Bleeding and Thrombosis in the Myeloproliferative Disorders

By Andrew I. Schafer

Bleeding and thrombosis are major causes of morbidity and mortality in patients with myeloproliferative disorders. The significance of uncontrolled polycythemia as a risk factor for thrombosis in these patients has been established. However, the role of thrombocytosis in the pathogenesis of hemostatic complications remains controversial. Abnormalities of platelet function and prolongation of the bleeding time occur in a highly variable number of cases. Specific platelet defects that have been identified in the myeloproliferative disorders include abnormal platelet morphology, acquired storage pool disease, platelet membrane abnormalities, and abnormal arachidonic acid metabolism. Causal relationships between any of these specific abnormalities and either bleeding or thrombosis have not been clearly established. The therapeutic efficacy of myelosuppression to reduce the platelet count in patients with thrombocytosis and the role of antiplatelet drugs in the myeloproliferative disorders are controversial issues.

In 1895, a 46-year-old masseuse with polycythemia presented to Dr Richard C. Cabot of Boston with a history of transient ischemic attacks and spontaneous bruising. Following a dental extraction, she developed "very free hemorrhage, lasting half a day, and controlled only by packing the cavity with gauze." Since this report, bleeding and thrombosis have been recognized as major causes of morbidity and mortality in patients with the related diseases of the bone marrow stem cell that have been traditionally classified as myeloproliferative disorders (MPD), including polycythemia vera, essential thrombocythemia, chronic myelogenous leukemia, myeloid metaplasia, and myelofibrosis. In this review, the clinical problems of bleeding and thrombosis in the MPD will be defined, current understanding of the pathophysiology of these complications will be summarized, and strategy for clinical evaluation and management will be proposed.

CLINICAL MANIFESTATIONS OF BLEEDING AND THROMBOSIS IN THE MPD

Table 1 summarizes the incidence of bleeding and thrombosis in the MPD, culled from numerous large studies reported in the literature. Considerable variation in the incidence of these complications is noted among different series. This probably reflects the heterogeneity of patient populations and treatment modalities, as well as differences in identifying complications in these mostly retrospective studies. Nevertheless, certain generalizations can be drawn from these reports.

First, there are some differences in clinical hemostatic complications among the MPD. It is clear that both bleeding and thrombosis occur the least frequently in chronic myelogenous leukemia during stable phase. In the other MPD, the incidence of these complications is quite comparable, although it has been considered that patients with polycythemia vera are particularly prone to thrombosis, whereas patients with myeloid metaplasia/myelofibrosis and essential thrombocythemia tend to have more hemorrhagic problems. It should be noted that, whereas some individuals with MPD exhibit a pattern of either exclusively bleeding or thrombotic events, many others have both bleeding and thrombosis during the course of their disease. Furthermore a patient with an MPD may apparently shift from being primarily a "bleeder" to being primarily thrombosis prone, or vice versa, as the disease progresses. This unpredictability makes...
Table 1. Bleeding and Thrombosis as Causes of Morbidity and Mortality in Patients With MPD

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>No. of Patients</th>
<th>Morbidity (%)</th>
<th>Mortality (%)</th>
<th>Reference</th>
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*MPD, myeloproliferative disorders; PCV, polycythemia vera; MMM, myeloid metaplasia and myelofibrosis; ET, essential thrombocythemia; CML, chronic myelogenous leukemia.
† Only patients with bleeding complications included in study.
‡ Not including 17 other patients who had been splenectomized: among these patients, 12/17 (70%) had bleeding and 12/17 (70%) had thrombotic complications.
§ Thrombotic or hemorrhagic episodes were directly involved in 9/23 deaths (39%), and there were other instances in which this relationship was suggested.
| Autopsy study. |
| Causes of death in 27 patients: 3 due to gastrointestinal hemorrhage, 3 due to cerebrovascular accident. |

Clinical management of these patients particularly difficult. Another important clinical observation noted in some of the studies cited in Table 1 is the considerably higher incidence of thrombohemorrhagic complications in older patients. The Polycythemia Vera Study Group has reported a markedly increased risk of thrombosis in patients over 70 years old, particularly those with a prior thrombotic event. In contrast, Hoagland and Silverstein have described a subset of young patients with essential thrombocythemia who were remarkably free of these complications. Such age-related differences may be due to coexisting vascular disease among older patients.

