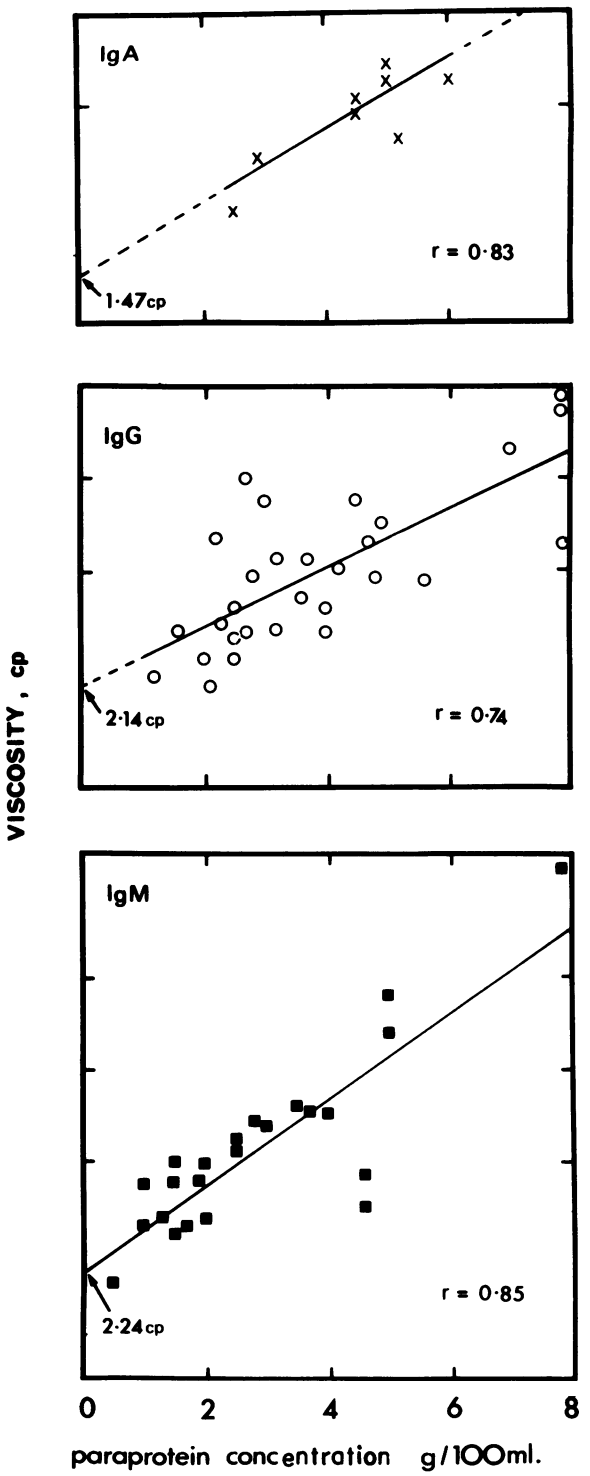

FIGURE 2 Plasma viscosity in paraproteinemia. Rate of shear 1.5 s^{-1}. The regression analyses for the logarithmically transformed viscosity data are indicated by the continuous lines. Paraprotein class identification, IgG, ○; IgA, ×; IgM, ■.

It can also be seen that with increasing paraprotein concentrations there is a progressive decrease in the hematocrit. In the 0–2 g/100 ml range, 14 (93%) of the 15 patients studied had a venous hematocrit above 30, whereas of the 26 patients with a concentration of paraprotein above 4 g/100 ml only 8 (31%) had a venous hematocrit above 30. The whole blood viscosity at high concentrations of paraprotein is therefore modified by a reduced hematocrit.

There were four patients with IgG paraproteinemia in whom the concentration was >6 g/100 ml, whereas there was only one patient in each of the IgM and IgA classes in whom the concentration was above this level. This is an explanation for the broad scatter of results in the IgG class at the >4 g/100 ml concentration range (Fig. 1).

Effect of immunoglobulin class on blood viscosity. Blood hyperviscosity was present in all patients with an IgA paraprotein, in 92% of those with an IgM, and in 87% of those with an IgG paraprotein. However, in the IgA class there was a relatively greater number of patients when paraprotein concentration was >4 g/100 ml compared to the other immunoglobulin classes.

