Editorial

Intravascular Coagulation, the Shwartzman Reaction and the Pathogenesis of T.T.P.

By Robert N. Taub, F. Rodriguez-Erdmann and William Dameshek

Thrombocytopenic Purpura (TTP) is a disorder characterized chiefly, as Singer pointed out, by the triad of hemolytic anemia, thrombocytopenia and symptoms referable to generalized occlusions of terminal arterioles and capillaries.

The pathogenesis of this entity has thus far eluded final solution. A particular problem has been the apparently inseparable association between the three basic abnormalities of blood vessels, red cells and platelets. Our interest in autoimmune disorders led us to assume at one time that antibodies or antibody-like substances were involved, acting specifically and directly against each of these elements. To be sure, a few cases show a positive Coombs antiglobulin test; and some cases, particularly after splenectomy, have developed the complex autoimmune disorder, systemic lupus erythematosus (SLE). It has been difficult, however, to demonstrate any other supporting evidence for this assumption. The passive transfer of serum from patients with the disease into normal volunteers has not succeeded in producing any vascular or hematologic abnormality. The Coombs test is almost invariably negative; neither hemolysins nor red cell or platelet agglutinins have been demonstrated; the production of endothelial injury by specific antibodies and by other agents is not followed by the development of any of the typical features of thrombotic thrombocytopenic purpura; nor do these features develop after intravascular injection of clumped platelets or of materials which induce platelet clumping.

The nature of the small blood vessel lesion of TTP, at first thought to be due to platelet agglutination and deposition, has been clarified in the past several years by various histologic, histochemical and immunofluorescent technics. Gore and Orbison characterized the principal histologic abnormality as the deposition of eosinophilic hyaline material within the lumina of arterioles and capillaries. The various features of immune vasculitis, including perivascular infiltration with lymphoid and other mononuclear cells, and fibrinoid necrosis, are notably lacking. Histochemical studies by a number of observers suggest that the hyaline material is fibrinous in nature. Craig and Gitlin, using immunofluorescent sera, have demonstrated that the thrombi in the small vessels are not composed of aggregated platelets as was first thought,

From the Blood Research Laboratory, Pratt Clinic-New England Center Hospital and the Department of Medicine, Tufts University School of Medicine, Boston, Mass.

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but that platelets are, in fact, conspicuously lacking. The hyaline thrombi appear, then, to be wholly or largely composed of fibrinogen or fibrin.

The presence of precipitated fibrin in blood vessels must be regarded as an indication that intravascular coagulation has occurred; if this is so, then it might be advantageous to compare the pathogenesis of TTP with other syndromes of widespread intravascular coagulation or “defibrination.” The generalized Shwartzman reaction (GSR) in experimental animals is one such syndrome. In this reaction, severe alterations in the clotting mechanism with consumption of plasma clotting factors lead to the intravascular deposition of fibrin. Under normal circumstances, the reticuloendothelial system acts quickly to clear precipitated fibrin from the circulation. In the Shwartzman reaction, apparently because of prior depression of the phagocytic function of the reticuloendothelial system, fibrin cannot be cleared, and the precipitate remains within the vessels.

It is tempting to speculate that similar mechanisms are responsible for the lesions of both TTP and GSR. This similarity was, in fact, first noted and commented upon by Shwartzman et al. More recently, several cases of TTP have been reported in which the fibrinogen level was reduced suggesting the possibility of widespread intravascular coagulation. The similarity of the histologic lesions seen in clinical TTP and in the experimental animal with the Shwartzman reaction has been repeatedly emphasized. Furthermore, lesions resembling those of TTP have been produced in rats made hyperlipemic by the prolonged feeding of a high-choline diet. The GSR can be similarly induced.

The assumption that intravascular deposition of fibrin occurs in TTP might account satisfactorily for both the hemolytic anemia and the thrombocytopenia. The nature of the hemolysis encountered in TTP has been investigated by Brain, Dacie and Hourihane, who suggested that mechanical or “microangiopathic” factors were responsible. Peculiar red cell alterations are observed in this disease, consisting of fragmented, triangular and “helmet” shaped erythrocytes. Hemolytic anemia with identical red cell morphology but without thrombocytopenia, has also been seen following some cases of open heart surgery, in which operative intervention has resulted in the spurring of a jet of blood against an unendothelialized teflon surface of an intracardiac prosthesis, with the resultant quick destruction of many red cells. It is thus conceivable, as suggested by Dacie and his group, that fibrin deposits in TTP, by altering both the calibre of the small vessel lumen and the texture of its endothelial surface, can induce significant and even severe hemolysis if the lesions are disseminated and numerous. The demonstration of both intra- and extracorpuscular defects in the hemolytic anemia of TTP also supports such a mechanical origin of the hemolysis.

As for the thrombocytopenia, it is evident that this can be induced by widespread intravascular coagulation and may be related to the presence of intravascular thrombin released during the coagulation process. Plasma thrombin activity has been demonstrated in the generalized Shwartzman phenomenon. In the ensuing thrombocytopenic state, platelet function has been shown to be impaired in the remaining platelets.
Since platelets are altered during the coagulation process, and since they have not been demonstrated in the histologic lesions of TTP,\textsuperscript{17} it is possible that injured platelets are rapidly removed from the circulation by the physiologic splenic mechanism. This would explain the short platelet survival time in the disease and the apparently significant benefit of splenectomy in some cases.

The therapy of thrombohemolytic thrombocytopenic purpura has been generally unsatisfactory. One case report of prolonged remission following anticoagulation with heparin has been recorded.\textsuperscript{42} The use of massive doses of corticosteroids, either alone\textsuperscript{43} or combined with splenectomy\textsuperscript{44,46} has recently come to the fore as a therapeutic procedure of possible great value. It is of interest in this regard that the last four cases of TTP treated on our service by massive doses of ACTH (up to 1000 units) and prednisone (up to 1000 mg.), followed by quick splenectomy, have shown either complete or incomplete recovery, whereas our previous methods of therapy were wholly ineffective. The mechanism of action of massive corticosteroid therapy in these cases remains to be clarified. Although the likelihood that TTP is an autoimmune disorder is small, the possibility still remains that at least some cases are initiated by an antigen-antibody reaction; both the local and the generalized Shwartzman reaction can be induced in such a manner.\textsuperscript{47,48} Conceivably, steroids may act to prevent the triggering of intravascular coagulation by inhibiting antigen-antibody reactions, rather than by exerting any direct effect on an already established coagulation process.

The accumulated data concerning thrombohemolytic thrombocytopenic purpura thus suggest that many of the clinical, hematologic and histologic aspects of this condition can be explained on the basis of intravascular coagulation (defibrination). The thrombocytopenia may arise as the result of platelet injury during the intravascular coagulation process, and the hemolytic anemia may develop because of trauma to the red cells in their passage through abnormally narrowed and altered vascular channels, the result of fibrin deposits. As a working hypothesis, the possibility that many aspects of TTP are analogous to those of the generalized Shwartzman reaction must be considered.

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Robert N. Taub, M.D., Research Fellow in Hematology, Blood Research Laboratory, New England Center Hospital, Boston, Mass.

F. Rodriguez-Erdmann, M.D., Research Fellow in Hematology, Blood Research Laboratory, New England Center Hospital, Boston, Mass.

William Dameshek, M.D., Director, Blood Research Laboratory, New England Center Hospital; Professor of Medicine, Tufts University School of Medicine, Boston, Mass.
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ROBERT N. TAUB, F. RODRIGUEZ-ERDMANN and WILLIAM DAMESHEK

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