

The Hyperviscosity Syndromes

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ABSTRACT Impaired blood flow due to abnormal rheologic characteristics results in a multiplicity of clinical manifestations, collectively termed the *hyperviscosity syndrome*. A basic knowledge of the principles of rheology is important in the understanding of its pathophysiology, especially the relationship between viscosity and flow conditions. The flow characteristics in different types of blood vessels are also determinants in the location of the clinical manifestation. The syndrome can occur in a wide variety of diseases and is best grouped according to the causative element or elements in blood. Abnormalities in the cellular components of blood can occur in the quantity and the quality of erythrocytes, leukocytes, and platelets. Abnormal plasma components can also be in both the quantity and quality of the plasma proteins. Clinical manifestations are the result of vascular occlusion, especially in the microcirculation. The altered rheologic characteristics of either the cellular or the protein component may be temperature dependent, being abnormal only at temperatures below 37°C, so that only the cooler parts of the body are affected. The management of these conditions should be primarily directed at the removal of the abnormal component. At the same time, it should be accompanied by measures that can control the production of the causative element.

Keywords: Hyperviscosity, hemorheology, cancer, thrombosis, hemostasis

The hyperviscosity syndromes consist of a group of pathologic conditions in which blood flow is impaired due to abnormal flow characteristics of the blood. Many thromboembolic complications of hyperviscosity occur

in the setting of underlying neoplastic or paraneoplastic conditions, and are thus of important consideration for discussion in the current issue devoted to the thrombophilic state in cancer. To recognize and correctly diagnose the clinical manifestations of hyperviscosity, the clinician needs to have a clear understanding of its pathophysiology and its relevance to the commonly associated diseases in order to provide the proper management.

RHEOLOGIC CONSIDERATIONS

The flow properties of blood are dependent on both its fluid (plasma) and cellular contents. The hemodynamic factors influencing the flow of blood through blood vessels have been well defined and the reader may wish to refer to detailed descriptions in a number of reviews.¹⁻⁴ Certain commonly used rheologic terms need to be first defined. The velocity of flow through a cylindrical vessel is a function of the radial distance from the vessel wall, being highest in the center line of flow (axial flow) and lowest adjacent to the vessel wall (marginal flow). The relative velocity of flow through parallel fluid layers is termed the *shear rate*, being a measurement of how fast adjacent planes of fluid slide past each other. Fluid at the margin of a vessel flows at a higher shear rate than that occurring in axial (central) flow. *Viscosity* is a measure of the resistance to deformation of a fluid. The force exerted on the vessel wall during the flow is termed *wall shear stress*, and is a function of the shear rate and the viscosity of the blood. The flow rate, hence the shear rate, is much higher in arterioles than in veins.

Thus, provided that the viscosity remains unchanged, the wall shear stress is also much higher in arterioles than in veins, and can be quite high in stenotic vessels. A high shear stress has functional significance in that it increases platelet aggregation.^{5,6} This form of modulation of endothelial cell metabolism plays an important role in atherogenesis and increased thrombotic risk in stenotic vessels where the shear stress is high. The viscosity of whole blood is a function of the plasma viscosity, hematocrit, and red cell aggregation. In a fluid

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suspension of noncompressible particles (known as a Newtonian fluid), the shear stress is a linear function of the shear rate. In contrast, whole blood is a nonNewtonian fluid, in which the shear stress increases greatly with any increase in the viscosity of blood, especially at low shear rates. Whole blood viscosity is dependent on both the cellular and the plasma contents of blood. A high hematocrit has a higher viscosity at all shear rates. Factors governing the plasma viscosity are the concentration of plasma proteins and the characteristics of the proteins. For example, the viscosity of blood is directly proportional to the plasma fibrinogen level. This was well demonstrated by Bell et al⁷ in therapeutic defibrination of patients with Ancrod (Fig. 1). At a normal fibrinogen level, the blood is a Newtonian fluid, whereas after defibrination, at fibrinogen levels of 5 mg/dL, the viscosity is not only decreased but is a direct function of the shear rate, behaving as a Newtonian fluid. Increased gamma-globulin levels and their abnormal characteristics (such as large molecular size in macroglobulinemia) are also major determinants in hyperviscosity syndromes in plasma cell dyscrasias. Flow is also affected in conditions where abnormally increased red cell aggregation occurs, especially in the microcirculation. At low shear rates, red cell aggregation leads to a greater viscosity, while at high shear rates, red cell aggregates are deformed (disaggregated), resulting in a lower viscosity⁸ (Fig. 2). Abnormal deformability of red cells, as seen in sickle cell disease,⁹ influences the nature of the red cell aggregates and hence whole blood viscosity.