The sites of bleeding complications in the MPD are characteristic of platelet and vascular disorders. Bruising, epistaxis, and superficial mucosal hemorrhages (eg, gastrointestinal, genitourinary, gingival) are the most commonly noted, whereas deep tissue and visceral bleeding (eg, hemarthroses, retroperitoneal hemorrhage) are distinctly unusual. Thrombotic events are most frequently those seen in other conditions, including deep-vein thrombophlebitis, pulmonary embolism, and cerebrovascular, coronary, and peripheral vascular occlusion. However, patients with MPD may develop thrombosis at unusual anatomic sites, particularly involving splenic, hepatic, portal, and mesenteric vessels. In fact, the most frequently identified underlying conditions associated with hepatic-vein thrombosis (Budd-Chiari syndrome) are the MPDs. In these cases, hepatic- and portal-vein thrombosis has been attributed in part to local factors, such as splenomegaly, increased portal blood flow, and extramedullary hematopoietic proliferation within the hepatic sinuoids. However, systemic abnormalities are probably also important in these patients: Budd-Chiari syndrome is also strongly associated with paroxysmal nocturnal hemoglobinuria (PNH), a related stem-cell disorder in which these local factors are not generally operative.

Two specific clinical syndromes of vascular occlu-
sion are characteristically seen in patients with MPD, particularly in essential thrombocythemias. Some patients may develop microvascular thrombosis causing digital ischemia. These patients typically present with painful burning of the hands or feet, sometimes associated with discoloration and paresthesias. A high incidence of neurologic manifestations has also been found in patients with essential thrombocythemia, which is characterized by a progressive decrease in the cerebral circulation. Transient ischemic attacks of both the anterior and posterior cerebral circulation, headaches, paresthesias, visual disturbances, and epileptic seizures are the most common clinical manifestations. These two characteristic syndromes of microvascular thrombosis are important to recognize, as they are frequently the presenting features in patients with undiagnosed MPD, and, as discussed below, they may respond dramatically to lowering of the platelet count and/or antiplatelet drugs.

Finally, the risks of serious thrombohemorrhagic complications occurring with surgery in MPD patients should be emphasized. Several reports have noted excessive bleeding following dental surgery, as well as more major surgery, in these patients. The incidence of thromboembolic complications following surgery in patients with MPD appears to exceed that attributed to the postoperative "hypercoagulable" state associated with other conditions. In one series of 26 patients with polycythemia vera undergoing surgery, 50% had serious thrombotic and hemorrhagic complications. Wasserman and Gilbert have estimated that more than three fourths of the patients with uncontrolled polycythemia undergoing major surgery develop bleeding or thrombotic problems, and one third die as a result of these complications. The therapeutic implications of these observations are discussed below.

**PATHOPHYSIOLOGY OF BLEEDING AND THROMBOSIS IN THE MPD**

**Polycythemia**

In patients with polycythemia vera, an elevated hematocrit value and increased blood viscosity clearly play a role in the pathogenesis of thrombotic complications. Pearson and Wetherley-Mein have demonstrated a positive correlation between the incidence of vascular occlusive episodes and the hematocrit level in patients undergoing treatment for polycythemia vera. With hematocrit levels in the 40%-44% range, only 0.2 thrombotic episodes per 10 patient-years occurred, whereas there were 7.5 episodes per 10 patient-years with hematocrit value levels >60%. Even within the normal range of hematocrit values, patients with higher hematocrits had more thrombotic events.

