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HEMORRHAGIC COMPLICATIONS OF POLYCYTHEMIA VERA*

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The predominant interest and therapeutic effort has been directed at the thrombotic complications of polycythemia vera. This is proper inasmuch as thrombosis is the chief source of disability in the disease. This tendency to thrombosis is readily explained by the increased blood viscosity, the high platelet count and the slowed rate of blood flow.

Another major source of disability and occasional cause of death is the co-existent tendency to excessive bleeding. This is not often spontaneous bleeding, and attempts to demonstrate a consistent defect in hemostasis have yielded equivocal results. This would lead the casual observer to doubt that any real hazard of bleeding exists. Nevertheless, this is a very real complication in terms of incidence and morbidity.

Bleeding may be particularly troublesome because:

- a) It is often unexpected in the absence of relevant family and past history.
- b) It may occur only after surgery or trauma, and
- c) Blood loss may be so severe that it masks the underlying disease.

Post-Operative	
Post-Traumatic	23%
Purpura	20%
Gastro-Intestinal	9%
Menorrhagia	9%
Epistaxis	3%

Figure 1
Site of bleeding in polycythemia.

A review of several large series indicates an incidence of hemorrhagic complications as high as 30%¹⁻⁴. While this is often limited to post-traumatic hemorrhage, spontaneous bleeding does occur. The site of bleeding is variable as indicated in fig. 1. Purpuric and ecchymotic lesions may be quite extensive⁵ as shown in fig. 2.

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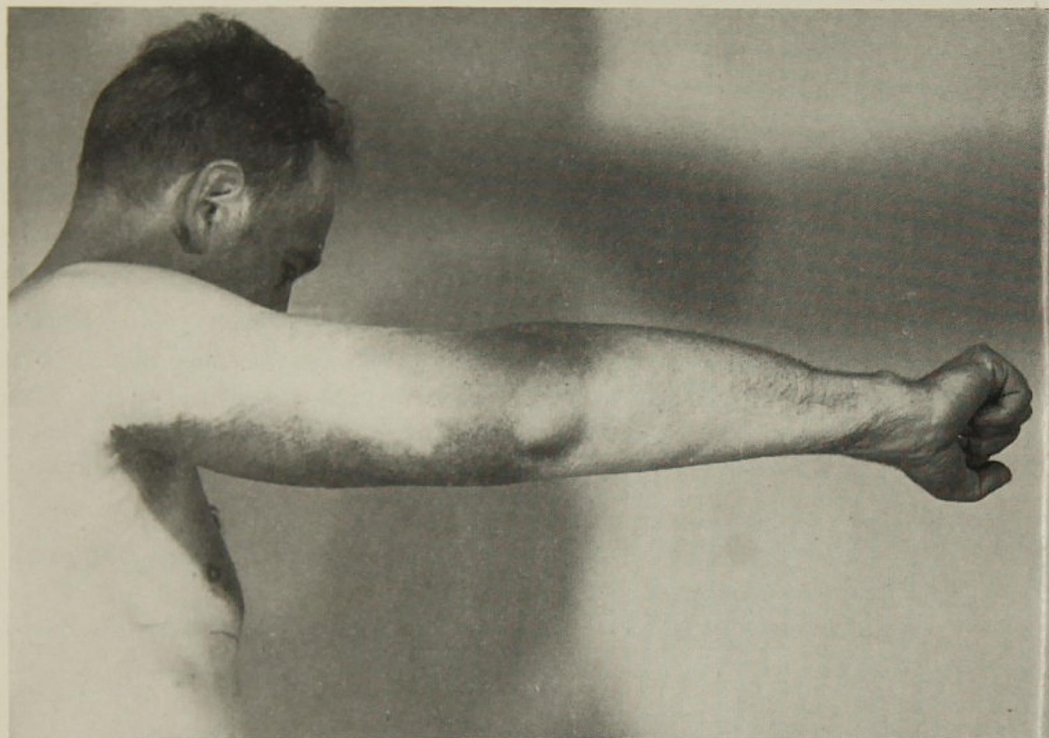


Figure 2
Extensive hematoma of the arm — an initial symptom in this patient.

MATERIALS AND METHODS

Thirty patients with polycythemia vera who have been treated regularly at the Henry Ford Hospital were studied. This was a representative group, including patients with treated, untreated and spent polycythemia. Their records were reviewed in order to determine the nature of hemorrhage in this disorder — its incidence, severity and duration, as well as the precipitating factors. After clinical evaluation, these patients had a hemostatic survey which included conventional bleeding time, coagulation time, tourniquet test, prothrombin time, prothrombin consumption, fibrinogen determination, and plasma clotting time. In addition, isolated platelets of these patients were assayed for factor 3 activity. Also, detailed and quantitative observations were made of the abnormal behavior of the polycythemic clot.