EFFECTS OF SHEAR STRESS AND CYCLICAL STRAIN ON ENDOTHELIAL AND SMOOTH MUSCLE CELLS

In addition to shear stress, the vascular wall is also subjected to cyclical strain caused by the pulsatile circumferential stress from the pulsatile pump action of the heart, more so on the arterial than on the venous wall.¹⁰ An important biologic role of both shear stress and cyclic strain is their modulation of the expression of proteins by both endothelial and smooth muscle cells in the vascular wall. These proteins are involved in a wide range of cellular functions.¹ Some of these need special consideration. Endothelin-1 is a peptide produced by endothelial cells that is both a vasoconstrictor and smooth muscle cell mitogen. While increased shear stress results in a decrease in endothelin-1, cyclical strain increases its synthesis and secretion.¹¹ The plasminogen/plasmin system is also affected. A high shear stress increases the endothelial synthesis and secretion of t-PA but not PAI-1, whereas cyclical strain increases PAI-1 without affecting t-PA.^{12,13} Endothelial synthesis of prostacyclin, a potent vasodilator and antiplatelet aggregating peptide, is increased by increased shear stress¹⁴ and cyclical strain.¹⁵ These changes in protein synthesis are believed to be

due to stress modulation of the respective gene expression and activation of multiple transcription factors such as AP-1, NFkB, Sp-1, and Egr1.^{16,17} Though much of these studies are aimed at the pathogenesis of thrombosis and arteriosclerosis, the findings can also be applied to tumor biology. The influence of the altered blood flow in tumors and in metastatic lesions has largely been ignored until recently, and should well be a fertile area of future investigations.

CELLULAR COMPONENTS OF BLOOD

The viscosity of blood is dependent on the concentration of its cellular components or its cytocrit. A high-packed cell volume can be caused by an increase in any one of the cellular components, red cells, leukocytes, or platelets. An increase in blood viscosity can result in any one of these conditions.

Increased Hematocrit

Blood viscosity is raised in commonly encountered clinical situations in which the hematocrit is increased from a shrunken plasma volume, such as in dehydration and in spurious polycythemia (Gaisbock syndrome). One of the most common causes of a high hematocrit in cancer patients is dehydration. However, its significance in causing an increased viscosity is not always recognized. Loss of water in the plasma compartment may also increase the protein concentration and this, in turn, raises the viscosity through a number of ways, including an increase in red cell aggregation. A high hematocrit also results in an increase in the axial migration of the red cells while the marginal plasmatic zone narrows. This will result in an increase in the shear rate and shear stress and will allow a greater platelet-endothelial cell interaction. At higher shear rates, the binding of von Willebrand factor to GpIb and to GpIIb/IIIa on platelet cell surface is increased, and thus resulting in platelet activation.^{6,18}

The various causes of erythrocytosis with a high hematocrit are listed in Table 1. The most common cause of erythrocytosis that gives serious concerns for thromboembolic complications is polycythemia vera. In this condition, an increased risk for thromboembolic complications has been long recognized. The data derived from the Polycythemia Study Group indicated that over 10 years of the study, thrombosis was the most common cause of mortality accounting for 29% of the deaths.¹⁹ These data are strongly supported by an Italian study of 1213 patients over 20 years,²⁰ showing that thromboembolic complications account for 30% of the deaths. Among the initial thrombotic events, cerebral vascular accidents were the most frequent (34%), followed by myocardial infarction (13%), and peripheral arterial occlusion (9%), while venous thrombosis accounted for

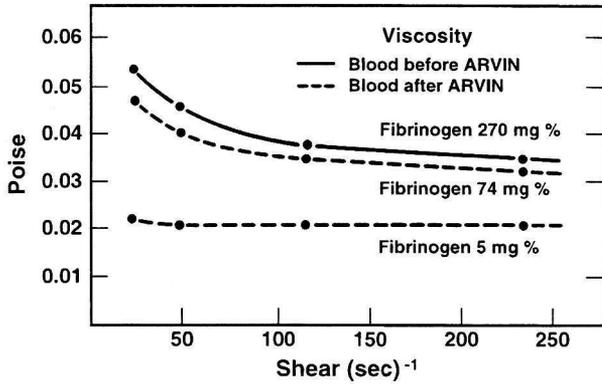


FIG. 1. Blood viscosity following defibrinating therapy with Anrod, showing the rheologic properties of the blood change as the fibrinogen level falls with the therapy. The normal nonNewtonian characteristics of normal blood change to those of a Newtonian fluid as the fibrinogen is removed progressively. (Reprinted with permission from reference 7.)