The hematocrit value is the single most important determinant of blood viscosity at a constant temperature and shear rate. Furthermore, the hematocrit value has a progressively increasing influence on blood viscosity as the shear rate is reduced. The clinical features of hyperviscosity, being most prominent in the brain, retina, and lungs, reflect the different patterns of circulation in different organs. Many of the clinical manifestations of uncontrolled polycythemia, including drowsiness, headaches, and visual disturbances, are due to viscosity-associated impairment of cerebral and retinal blood flow. It is therefore not surprising that cerebral thrombosis is a particularly prominent complication among patients with polycythemia vera. Chievitz and Thiede, in fact, found that death due to cerebral thrombosis in polycythemia vera was fivefold increased over that in a comparable, age-matched, nonpolycythemic population. An increased hematocrit value is associated with decreased cerebral blood flow: this relationship is found in patients with polycythemia vera, as well as in patients with relative polycythemia. Furthermore, this inverse correlation between cerebral blood flow and hematocrit value or blood viscosity applies even within the normal range of hematocrit. These observations may have important implications for the goals of therapy in patients with polycythemia vera.

It should be stressed that the effect of polycythemia on the pathogenesis of thrombosis is unlikely to be exclusively due to the associated increase in blood viscosity. Polycythemia may influence the circulation in other ways. For example, as a function of the axial migration of RBCs, an increased hematocrit value may permit platelets to achieve more intimate contact with the vessel wall. Prolonged polycythemia may also cause alterations in vascular distensibility.

Although the increased RBC mass and blood volume, per se, undoubtedly contribute to the thrombotic complications of patients with polycythemia vera, other factors are probably at least as important. Patients with extreme secondary polycythemia (eg, with congenital cyanotic heart disease) are clearly at risk for thrombosis, but patients with lesser degrees of other secondary forms of polycythemia are relatively free of vascular complications. An exception to this occurs in patients with spurious or relative polycythemia (Gaisbock's syndrome), in whom there is clearly a high incidence of vascular occlusive disease. However, these complications are probably due to other risk factors, such as hypertension, smoking, obesity, hyperlipidemia, and emotional stress.
which are characteristically associated with this disorder.26

**Thrombocytosis**

The role of thrombocytosis in the pathogenesis of hemostatic complications in patients with MPD has not been clarified. Some investigators have concluded that high platelet counts contribute to bleeding and thrombotic complications in these patients.27,28 In one study, patients with thrombocytosis associated with MPD were found to have increased fibrinogen and prothrombin turnover that tended to normalize with therapeutic suppression of the platelet counts;29 however, there was no correlation between the turnover rate of fibrinogen and prothrombin and the degree of thrombocytosis. The weight of evidence in the literature fails to demonstrate a clear correlation between the platelet count and the incidence of hemorrhage or thrombosis.30 or between the platelet count and abnormal platelet function.31-32 Kessler et al have recently reported a retrospective analysis of the natural course of uncontrolled thrombocytosis in patients with MPD.4 They found no correlation between the frequency of bleeding or thrombotic events and the extent of thrombocytosis. The implications of these observations for the necessity of aggressively lowering the platelet count in asymptomatic patients will be discussed below.

In contrast, a number of investigators have reported that lowering the platelet count in patients with MPD who have active bleeding or thrombotic problems may result in symptomatic improvement.33-39 In some of these cases, thrombocytosis was treated by alkylating agent chemotherapy34,36,37 and in others by plateletapheresis.38,39 It should be stressed that clinical improvement with lowering of the platelet count in these anecdotal cases has been inconsistent. Situations in which the treatment of thrombocytosis, with or without the concomitant use of aspirin, may result in particularly prompt and dramatic clinical response are the syndromes of digital11,36 and cerebral12 ischemia due to microvascular occlusion. In some of these cases, even apparently irreversible gangrenous lesions of the extremities have responded completely to lowering of the platelet count.11 For unclear reasons, improvement in platelet function has also been occasionally detected following treatment of thrombocytosis,34,38,40 but this is certainly not a consistent finding.41