Abnormalities in the rate of clot retraction,⁶ the electrolytic resistance of the retracting clot,⁷ and the retention of red cells by the clot⁸ have been previously noted. In vitro, the clot is typically of small volume, and most of the red cells are lost from the clot, falling to the bottom of the test tube (fig. 3) We have devised a quantitative measure of the loss of red cells from the retracting clot — the "fall-out" phenomenon. In essence this involves a quantitative determination of the hemoglobin lost by the clot from a measured volume of blood. The latter may then be expressed as a per cent of the whole blood hemoglobin. In forty normal controls this value was in the range of 20-40%.

RESULTS AND COMMENTS

Clinically significant bleeding occurred at some time during their course in 36% of these patients. The sites of bleeding are indicated in fig. 1. Whole conventional studies of the hemostitic mechanism in polycythemia vera returned normal values, this study revealed consistent deficiencies in platelet factor 3 activity and in the platelet-fibrin network of the clot. The former was reflected in the factor 3 assay of polycythemic platelets (fig. 4) and in the thromboplastin generation test. The latter was reflected in the excessive fall-out value of polycythemic clots. The loss of red cells from the clot consistently exceeded 45%, and was often in the range of 60-95%.

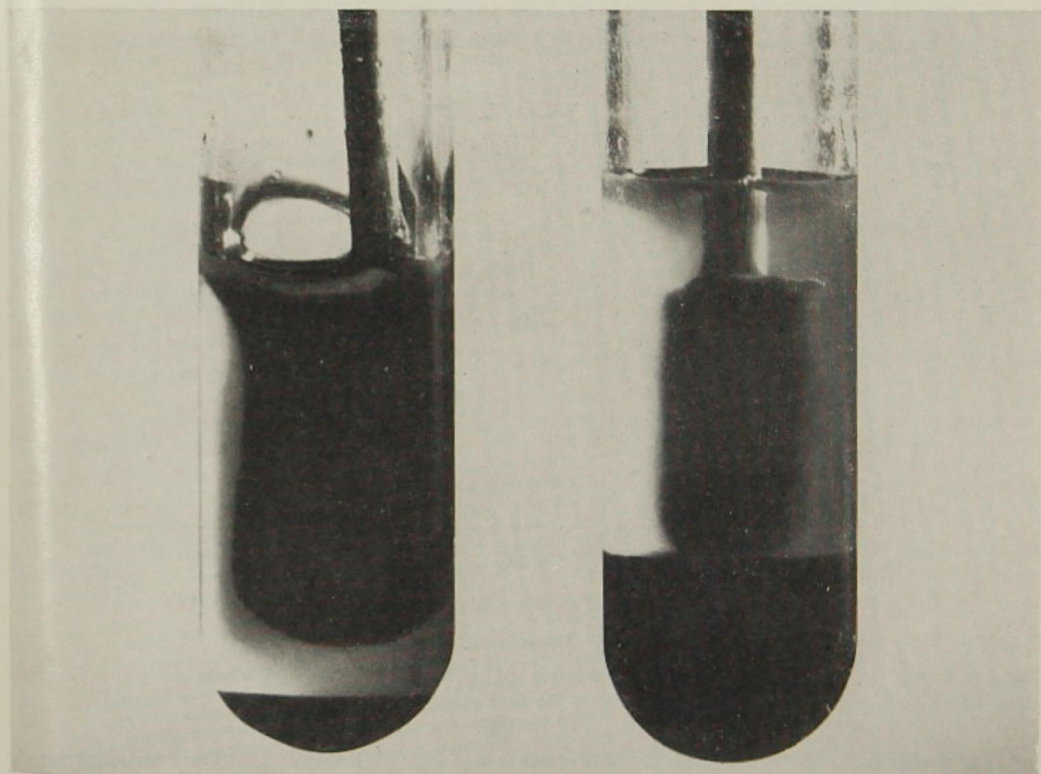


Figure 3

The "fall-out" phenomenon. The polycythemic clot (right) has lost much of the red cell mass. Control is on the left.

This excessive fall-out was apparent in patients with polycythemia vera who had manifest thrombocytosis at some time during their course. It was reduced by treatment, but was not abolished even when hematocrit and hemoglobin values were reduced to subnormal values. Thrombocytoses due to other cause, and moderate elevations of hemoglobin due to other forms of erythrocytosis were not reflected in excessive fall-out, suggesting that the test may have some diagnostic screening value in relation to polycythemia vera. However, very marked elevations of hemoglobin (in excess of 20 gms.) in secondary polycythemia were associated with excessive loss of red cells from the clot. The test is of greatest value prior to treatment in that the fall-out is often reduced temporarily by venesection or radioactive phosphorus treatment.

