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This Week's Citation Classic

Verstraete M, Vermylen C, Vermylen J & Vandenbroucke J. Excessive consumption of blood coagulation components as cause of hemorrhagic diathesis. *Amer. J. Med.* 38:899-908, 1965.
[Lab. Coagulation-Proteolysis, Dept. Medicine, Univ. Leuven, Belgium]

Evidence is presented that excessive consumption of certain coagulation factors may cause bleeding in the course of various diseases and unrelated syndromes, of which 12 examples are selected for discussion. The indicative value of thrombocytopenia, low fibrinogen level, and prolonged one-stage prothrombin time, mainly due to factor V depletion, is discussed. [The SCI® indicates that this paper has been cited in over 185 publications since 1965.]

M. Verstraete
Center for Thrombosis and
Vascular Research
Campus Gasthuisberg
University of Leuven
3000 Leuven
Belgium

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"In the 1950s, I told my father, an obstetrician-gynecologist, that I deeply admired his permanent standby for unscheduled medical events but preferred to engage in haematologic research rather than succeed him. He made me promise that I should try to solve the bleeding problem associated with abruptio placentae and amniotic fluid embolism. As amniotic fluid is readily available material, I soon uncovered its thromboplastic properties and could induce fatal lung emboli or serious bleeding in dogs, depending on the perfusion rate of the phospholipid fraction of the fluid. Similar experiments with commercialized hemostatic agents, which had in common their tissue origin and clinical inefficacy, resulted in the same observation. Depending on the dose, dogs were tolerant to the infusion of this thrombin preparation, but had a gradual decrease of fibrinogen and prothrombin levels. It was therefore tempting to look for a clinical counterpart of these animal experiments. The unclottable blood of patients with abruptio placentae and those surviving amniotic fluid embolism were found to have similar characteristics as those found after thrombin or tissue thromboplastin perfusions in dogs.

"In the late 1950s and early 1960s, acquired hypofibrinogenemia was usually thought to result from proteolysis of fibrinogen by plasmin. Our concept that low fibrinogen was a consequence of its conversion by thrombin was substantiated by the corrective effect of heparin infusions in patients. This allowed the conclusion that the fibrinolytic response follows rather than causes fibrinogen depletion.

"Another reason why this article attracted attention and has been cited may be because activation or release of a coagulation promoting substance from erythrocytes, platelets, leukocytes, endothelium, complement, or from tissues was linked to intravascular coagulation and excessive consumption of hemostatic components—a common pathogenic thread in a heterogeneous group of clinical syndromes.

"Our group manifested its continued interest in the diagnosis and treatment of disseminated intravascular coagulation (DIC) by determining the survival time of radiolabeled fibrinogen, prothrombin,[1] antithrombin III, and plasminogen and by studying the effect of some drugs on the survival time of these proteins.[2,3] It was also shown by our group that complex formation of thrombin and plasmin with natural inhibitors leads to formation of neoantigens.[4,5] Specific monoclonal antibodies directed against these complexes have been produced, and clinically applicable assays are currently being developed. As the half-life of plasmin-antiplasmin and thrombin-antithrombin complexes is in the order of hours, such tests may constitute a significant improvement for the rapid and more specific detection of DIC.

"J. Vermylen and I are professors of medicine at the University of Leuven and continue in the Center for Thrombosis and Vascular Research our symbiotic scientific collaboration which has gone from strength to strength. J. Vandenbroucke retired as chairman of the department of internal medicine a few years ago; Carl Vermylen became director of the Transfusion Center of the Belgian Red Cross in Leuven, Belgium."

1. **Tytgat G N, Collen D & Verstraete M.** Metabolism of fibrinogen cirrhosis of the liver. *J. Clin. Invest.* 50:1690-701, 1971.
2. **Verstraete M, Vermylen J & Collen D.** Intravascular coagulation in liver disease. *Annu. Rev. Med.* 25:447-55, 1974.
3. **Collen D, Schetz J, De Cock F, Holmer E & Verstraete M.** Metabolism of antithrombin III (heparin cofactor) in man: effects of venous thrombosis and of heparin administration. *Eur. J. Clin. Invest.* 7:27-35, 1977.
4. **Collen D, De Cock F & Verstraete M.** Plasminogen turnover and plasmin-antiplasmin complex formation in clinical conditions with primary or secondary activation of the fibrinolytic system. (Paoletti R & Sherry S, eds.) *Thrombosis and urokinase.* New York: Academic Press, 1977. p. 27-41.
5. **Collen D & De Cock F.** Neoantigenic expression in enzyme-inhibitor complexes: a means to demonstrate activation of enzyme systems. *Biochim. Biophys. Acta* 525:287-90, 1978.