Further evidence that thrombocytosis, per se, is not an important risk factor for the development of bleeding or thrombotic complications in patients with MPD comes from observations in patients with secondary thrombocytosis, in whom these complications rarely arise. For example, earlier reports of sometimes fatal thrombotic complications in patients with postsplenectomy thrombocytosis42 prompted recommendations for the use of prophylactic anticoagulants or antiplatelet drugs in this setting. However, larger studies and more critical evaluation of this problem have not shown an excessive incidence of thromboembolism in postsplenectomy patients compared to other postoperative groups.43-45 Furthermore, when postsplenectomy thromboembolism does occur, there does not appear to be a clear correlation with absolute platelet count, even when >1,000,000/μL.43 One possible exceptional situation has been considered to occur in some patients who develop persistent thrombocytosis following splenectomy for hemolytic anemias or hemoglobinopathies, in whom the anemia does not resolve after splenectomy.46 However, it has been noted that patients with hemolytic anemia are at risk of thrombosis, irrespective of splenectomy.47 In general, patients with secondary thrombocytosis of various etiologies are not at excessive risk for hemostatic complications and have normal platelet function.34,48

**Defective Platelet Function**

Qualitative platelet abnormalities are commonly found in patients with MPD. Either defective platelet function (hypoaggregability) or increased platelet reactivity (hyperaggregability) has been found in a high percentage of cases. A variety of specific biochemical, metabolic, and morphological platelet abnormalities have been recently described in patients with MPD,48 and these are discussed below. In the clinical laboratory, functional platelet defects in these patients may be evaluated by bleeding times and platelet aggregation. Table 2 summarizes results of bleeding times and platelet aggregation in response to epinephrine, collagen, and adenosine diphosphate (ADP) in a number of reported series. These studies were selected from the literature because they explicitly excluded patients who had taken aspirin or other antiplatelet drugs prior to testing.

As indicated in Table 2, the most frequently found abnormality was the lack of platelet responsiveness to epinephrine. In many cases, there is a complete absence of aggregation with epinephrine stimulation. This is in contrast to the commonly encountered aspirin-type release defect, in which a primary wave, but not a secondary wave, of aggregation is induced by epinephrine. Platelet aggregation abnormalities in response to collagen and ADP are a less common and a more inconsistent finding in patients with MPD. In 11 of the 14 series shown in Table 2, abnormal epinephrine-induced aggregation was found in ≥50% of indi-
BLEEDING AND THROMBOSIS IN MPD

Table 2. Platelet Aggregation and Bleeding Time in Patients With MPD

<table>
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*See Table 1.
†Ten of the 12 patients with prolonged bleeding times had myelofibrosis.
‡Totals.

Table 3. Qualitative Platelet Abnormalities in Patients With MPD

- Abnormal platelet morphology
- Acquired storage pool disease
- Platelet membrane abnormalities
  - Glycoprotein abnormalities
    - a-Adrenergic receptors
    - Prostaglandin D2 receptors
    - Fc receptors
  - Defective arachidonic acid release
  - Abnormal coagulant activity
- Abnormal arachidonic acid metabolism

Specific Qualitative Platelet Abnormalities

A number of specific morphological, biochemical, and metabolic abnormalities of platelets have been identified in patients with MPD (Table 3). Some of these platelet defects (eg, decreased a-adrenergic complications, most studies have failed to identify patients prone to bleeding or thrombosis by the use of platelet aggregation studies or bleeding time. The reasons for this disappointing lack of association between clinical tests and complications are not clear. However, it is possible that many of these patients have simultaneously complex and multiple platelet defects. Furthermore, the population of abnormal platelets in the circulation may change with treatment or with the natural progression of the disease, making correlation between platelet function and past clinical history of bleeding or thrombosis unpredictable.
receptors) appear to be unique among the myeloproliferative syndromes, whereas others (eg, storage pool disease) are in common with other acquired and congenital disorders.