26% of these events.^{19,20} Of significance is the finding that 35% of the thrombotic events were fatal. The high rate of thrombotic events in the cerebral circulation has been found to be due to impaired cerebral blood flow as the result of increased arterial oxygen. The cerebral

TABLE 1. Conditions Associated with Erythrocytosis.

Primary erythrocytosis
Polycythemia vera
Relative polycythemia (decreased plasma volume)
Spurious polycythemia (Gaisbock syndrome)
Dehydration, capillary leak syndrome
Secondary erythrocytosis:
Hypoxia (cyanotic heart disease, chronic obstructive pulmonary disease, hypoventilation syndrome, high-altitude mutant hemoglobins with increased oxygen affinity)
Increased erythropoietin production (kidney neoplasms, polycystic kidneys, hepatocellular carcinoma, cerebellar hemangioblastoma, uterine leiomyoma, adrenal neoplasms, drug-induced; by erythropoietin or androgens)

blood flow returns to normal on reduction of the hematocrit.

The management of polycythemia vera is well described in many reviews²¹⁻²³ and will not be detailed here. The main objective is to reduce the whole blood viscosity to prevent thromboembolic complications. Increase in whole blood viscosity is proportional to the

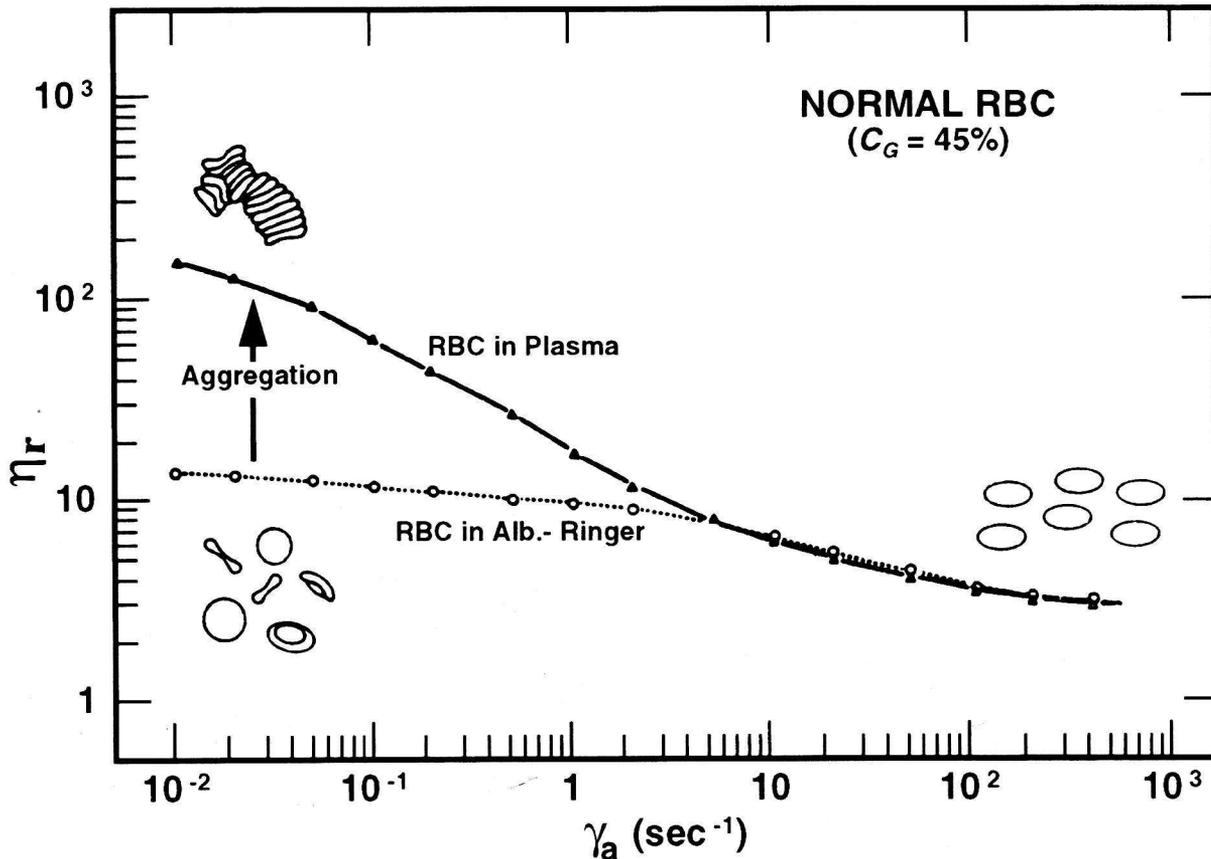


FIG. 2. Logarithmic relation between relative apparent viscosity (η_r) and apparent shear rate (γ_a) for suspensions of human normal red cells in autologous plasma and in albumin-Ringer solution. In both suspensions, the cell volume concentration is 45% and the external fluid viscosity is 1.2 cP with the temperature at 37°C. Drawings show the aggregation of red cells in plasma, but not in albumin-Ringer solution, at low shear rates. Note the deformation into monodispersed red cells in both suspensions at high shear rates. Reprinted with permission from reference 8.