The regression analyses indicated that, for any given hematocrit and protein concentration, the blood viscosity level in the IgM class is, in general, greater than in the IgG and IgA classes.

Plasma. Plasma hyperviscosity was found in 45 (75%) of 59 patients examined, comprising 7 of 8 patients with an IgA paraprotein, 20 of 29 with an IgG, and 18 of the 22 with an IgM paraprotein. In the IgA group all 8 (100%) patients had a paraprotein concentration above 2.5 g/100 ml, whereas only 23 (79%) patients in the IgG class and 10 (45%) patients in the IgM class had paraprotein concentrations above this level (Fig. 2). For each class of immunoglobulin the relationship between concentration of paraprotein and plasma viscosity was found to be nonlinear and followed a log-normal distribution. The plasma viscosity in IgM paraproteinemia at a given concentration of protein, was found to be greater than that found in either the IgG or IgA classes and this class difference was shown to increase markedly with increasing protein concentration.

Plasma volume. A significant linear correlation was found between the plasma viscosity and the plasma volume in the 18 patients studied (Fig. 3). This group included nine patients with an IgG paraprotein, six with an IgM, and three with an IgA paraprotein. The regression line relating these two parameters predicts that plasma hypervolemia will occur when plasma viscosity measured at 1.5 s^{-1} exceeds 4.3 cp.

The prevalence of clinical complications was deter-

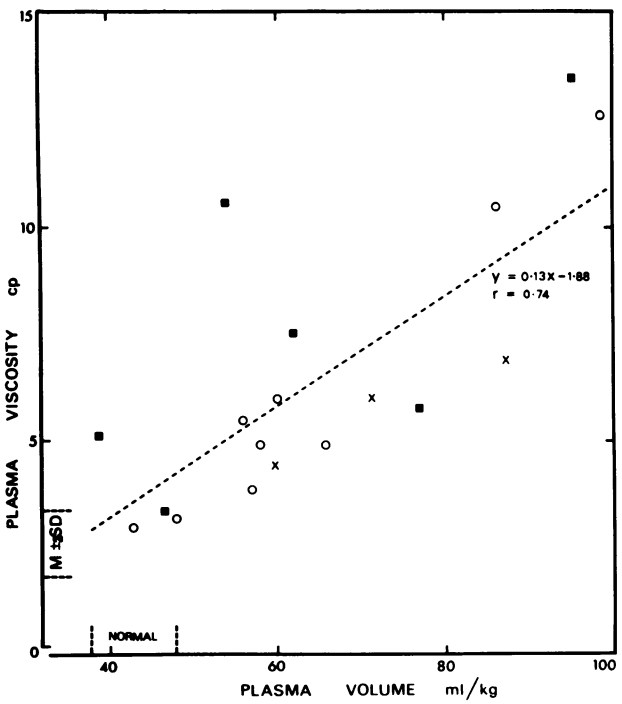

FIGURE 3 Relationship between plasma viscosity at 1.5 s^{-1} and plasma volume. The regression coefficients are indicated. Paraprotein class identification, IgG, ●; IgA, ×; IgM, ■.

mined separately for four groups of patients according to whether the blood viscosity measured at 0.18 s^{-1}, was between 20 and 40 cp, 40 and 60 cp, 60 and 80 cp, or above 80 cp (Fig. 4). There was a progressive increase in the prevalence of clinical complications with increasing blood viscosity. Within each immunoglobulin class the higher the viscosity level the greater the prevalence of abnormalities involving the central nervous system, retinal circulation, and peripheral vascular system. In the group of 22 patients whose blood viscosity was less than 40 cp, clinical abnormalities included involvement of the central nervous and peripheral vascular systems in 3 (14%) patients and the retinal circulation in 5 (23%) patients, whereas, in the group of 12 patients whose blood viscosity was greater than 60 cp, the central nervous system was affected in 11 (92%) patients, the retinal circulation in 10 (83%) and the peripheral vascular system in 8 (75%).

DISCUSSION

A characteristic clinical feature of paraproteinemia is a high incidence of vascular complications which have been attributed to blood hyperviscosity. This is considered to be a consequence of markedly increased erythrocyte and plasma protein interactions, particularly in the micro circulation. The promotion of erythrocyte aggregation by plasma globulins has been repeatedly emphasized (6, 8, 10, 13, 27) and the greatly increased erythrocyte sedimentation rate, which is characteristic of paraproteinemia, supports these conclusions.