**Abnormal platelet morphology.** Platelet morphology by light microscopy may be strikingly abnormal in patients with MPD, particularly in chronic myelogenous leukemia in accelerated phase, myelofibrosis, and myeloid metaplasia; both small platelets and giant, bizarrely formed platelets with decreased granulation are commonly seen. Increased numbers of circulating megakaryocytes, detected by light microscopy of cells retained on Millipore filters (Bedford, Mass) of blood samples, have been noted. The heterogeneity of the circulating platelet population is reflected by the characteristically increased dispersion of Coulter counter (Hialeah, Fla) size distribution in these patients. This may influence the interpretation of platelet aggregation studies. The larger platelets characteristically seen in some patients with MPD may be selectively lost during the preparation of platelet suspensions by centrifugation. Therefore, functional studies of such platelet preparations may not reflect the total platelet population accurately. This consideration has been neglected in most published reports of qualitative platelet defects in patients with MPD. Ultrastructural platelet abnormalities are frequently seen by electron microscopy in patients with MPD, including disorganization and scarcity of microtubules, decreased numbers of granules, and hypotrophy of the dense tubular and open canalicular systems.

**Acquired storage pool disease.** Some patients with MPD have morphological and metabolic platelet characteristics that are indistinguishable from those seen in congenital platelet storage pool disease. In one series of eight patients with chronic myelogenous leukemia, seven were found to have absent second-wave platelet aggregation in response to epinephrine, despite normal thromboxane synthesis; these patients had a marked decrease in the platelet content of ADP and serotonin. Other studies have also found diminished intracellular and releasable platelet adenine nucleotides or diminished serotonin uptake and release by platelets in association with aggregation abnormalities consistent with storage pool disease. Furthermore, decreased numbers of platelet-dense granules have been noted directly both by electron microscopy and by fluorescent mepacrine labeling. In addition to actual ultrastructural loss of platelet granules, one study has found a markedly decreased rate of serotonin uptake and diminished intensity of mepacrine fluorescence in the platelet-dense bodies of patients with MPD, suggesting an additional defect in active membrane transport. The finding of depleted intracellular levels of β-thromboglobulin associated with increased plasma levels of the same platelet granule protein has raised the possibility that storage pool deficiency in the MPD is acquired by activation and exhaustion of platelets in the circulation or the bone marrow, ie, in vivo platelet release.

**Platelet membrane abnormalities.** A variety of platelet defects have been recently recognized in a high percentage of patients with MPD, which indicates major abnormalities in membrane composition. Abnormal platelet membrane glycoprotein patterns have been reported in patients with various MPD, but no correlation was found with platelet function or clinical complications. Kaywin et al studied two patients with essential thrombocythemia who had absent platelet aggregation and release in response to epinephrine, but normal ADP, collagen, and thrombin-induced aggregation. By direct radioligand-binding experiments using the α-adrenergic antagonist [3H]-dihydroergocryptine, they found <50% of the α-adrenergic receptors of normal platelets or the platelets of patients with MPD who have normal epinephrine responsiveness. The finding of normal binding kinetics for [3H]-dihydroergocryptine showed that the platelets of these patients have a loss of receptors, rather than decreased affinity for the ligand. The high frequency of absent epinephrine-induced platelet aggregation (see Table 2) suggests that deficiency of patient α-adrenergic receptors is a common abnormality among these patients.

Among 23 patients with various MPD, we have found 20 whose platelets exhibited a selective loss of response to prostaglandin D2 (PGD2), a platelet cyclooxygenase product that is an inhibitor of platelet activation. The platelets of these patients required concentrations of PGD2 tenfold higher than normal to inhibit collagen-induced platelet aggregation and serotonin release, and this was due to a corresponding loss of PGD2-activated platelet membrane adenylate cyclase. Response to other prostaglandins (PGE1 and PG12) was entirely normal, confirming the presence of separate platelet receptors for PGD2 and PGE1/PG12. Because PGD2, as an inhibitor of platelet function, has been postulated to be a feedback regulator to limit platelet aggregation, loss of platelet sensitivity to this hormone may be expected to cause a thrombotic diathesis. Patients with abnormal platelet PGD2 response tended to have more problems with thrombosis, but this association was not clear cut. Subsequently, radioligand binding studies directly confirmed a loss of platelet PGD2 receptors in these
patients. As is the case with the loss of α-adrenergic receptors, normal binding affinity of the hormone was found, and approximately 50% of the receptors were found to be lost. This platelet receptor defect may not be entirely specific for patients with MPDs, as another study showed a deficiency of PGD₂ receptors (although less pronounced) in otherwise normal patients during the acute phase of deep-vein thrombophlebitis or pulmonary embolism.