shear rate of blood flow. At a moderately raised hematocrit level of 60%, for example, the whole blood viscosity is twice that of blood with a hematocrit of 40% at shear rates of 12 per sec, calculated to be the flow conditions in a medium arteriole.²⁴ Thus, the mainstay of therapy is the reduction of the hematocrit. This should be carried out by the least toxic and leukemogenic measures for the whole duration of the disease.

Abnormal Red Cell Aggregation

In addition to the increased viscosity caused by an increase in the hematocrit, blood flow may be impaired by abnormal rheologic properties of the red cells. The most frequent is an increased red cell aggregation. Different forms of aggregation can occur, the best known being rouleaux formation observed in the peripheral blood smears of patients with plasma cell dyscrasias. Detailed in vitro studies by Dintenfass and others have revealed that in normal blood, red cell aggregates of six to 20 cells may occur in experimental flow models.^{25,26} These small aggregates break down easily and do not cause a block in the microcirculation. In contrast, large aggregates were observed in diabetes, hyperlipidemia, and certain forms of cancer, with each single aggregate consisting of up to 10^5 red cells.^{27,28} These large aggregates do not disperse easily and are believed to be the cause of impaired microcirculation. We have observed abnormally intense red cell aggregation in a number of patients with acquired dysfibrinogenemia of unknown etiology (Fig. 3A, B).²⁹ These patients had symptoms of microvascular occlusion. In one patient, following therapeutic defibrination with Ancrod, the red cell aggregation decreased with a dramatic relief of the ischemic symptoms.²⁹ We have also used low molecular weight Dextran (Rheomacrodex) to treat patients in whom we had demonstrated the presence of abnormally increased red cell aggregation caused by their abnormal fibrino-

gen. Invariably the peripheral microvascular occlusive manifestations abated following an improvement in objective observations of decreased red cell aggregation (unpublished observations). Interestingly, experiments performed on the space shuttle orbiter "Discovery" showed that the abnormal red cell aggregation found at ground level reverted to normal red cell distribution at zero gravity, suggesting that gravity may play a role in the cell-cell interaction.³⁰

Increased Leukocrit

Impaired microcirculation can result from either a high leukocyte count with a greatly increased leukocrit or abnormal leukocytes in acute leukemia. Under normal circumstances, leukocytes respond to inflammatory stimuli by margination and extravasation from the circulating blood. This process consists of several steps beginning with contact of the leukocytes in the marginal zones of the vessel wall, followed by rolling of the cells along the endothelial surface, then by firm adhesion to the endothelium, and, finally, by diapedesis or migration through the wall. This series of steps is modulated by a number of cell adhesion molecules (CAMs).³¹⁻³³ The CAMs are classified into four families: (a) The Ig superfamily of CAMs, which are cell surface glycoproteins expressed on endothelial cells, consisting of ICAM-1 (CD54), ICAM-2 (CD102), ICAM-3 (CD50), and VCAM-1 (CD106), and on platelets of PECAM (CD31). By binding to other adhesive molecules, they enhance the adhesion between the endothelium and leukocytes.^{34,35} (b) The integrins, which are heterodimeric transmembrane glycoproteins involved in cell-cell adhesion and cell-matrix interactions.^{36,37} A good example is $\alpha_{IIb}\beta_3$ (GpIIb/IIIa or CD41/61) on the platelet surface, which on binding with von Willebrand factor initiates platelet adhesion to vessel wall and subsequent aggregation. In leukocytes, the integrin $\alpha_L\beta_2$ (CD11a/18)(or