The measurement of the blood viscosity provides an assessment of the degree of interaction between the various components of blood (6, 9, 11) and there-

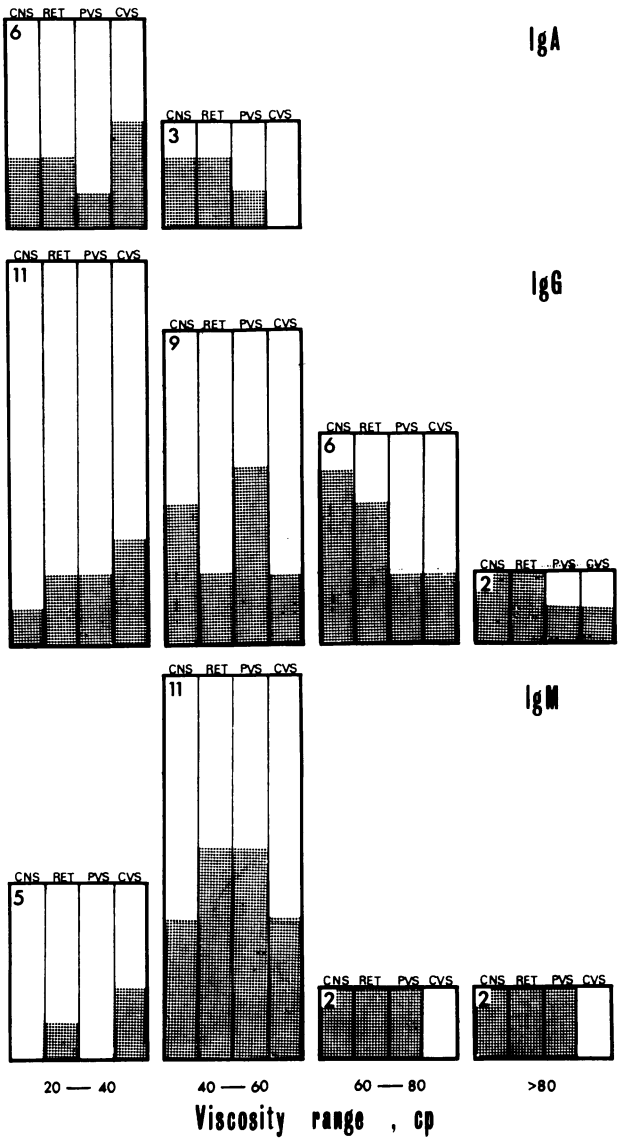

FIGURE 4 The prevalence of clinical abnormalities (stippled areas) in paraproteinemia. The data were grouped according to the blood viscosity. The numbers at the top indicate the number of patients within the group. CNS, central nervous system; RET, retinal circulation; PVS, peripheral vascular system; CVS, cardiovascular system.

fore, of the intrinsic resistance to flow. In support of this concept are the observations by Rosenblum and Asofsky (8, 9, 28) of the cerebral micro circulation in mice transplanted with an IgM producing tumour. The cerebral vascular changes in these animals are similar to the vascular abnormalities found in human paraproteinemia. The basis of the vascular changes is massive, intravascular erythrocyte aggregation which correlates with the level of the blood viscosity determined in vitro. Most rheological studies of biological fluids have involved the use of capillary tubes, but these have an important limitation, namely, the restriction of measurement of viscosity to the high shear rate range which excludes an evaluation of erythrocyte aggregation, a phenomenon which occurs at low rates of shear. The rotational viscometer used in the present study has the property of shearing the greatest proportion of the blood or plasma at a uniform, defined rate of shear and is therefore a more suitable instrument for studying a non-Newtonian material such as blood.

The present findings illustrate the increase in whole blood and plasma viscosities caused by a paraprotein and document the important influences of protein concentration and hematocrit. The incidence of selected clinical complications is shown to be directly related to the level of blood viscosity at a low rate of shear.