Moore and Nachman have identified another specific platelet receptor defect in patients with MPD. They found increased expression of platelet Fc receptors, membrane receptors for immune complexes or aggregated immunoglobulin. Only 3% of normal platelets, but 76% of myeloproliferative platelets, stained with fluorescein-conjugated immune complexes. These observations were independent of platelet size. They also found that the platelets of these patients had a selectively exaggerated response to immune complexes or aggregated IgG in inducing serotonin release, whereas response to thrombin stimulation was normal. Because circulating immune complexes can be detected in the plasma of some patients with myeloproliferative syndromes, interaction of immune complexes with platelets bearing increased Fc receptors may contribute to abnormalities of hemostasis in these patients. However, in this study, no clear correlation with clinical complications was found.

Jubelirer et al. found normal uptake of [³H]-arachidonic acid into platelet membranes but impaired thrombin-induced release of [³H]-arachidonic acid from the platelet membrane phospholipid pools of patients with chronic myelogenous leukemia. Castaldi et al. likewise reported evidence of defective arachidonic acid mobilization from platelet membrane phospholipids of patients with various myeloproliferative syndromes. They found decreased collagen-induced platelet aggregation and thromboxane production, but normal response to arachidonic acid (which bypasses the phospholipase reaction) in these patients.

Variations in platelet coagulant activity, the property of membrane phospholipids of activated platelets that accelerates fluid phase coagulation, have been noted in some patients with MPD. Walsh et al. and Semeraro et al. demonstrated decreased platelet coagulant activity in patients who tended to have bleeding problems and normal or increased platelet coagulant activity in those with histories of thrombosis or no clinical hemostatic complications.

Abnormal arachidonic acid metabolism. Two pathways of arachidonic acid oxygenation are active in platelets. The aspirin-inhibitable cyclooxygenase pathway generates primarily thromboxane A₂, a potent vasoconstrictor and inducer of platelet aggregation, whereas the lipoxygenase pathway leads to the production of the labile hydroperoxy-fatty acid 12-HPETE and the hydroxy-fatty acid 12-HETE. The latter metabolites are chemotactic for leukocytes, but their role in the control of hemostasis is unclear at this time. Keenan et al. reported that the production of malonaldehyde, an indicator of lipid peroxidation, was decreased after N-ethylmaleimide stimulation of platelets of patients with MPD. Russell and Jubelirer and their colleagues subsequently showed that various abnormalities of arachidonic acid metabolism existed in patients with MPD. Okuma and Uchino were the first to call attention to an abnormal platelet lipoxygenase pathway in some patients with MPD by demonstrating loss of lipoxygenase products on thin-layer chromatography. Using a direct assay of platelet lipoxygenase activity, selective deficiency of this enzyme activity was found in 24/60 patients with various myeloproliferative syndromes, whereas platelet lipoxygenase activity in patients with reactive thrombocytosis or secondary polycythemia was normal. The platelets of patients with lipoxygenase deficiency produced increased amounts of thromboxane, presumably because arachidonic acid could be metabolized only through the cyclooxygenase pathway in these patients. Somewhat surprisingly, patients with platelet lipoxygenase deficiency were found to have an associated bleeding tendency, despite enhanced thromboxane generation. This has raised the possibility that platelet lipoxygenase metabolites may have a physiologic role in the control of hemostasis.

Nature of Qualitative Platelet Abnormalities in the MPDs

All of the myeloproliferative syndromes have now been unequivocally established as being clonal disorders originating in a multipotential hematopoietic bone marrow stem cell. It is likely that many, if not all, of the qualitative platelet abnormalities described above are the result of intrinsically defective platelets produced by an abnormal clone of megakaryocytes in patients with MPD.