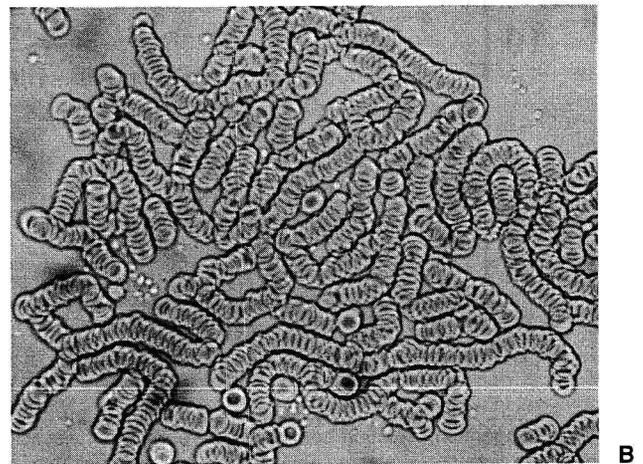
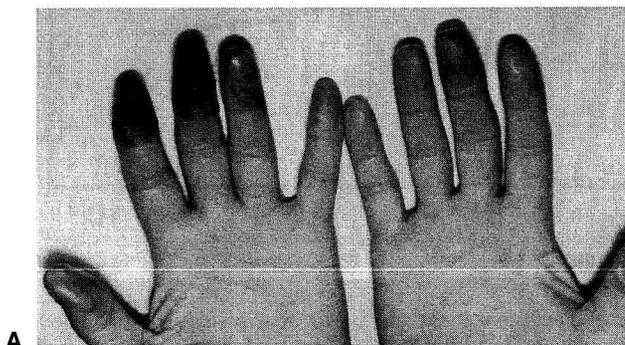


FIG. 3. Ischemic changes in the digits of a patient with increased red cell aggregation due to an acquired dysfibrinogenemia showing gangrene of two fingers in the left hand (A). A cover-slip preparation of his blood shows marked *rouleaux* formation of his red cells in long chains (B). (Reprinted with permission from reference 29.)

LFA-1) in lymphocytes, the integrin $\alpha_M\beta_2$ (CD11b/18) (or Mac-1) and the integrin $\alpha_x\beta_2$ (CD11c/18) (or p150/95) in neutrophils and monocytes are responsible for binding of these respective leukocytes to the endothelial surface and are inducible by inflammatory cytokines.^{38,39} (c) The cadherins are also transmembrane glycoproteins and mediate cell adhesion through a calcium-dependent mechanism.^{40,41} They are believed to be involved in tumor invasion and metastasis.⁴² (d) The selectin family, consisting of E-selectin (CD62E) in endothelial cells, P-selectin (CD62P) in both platelets and endothelial cells and L-selectin (CD62L) in leukocytes.⁴³⁻⁴⁵ The selectins recognize ligands with carbohydrate structures such as a 150 kDa protein E-selectin ligand-1, expressed in leukocytes. Another example is the ligand sialyl-Lewis X, expressed in cancer cell surfaces, which mediates the adhesion of tumor cells to endothelium through E-selectin.⁴⁶

In leukostasis, these adhesive molecules are believed to be taking part in the adhesion and extravasation of leukocytes, though this process has not been extensively studied. They have also been shown to be involved in the metastatic spread of tumor cells.⁴⁷⁻⁴⁹ Leukostasis is encountered when the whole blood viscosity is increased from either a very high leukocyte count, as in chronic leukemias, or from a high myeloblast or lymphoblast count in acute leukemias, and in high-grade nonHodgkin's lymphoma. Whole blood viscosity is increased when a leukocrit of 20 to 25% is reached, as seen with 4 to 6×10^5 myeloblasts/ μL or 5 to 10×10^5 lymphoblasts or lymphocytes/ μL . The risk of this complication is highest with acute myeloblastic leukemia because the myeloblasts are less deformable. Because the process of leukocyte/endothelial cell interaction can be activated by inflammatory cytokines, such as IL-1b and TNF α , a local inflammatory process can often precipitate leukostasis of leukemic cells. Leukostasis under local inflammatory conditions can thus occur at a lower leukocyte count. An example is the occurrence of pulmonary leukostasis in a leukemic patient with pneumonia.⁵⁰ The properties of the activated leukocytes are altered by the cytokines allowing a greater adhesion to the vessel wall. For example, the activated leukocyte is flattened out on the endothelial surface, allowing increased bonding to the endothelium. Additionally, the altered hemodynamics of decreased fluid drag and torque on the flattened leukocytes results in greater adhesion.⁵¹ There is evidence that the E-selectin is activated in Hodgkin's disease and anaplastic large cell lymphoma.⁵² In the lymph nodes of these diseases, a good correlation was found between a high E-selectin expression in the lymphoma cells and the presence of intravascular thrombi and the immuno-histochemical identification of tissue factor in the endothelial cells. In contrast, the E-selectin expression and tissue factor staining in nonmalignant reactive lymph nodes are uncommon. The resulting occluded microcirculation is due to both adhesion