The whole blood and plasma viscosities were shown to increase with increasing paraprotein concentration, an observation also extensively studied by others (4, 5, 29). The nonlinear relationship between paraprotein concentration and blood viscosity explains the fact that, in hyperviscosity, small reductions in paraprotein concentration (e.g. by plasmapheresis), may effect a considerable drop in blood viscosity with a concomitant abatement of clinical complications.

The observations confirm the presence of immunoglobulin class differences in the contribution of a paraprotein to blood and plasma viscosities. Paraproteins of the IgM class, for example, were shown to result in higher blood and plasma viscosities than the other immunoglobulin classes at a given concentration of paraprotein and hematocrit. This emphasizes that the IgM macromolecule has a more marked effect on protein and cellular interactions than either IgA or IgG and is consistent with other physicochemical differences known to exist between these classes. However, the prevalence and severity of blood hyperviscosity in patients with IgM paraproteinemia was modified by the tendency to lower paraprotein concentrations within this class compared to those in the IgA and IgG classes.

Under the conditions of this study the viscosity of normal blood was shown to increase exponentially with increasing hematocrit, presumably due to increasing erythrocyte-erythrocyte and erythrocyte-protein interactions. Other authors have claimed that there is either a linear or curvilinear relationship between hematocrit and the logarithm of the blood viscosity over a wide range of shear rates (18, 22, 24–26). The present results also indicate that, in general, this relationship between viscosity and hematocrit holds true for paraproteinemia of the IgM, IgG, and IgA classes, thus confirming the previous observations for IgM (29) extending these to the other major immunoglobulin classes. The influence of hematocrit on blood viscosity is seen to be most marked at high concentrations of protein, particularly in the IgM class. This finding contrasts with the relationship defined by Mannik (29) who found that the slope of the regression line relating hematocrit to log viscosity tended to decrease as the macroglobulin concentration increased. This difference may be due, at least in part, to the higher shear rate used in the latter study.

An additional finding in these studies is the lower hematocrit found in those patients having a higher concentration of paraprotein. This may be partly a result of plasma hypervolemia as indicated by the linear relationship found between increasing plasma volume and increasing plasma viscosity. A number of other investigators (30–35) have also reported plasma hypervolemia in paraproteinemia. Therefore the reduced hematocrit in these patients can be considered, at least in part, as a dilutional anemia. Attempts to correct this anemia by transfusion can precipitate very high levels of blood viscosity which may be dangerous to the patient. The blood viscosity should be carefully monitored during procedures such as plasmapheresis and blood transfusions because of the important contribution of the hematocrit to the blood viscosity in these patients.

The most frequently reported clinical complications of hyperviscosity are those involving the retinal circulation, the central nervous system, hemostatic mechanisms, cardiac function, and the peripheral vascular system. In the present study the prevalence of involvement of the central nervous system, retinal circulation, and peripheral vascular system increased progressively with increasing blood viscosity in each of the three immunoglobulin classes. However, other less frequent complications of paraproteinemia (e.g. amyloid, plasma cell infiltration, and neuropathy) cannot be excluded as causative factors. The final clinical expression of blood hyperviscosity will be influenced by various modifying factors such as primary vessel wall disease, the local temperature and pressure gradients, and tendency of the paraprotein to cryoprecipitation.

A number of investigators (1–3, 5, 36) have at-

tempted to correlate the clinical abnormalities in paraproteinemia with the serum or plasma viscosity. Such studies disregard the important rheological implications of both the hematocrit level and differing cell-protein interactions. Their collective influence on microvascular flow will only be indicated by the whole blood viscosity at low rates of shear.

The findings in the present study demonstrate the relationship between blood viscosity in paraproteinemia and protein concentration, immunoglobulin class, and hematocrit. The results emphasize that the frequency of clinical vascular complications in these patients is high and is related to the blood viscosity level. The finding of blood hyperviscosity will provide the basis for a more accurate interpretation of clinical features and supports an increased resistance to blood flow rather than a primary disease process. The nonlinear dependence of the blood viscosity on both the protein concentration and hematocrit forms the basis for constructing rational therapeutic guidelines in the management of the individual patient. Attention is also directed by this study to the protective nature of plasma hypervolemia with a low venous hematocrit and to the potential hazards involved in such procedures as blood transfusion and plasmapheresis when elevations in the hematocrit can cause marked increases in blood viscosity.

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