However, another possible mechanism for the formation of abnormal platelets in these disorders is by platelet activation during hemostatic encounters in the circulation (eg, disseminated intravascular platelet aggregation precipitated by immune complexes, leukocyte proteases, or disordered blood rheology), leading to in vivo platelet release and exhaustion. These “spent” platelets may recirculate with a relatively normal lifespan, giving rise to the various observed platelet abnormalities. There are several lines of evi-
dence against this argument, at least in regard to some of the platelet defects that have been described. If loss of platelet PGD₂ sensitivity was due to in vivo platelet activation, resulting in excessive PGD₂ generation and consequent desensitization (or “down-regulation”) of platelet PGD₂ receptors, this sequence of events should be aborted by aspirin treatment of the patients. We found persistent platelet resistance to PGD₂ in all patients who were treated with aspirin after their initial evaluation. Okuma et al reported that platelet lipoygenase deficiency was corrected in a patient with chronic myelogenous leukemia following successful engraftment of bone marrow from a genetically identical twin who had normal platelet lipoygenase activity. We have also found that absent platelet epinephrine-induced aggregation and loss of α-adrenergic receptors in a patient with chronic myelogenous leukemia were restored to normal following allogeneic bone marrow transplantation from a normal donor, and subsequently, the recurrence of the platelet abnormalities heralded loss of the graft (Schafer AI, Horne W, Rappeport JM; unpublished observations). These observations strongly suggest that these platelet abnormalities are due to intrinsically defective cells derived from abnormal clones of megakaryocytes.

The various specific platelet abnormalities that have been reported in patients with MPD can serve as natural models to provide important basic information about the role of platelets in the normal scheme of hemostasis. Some of the platelet abnormalities (eg, loss of PGD₂ receptors, increased coagulant activity, increased expression of Fc receptors) may be expected theoretically to cause thrombosis, whereas others (eg, loss of α-adrenergic receptors, storage pool disease) should theoretically cause bleeding problems. It is therefore disappointing to find that none of these well-characterized platelet abnormalities is unequivocally associated with clinical complications. There are several possible explanations for this. First, some of the morphological, metabolic, or biochemical defects may not be of sufficient physiologic importance to cause clinical manifestations. Second, it is possible that myeloproliferative platelets are simultaneously defective in more than one respect, perhaps with partially offsetting consequences on hemostasis. None of the studies has attempted to examine several specific platelet abnormalities simultaneously. Finally, it is conceivable that platelet abnormalities in these patients change with time, perhaps as a result of treatment or as part of the natural history of the disease. This may reflect changing populations of platelets arising from normal or abnormal clones of megakaryocytes. Long-term longitudinal studies of platelet function are required to answer this question, and platelets should be examined at the time of clinical bleeding and thrombotic complications.

MANAGEMENT OF PATIENTS WITH MPD AND ABNORMAL HEMOSTASIS

Cytoreduction

The importance of lowering the hematocrit value in patients with polycythemia vera to avoid thrombotic complications is now well established. In fact, the clinical and rheologic data cited above clearly dictate that the hematocrit should be maintained optimally below 45% in these cases. In contrast, the importance of lowering the platelet count in patients with thrombocytosis is not at all clear. The weight of evidence in the literature, though largely retrospective in nature, suggests that there is no clear correlation between the degree of thrombocytosis and the risk of bleeding or thrombosis in patients with MPD. The Polycythemia Vera Study Group has reported a lower incidence of thrombosis in patients treated with phlebotomy plus myelosuppression compared to those treated with phlebotomy alone. However, a causal relationship between lowering of the platelet count and these clinical observations is difficult to demonstrate, and this study could not attribute differences in risks of thrombosis to differences in platelet counts among the groups. There is presently no convincing evidence that lowering the platelet count in asymptomatic patients with thrombocytosis, even when the platelet count is >1,000,000/µL, protects these patients from hematologic complications. Furthermore, the leukemogenic risk of alkylating agent chemotherapy in this population should be considered in the decision to suppress the platelet count, although recent evidence suggests that some myelosuppressive agents, such as hydroxyurea, may not be associated with a comparable leukemogenic risk. The situation may be different in patients with thrombocytosis who have active bleeding and/or thrombotic problems. There is sufficient anecdotal evidence in the literature that some of these patients may benefit from lowering the platelet count. Although the results are unpredictable, an attempt should be made to reduce the platelet count with myelosuppressive agents in patients with thrombocytosis who have serious recurrent hemostatic complications. Older patients, especially those with a prior history of thrombosis, are at a greater risk of recurrent thrombosis; lowering of the high platelet count in this group may be particularly important. In the two distinct clinical syndromes of microvascular thrombosis described above, manifested by either digital ischemia or cerebrovascular ischemia, rapid lowering of the platelet count by plateletpheresis or chemother-
apy may result in dramatic clinical improvement. These are the only clinical situations in which treatment of thrombocytosis is unequivocally indicated.