and aggregation of abnormal leukocytes. Due to the local anatomical characteristics of blood vessels in the brain and the lungs, the leukostasis syndrome manifests most commonly in these organs, although histologic evidence of leukostasis can be also found in other parts of the body, especially in the liver and the spleen.⁵³ Post-mortem studies by McGee et al⁵⁴ have shown that all patients with leukocyte counts greater than 2×10^5 cells/ μL and 50% of those with leukocyte counts between 0.5×10^5 cells/ μL to 2×10^5 cells/ μL had prominent leukocyte aggregates in their tissues. Autopsy findings of the brain indicate that central nervous system leukostasis is more intensive in the medium-sized vessels in the white matter and the leptomeninges, and surprisingly affecting less frequently the cortical capillaries.⁵⁵ Leukocyte aggregates are present in the occluded vessels, and, in the case of acute leukemia, vessel wall penetration with perivascular infiltration ("cuffing") by myeloblasts or lymphoblasts can often be seen. Clinical manifestations of leukostasis in the brain are symptoms that range from headache to coma and death, with signs of increased intracranial pressure, often accompanied by focal neurologic deficits.⁵⁶ Leukostasis in the pulmonary circulation presents with acute respiratory failure and with bilateral pulmonary infiltrates prominent in the chest X ray.^{57, 58}

Leukostasis, in patients that are symptomatic, require emergency treatment with leukapheresis. Large number of cells in the range of 10^{11} to 10^{12} cells can be removed in a single apheresis procedure,^{59,60} depending on the patient's leukocyte count. Due to the smaller volume of blood removed in leukapheresis, most patients can tolerate the procedure better than plasma exchange. Prompt initiation of hydroxyurea administration can lower the white count, and thus the leukocrit, to bring about a decrease in the whole blood viscosity.^{61,62} For patients that are asymptomatic, this form of treatment may suffice without using leukapheresis. Concurrent chemotherapy for the leukemia should also be given.

Thrombocytosis

A high platelet count has been found to be associated with an increased risk of thrombosis and hemorrhage in number of studies^{63,64} in patients with platelet counts of greater than 5×10^5 cells/ μL . The majority of these patients had reactive thrombocytosis, secondary to disseminated cancer (36%), infection (8 to 21%), or rebound from hemorrhage (19%). Only 6% of the thrombocytosis were due to myeloproliferative disorders. When patients with counts of over 10^6 platelets/ μL were analyzed, 82% were due to reactive thrombocytosis. These were secondary to infection (31%), trauma (14%), malignant diseases (14%), and splenectomy (19%), while 14% were due to myeloproliferative disorders. Among the latter group, chronic myeloid leukemia constituted 42%, essential thrombocythemia 29%, and poly-

cythemia vera 13%. Clinically, the thromboembolic complications were much more frequently seen in the myeloproliferative disorders than in reactive thrombocytosis. This is presumably due to the transient nature of the latter condition. Platelets in essential thrombocythemia and in polycythemia vera have been found to have a number of abnormal characteristics that increase the thrombotic risks.⁶⁵ These include increased inhibitory activity against plasminogen activators and plasmin,⁶⁶ abnormal aggregation,⁶⁷ increased thromboxane generation, and increased thrombin generation due to the abnormal presence of phosphatidylserine on the surface of platelet membrane.⁶⁸ On the other hand, there are also abnormalities that render the patients more liable to bleeding complications. These include decreased intracellular adenine nucleotides,⁶⁹ decreased prothrombinase expression,⁷⁰ and deficient receptor function from decreased membrane glycoproteins.⁷¹

Thrombosis is more common in arteries than in veins, and the incidence is not directly correlated to the platelet count.⁷² The arterial thrombosis occurs in cerebral, retinal, cardiac, mesenteric, and peripheral arteries, resulting in the respective manifestations of transient ischemic attack (TIA), stroke, amaurosis fugax and blindness, myocardial infarction, bowel infarction and peripheral limb ischemia.⁷³ Microcirculatory impairment may also give rise to the syndrome of erythromelalgia, which consists of erythematous, painful and burning skin manifestations in the extremities and acrocyanosis.⁷⁴ The risk of thrombosis is increased with comorbid conditions such as hypertension, obesity, hyperlipidemia, and diabetes and with cigarette smoking. Despite earlier reports of low thrombotic risks in younger patients,^{75,76} it is now clear that the incidence of thrombosis or hemorrhage is just as high in the younger age group,⁷⁷⁻⁷⁹ and that treatment is indicated for all ages.

Treatment consists of antiplatelet agents in the form of aspirin, ticlopidine, or clopidogrel. The symptoms of erythromelalgia are often dramatically relieved after several days of aspirin therapy.