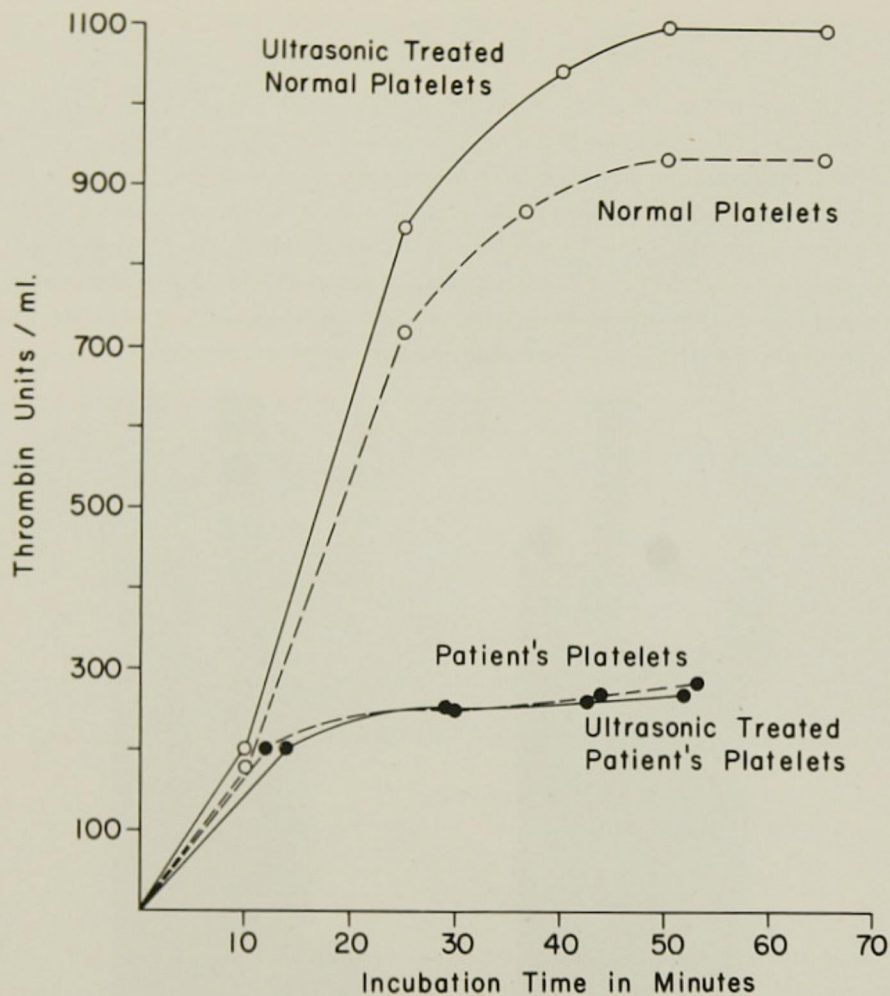


Figure 4

Platelet factor 3 assay. This activity of normal platelets is shown in contrast to the subnormal activity of patient's (polycythemic) platelets.

The previously noted defects are probably not the only factors contributing to excessive bleeding in polycythemia vera. a) Physical distention of the vascular system is a plausible cause of bleeding. b) Some observers have presented evidence that intravascular coagulation depletes prothrombin and fibrinogen to a point where bleeding occurs.⁹ c) The anticoagulant effect of excessive numbers of platelets has been confirmed by Spaet, Bauer and Melamed.¹⁰ d) On rare occasion, fibrinolytic activity has been noted in polycythemia vera.¹¹ e) Preliminary results with the partial thromboplastin test¹² in some of our patients have returned prolonged values, suggesting that the plasma of polycythemic patients may be less responsive to thromboplastin than is normal plasma.

Among the practical conclusions are the following: 1) Polycythemia should be suspected in bleeding patients whose conventional studies appear to be normal. 2) Treatment is of value in preventing hemorrhage as well as thrombosis. It is true that both complications occur in treated or controlled patients, but the incidence is

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considerably reduced by treatment. 3) Caution in the use of anticoagulants in these patients is of vital importance. 4) Elective surgery in the untreated patient should be deferred until control has been established with radioactive phosphorus. Emergency surgery should be preceded, if feasible, by reduction of blood counts to normal range by phlebotomy.

SUMMARY

The incidence and nature of hemorrhage in polycythemia vera has been reviewed. A functional defect in the polycythemic platelet has been demonstrated, and the aberrant behavior of the clot has been confirmed. The latter has been studied in detail and quantitatively determined. The clinical application of some of these findings in the management of patients with this disorder has been briefly outlined.

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