**Antiplatelet Drugs**

The use of aspirin or other antiplatelet agents in patients with MPD remains controversial, but certain guidelines can be deduced from the experience in the literature. The indications for aspirin treatment should be dictated primarily by the clinical picture, occasionally with the support of laboratory tests of platelet function. As emphasized above, laboratory tests alone have been generally unreliable in predicting risk of bleeding or thrombosis. The decision to use aspirin should be individualized and reevaluated periodically in the same patient. The indiscriminate use of aspirin in these patients is potentially hazardous. In a prospective randomized trial, the Polycythemia Vera Study Group found that aspirin (300 mg tid) and persantine (75 mg tid) do not prevent thrombotic complications in patients with polycythemia vera and are associated with an increased incidence of serious hemorrhage. Other groups have also noted major bleeding complications or unusual prolongations of the bleeding time with the use of aspirin in some patients with MPD. Even extreme thrombocytosis is not, by itself, an indication for the prophylactic use of aspirin: these patients are at least as likely to have bleeding problems as they are to have thrombosis.

One approach to the use of aspirin in patients with MPD is shown in Fig 1, which stresses the relative value and risk of aspirin therapy in various situations. Patients with prior histories of primarily bleeding problems, particularly when there is an associated prolongation of the bleeding time and/or defective platelet aggregation (performed off aspirin) may be at risk of serious bleeding complications with aspirin use. The relative benefits and risks of aspirin use in patients with mixed prior histories of bleeding and thrombosis or no prior history of either complication are not established. Even in patients with recurrent thrombosis, the utility of aspirin to prevent such complications in the future is unknown. In the special situations of microvascular arterial thrombosis involving the extremities or the cerebral circulation, the use of aspirin (in conjunction with treatment to lower the platelet count) is indicated. In a recent report, 15/16 patients with essential thrombocythemia, who had the digital and/or cerebrovascular occlusive syndromes, responded to aspirin (in conjunction with $^{32}$P or busulfan myelosuppression). In this study, ischemic pain was relieved more promptly by aspirin at a dose of 300–600 mg daily than at 40 mg daily. Controlled, prospective studies of antiplatelet therapy in these subpopulations of patients with MPD are required to document these recommendations. It is possible that more potent antiplatelet drugs, such as prostacyclin infusion, may be required in some patients with acute ongoing thrombosis.

**Surgery in Patients With MPD**

As alluded to earlier, surgery in patients with MPD poses a special risk of hemostatic complications. These patients may be extraordinarily difficult problems, as there are no clear guidelines of management. In polycythemic patients, the hematocrit value should be lowered to <45% prior to surgery and carefully maintained in the postoperative period. In most cases, aspirin use should be stopped at least 1 week prior to elective surgery. Finally, although there are no data to demonstrate the efficacy of any type of prophylactic anticoagulant regimen in these particular cases, the very high risk of postoperative thromboembolism in these patients should be kept in mind, and any clinical suggestion of such an event should be promptly and aggressively pursued.

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Al Schafer