Suppression of thrombocytosis can be accomplished by chemotherapy with hydroxyurea or anagride. Although there is a leukemogenic potential in long-term hydroxyurea therapy, it is unclear how significant this actually proves to be. Anagride, on the other hand, is a quinazolin derivative that interferes with megakaryocyte maturation⁸⁰ and does not carry the risk of leukemogenesis.⁸¹ However, it can cause certain side effects related to fluid retention.

PLASMA COMPONENTS OF BLOOD

The hyperviscosity syndromes can also be due to abnormalities of the plasma components of blood. The majority of these abnormalities are the presence of ab-

TABLE 2. Hyperviscosity Syndrome with Abnormal Plasma Proteins

Multiple myeloma
Waldenström's macroglobulinemia
Cryoglobulinemia
Pyroglobulinemia
Dysfibrinogenemia

normal immunoglobulins in blood in plasma cell dyscrasias (Table 2).

Multiple Myeloma

The paraproteins in multiple myeloma cause rheologic abnormalities by several mechanisms. These proteins increase red cell aggregation, seen in red cells shown in peripheral blood smears and are manifested in the peripheral blood as *rouleaux* formations (red cells stacked up in rows). The internal viscosity of the red cell is also increased with reduced red cell deformability.⁸² The increase in plasma viscosity is dependent on the quantity and quality of the paraproteins. The latter is determined by the molecular size and shape of the paraprotein. Thus, hyperviscosity syndrome is most common in Waldenström's macroglobulinemia, followed by IgA myeloma because of the frequent polymerization of the IgA paraprotein.⁸³⁻⁸⁵ In the case of IgM, the serum viscosity is proportional to the plasma concentration of this paraprotein up to 3 g/dL, then increases sharply at higher levels. In IgG myeloma with hyperviscosity syndrome, the paraprotein is usually that of IgG-3 class, as IgG-3 tends to form aggregates and complexes. The syndrome in IgG-3 myeloma is seen at a plasma level of 4 to 5 g/dL of this paraprotein, but in other forms of IgG, hyperviscosity is only encountered at levels above 15 g/dL. In IgA myeloma, the syndrome is seen at 6 to 7 g/dL with the polymeric form of IgA, whereas with the monomeric form the level has to reach 10 to 11 g/dL for symptoms to occur. Hyperviscosity is also seen in kappa light chain disease, again due to the formation of the light chain aggregates.

The degree of hyperviscosity is assessed by measurements of the serum viscosity, usually employing a capillary tube viscometer. The unit of viscosity is expressed as units of relative viscosity (relative to water of 1.0). The relative viscosity of normal serum is 1.4 to 1.8, while that of symptomatic patients is generally above 5. A more accurate rheologic analysis requires instruments that take into account the factor of shear rates, by placing the test liquid (whole blood, plasma, or serum) between two rotating surfaces. The viscosity at lower shear rates ranging from 0.18 to 1.5 s⁻¹ can be measured. These results give a much better correlation with the clinical symptoms.

In addition to increased viscosity, hemostatic function is impaired at high paraprotein levels. Global tests

of hemostasis such as bleeding time, prothrombin time, and activated partial thromboplastin time are often prolonged. The interaction between the paraproteins and the various clotting factors, including fibrinogen, factors V, VII, and VIII has been well studied. The paraproteins cause impaired reaction of these clotting factors at different stages of the cascade, resulting in the prolonged clotting times. Platelet function (adhesion and aggregation) is also impaired resulting in the lengthening of the bleeding time. These abnormalities are dependent on the level of the paraproteins and are reversible following therapy.

The clinical manifestations in this group of hyperviscosity syndrome are in many aspects similar to those seen in polycythemia vera. They are the results of vascular occlusion involving blood vessels of varying sizes and may affect any part of the body. In addition, there are also manifestations due to impaired hemostasis. Neurologic and visual symptoms are most frequent. Central nervous system manifestations include headache, dizziness, and impaired mentation up to coma. The impairment of retinal vein blood flow results in a characteristic fundal appearance of a "link-sausage" appearance, consisting of alternating venous segments with dilatation and constriction. This is associated with retinal hemorrhages and exudates. Peripheral neuropathy and myopathy due to occlusion of the neural vessels may also occur, often as the presenting symptoms.

The effectiveness of therapeutic apheresis of the paraproteins depends on the distribution of the proteins, whether they are intravascular or extravascular. The major fraction of macroglobulins and the larger aggregates of the other paraproteins are present in the intravascular space and can thus be effectively removed by plasma exchange. A plasmapheresis apparatus employing continuous flow removal is better tolerated by the patient and is most widely used. With the exchange of one plasma volume (39 to 44 mL per kg body weight), 65% of macroglobulin can be removed. If the IgM level before plasma exchange is high, the serum viscosity can be effectively reduced by 50% or more by just one exchange. However, the frequency of plasmapheresis is best guided by repeated serum viscosity measurements. This procedure is generally well tolerated with an incidence of complications of around 12 to 40%, usually of minor nature.⁸⁶ These are commonly due to citrate toxicity manifesting as paresthesia, muscle twitching, and cramps or tetany, and can be readily corrected by calcium administration. Plasma exchange may also remove a substantial number of platelets, erythropoietin, and certain antibiotics.

Cryofibrinogenemia was first described with multiple myeloma⁸⁷ in a patient with cold-precipitable proteins in the plasma but not in serum. Since then, cryofibrinogen has been found in patients with leukemia and metastatic carcinomas, often associated with thrombophlebitis migrans. Cryofibrinogen is a complex of fib-

rinogen, cold-insoluble globulin, fibronectin, and precipitates at 4°C, and often at room temperatures. Occlusion of vessels may occur in the cooler parts of the body such as the skin in the extremities, the digits, the ears, and tip of the nose, as a result of cold precipitation of the cryofibrinogen. These occlusive lesions manifest as cutaneous ulcerations, "purpura," and livedo reticularis.⁸⁸

Cryoglobulins are cold-precipitable proteins in serum.⁸⁹ Thus, at cooler parts of the body, they may pose the problem of impaired circulation as in cryofibrinogenemia. The incidence has changed dramatically in the last decade from being a complication seen in plasma cell dyscrasia to one that is associated with hepatitis C. They are classified according to their composition. Type I cryoglobulins are monoclonal immunoglobulins with IgM being the most common, followed by IgG and IgA. They may also be composed of light chains alone (Bence-Jones protein). They are seen in myeloma and Waldenström's macroglobulinemia, chronic lymphocytic leukemia, non-Hodgkins lymphoma, and benign monoclonal gammopathy, the latter also known as *essential monoclonal cryoglobulinemia*. Type II cryoglobulins, also known as mixed monoclonal cryoglobulins, are those with IgG complexes with an IgM, IgA or another IgG molecule. This form of cryoglobulin is found in infections, primarily hepatitis C, autoimmune disorders, and lymphoproliferative disorders. Type III cryoglobulins, also known as mixed polyclonal cryoglobulins, are complexes of one or more classes of polyclonal immunoglobulins and sometimes include complement and viral and other antigens. This group of cryoglobulins is associated with infections, most prominent being hepatitis C. It is seen in a variety of diseases in which a polyclonal immunoglobulin response occurs, such as in infections, parasitic infestation, and autoimmune disorders. The viral diseases include hepatitis A, hepatitis B, hepatitis C, infectious mononucleosis, and cytomegalovirus infection. Other associated infections include leprosy, syphilis, and lymphogranuloma venereum. Parasitic infestations include leishmaniasis, toxoplasmosis, and schistosomiasis. Autoimmune disorders include systemic lupus erythematosus, rheumatoid arthritis, and pemphigus. The manifestations are similar to those seen in cryofibrinogenemia.

Pyroglobulins are precipitable from serum at 56°C and redissolve when the serum is cooled. They are not found as commonly as cryoglobulins. Again, they can be found in multiple myeloma and Waldenström's macroglobulinemia.

HYPERVISCOSITY IN SOLID TUMORS

In recent years there were several reports showing that a hyperviscosity syndrome is present in patients with a wide variety of malignant tumors, whose clinical

course was complicated by thromboembolic events, usually deep vein thrombosis. Rheologic studies revealed that the abnormality was independent of the hematocrit.⁹⁰ These malignant tumors include carcinoma of breast,^{91,92} ovary,⁹⁰ lung,⁹³ head and neck,⁹⁴ and in melanoma.^{95,96} The factors responsible for the rheologic abnormality include increased fibrinogen levels, presence of fibrinogen degradation products, host inflammatory acute-phase proteins,⁹⁷ and perhaps other unknown causes that have yet to be discovered. In addition to causing increased plasma viscosity, all of these factors also lead to an increase in red cell aggregation.⁹⁴ The correlation of the increased viscosity with the stage of the cancer and the prognosis has not been established.⁹⁰ However, the clinician should be aware of this abnormality, as this is associated with increased risk for thromboembolic complications.

SUMMARY AND CONCLUSION

The wide variety of pathologic conditions that can be complicated by the occurrence of the hyperviscosity syndrome share one common pathophysiologic feature. They all have abnormal rheologic features, leading to impaired circulation of blood. A thorough understanding of the rheologic abnormalities will help explain the clinical manifestations, especially in the location of the vascular occlusion. Identification of the responsible pathologic component of blood is needed to enable its prompt removal from blood and direct the therapeutic approach to control its production.

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