COMPLEX ALTERATION of blood coagulation occurs in the course of a number of systemic disorders. In contrast to the congenital defects of hemostasis which are usually characterized by a single clotting factor deficiency, the changes which may accompany acquired disease are characteristically multiple. These multiple defects tend to form typical patterns which reflect the physiologic abnormality responsible for them. Accordingly, the identification of such patterns is often of considerable diagnostic value in the study and management of certain patients.

The logic of the abnormal coagulation patterns derives from known properties of the various clotting factors. Certain of these factors can be usefully classified together into groups on the basis of similar in vivo properties. These are outlined in table 1, which lists only those clotting factors relevant to the present discussion.

In our experience, four general patterns of clotting abnormalities have been most frequently encountered. This list is by no means exhaustive, but it provides an illustration of the approach we use.

1. Parenchymal Liver Disease

This pattern is characterized by depression of those factors which are synthesized by the liver. In effect, this means that only factor VIII is unaffected, since it alone is derived in whole or in part from extra-hepatic sources. The prothrombin and fibrinogen group are reduced. The relative degree of depression of the hepatic coagulation factors is somewhat variable, with fibrinogen being the least reliable index of this condition. Thus, the most critical finding which distinguishes the "hepatic" pattern from vitamin K deficiency is reduction of factor V in the former.

Identification of the "hepatic" pattern is of importance for two main reasons: It sometimes leads to discovery of previously unsuspected liver disease; and it serves warning that vitamin K therapy will be ineffective and may even be contraindicated. Administration of vitamin K to patients with damaged livers may cause further prolongation of the prothrombin time, often due to depression of all hepatic clotting factors.

2. Vitamin K Deficiency

Depletion of the body's vitamin K stores, or inhibition by metabolic antagonists such as the coumarin drugs and (rarely) salicylates may lead to this disorder. In either case, there is selective depression of the "prothrombin
group" of clotting factors. Indeed, this pattern is so characteristic that its presence without an obvious malabsorption syndrome or jaundice virtually means coumarin drug intoxication. If there is no drug history, it can be concluded that there is accidental or deliberate self-intoxication, or foul play.

Although administration of vitamin K is a specific for the deficiency, the use of small doses can lead to additional diagnostic information. Since the daily requirement of this vitamin is on the order of 0.5 µg./Kg./day, a few milligrams parenterally of either fat- or water-soluble compounds are sufficient to restore normal clotting to the patient with a simple deficiency. Failure of this dose to be effective indicates the presence of a metabolic antagonist.

3. The "Defibrination" Syndrome

Depression of those factors consumed in the coagulation process is a frequent event in the presence of widespread or massive fibrin deposition. In these conditions the fluid component of the blood comes to resemble serum rather than plasma, with reduction of fibrinogen, prothrombin, factor V and especially of factor VIII. Thrombocytopenia is also present. Often there is an accompanying fibrinolytic reaction, and the picture may be further complicated by the presence of fibrinogen digestion products which interfere with fibrin polymerization. Under these circumstances, circulating anticoagulants are encountered which are most easily demonstrated by the presence of a prolonged thrombin time of the patient's plasma. Although this syndrome may accompany sepsis, a generalized Schwartzman reaction, certain obstetrical complications, or hemolytic transfusion reactions, we have seen it most frequently in the course of malignant disease, particularly with bone metastases. Indeed, this pattern has often been the presenting sign which has led to the diagnosis of an hitherto undiagnosed tumor. The syndrome in its most dramatic form is accompanied by hemolytic anemia, and may give a clinical picture resembling that of thrombotic thrombocytopenic purpura.

Paradoxically, this hemorrhagic disorder has been successfully treated with heparin, which appears to arrest the process of defibrination and leads to restoration of the depressed clotting factors. However, despite re-establishment of hemostatic equilibrium and arrest of bleeding, cancer patients with the defibrination syndrome usually succumb to their underlying disease; the syndrome is evidently a preterminal event.
Fibrinolytic syndromes may also develop in the same type of patients who are liable to the defibrination syndrome: this complication with prostatic carcinoma is familiar. Since fibrinolysis can be effectively treated with antifibrinolytic agents such as epsilon-aminocaproic acid (EACA), the distinction is clinically important. Moreover, the use of EACA in the defibrination syndrome may prove to be disastrous.6 Differentiation of primary fibrinolysis from the defibrination syndrome with some secondary fibrinolysis may be extremely difficult, but we have found that significant depression of factor VIII is more characteristic of defibrination and is less often found in primary fibrinolysis.

4. Circulating Anticoagulants

There is a variety of abnormal plasma proteins which can interfere with the normal clotting process. Specific inhibitors of factor VIII, and certain macro- or cryoglobulins which interfere with fibrin polymerization are well known. These are often a reflection of a lymphoproliferative disease and can be screened by tests such as the partial thromboplastin time. Of particular interest is the anticoagulant which often accompanies disseminated lupus erythematosus.8 This anticoagulant appears to have selective activity against the activated form of factor X (product I) or the clotting reactions immediately following factor X activation.9 In addition, these patients may show selective prothrombin depression and a prolonged thrombin time. We have encountered this pattern only in lupus patients, and at least half of the untreated group show some degree of it.10

Characteristically, the acquired clotting defects discussed above present a prolonged one-stage “prothrombin” time, since each of the patterns includes depression of one or more factors required for optimal prothrombin conversion in the presence of tissue factor. Thus, the one-stage test is the screening procedure of choice to indicate the necessity of further investigation. It is important to note that “minor” prolongation of the prothrombin time may be significant: an abnormality of a few seconds represents relatively major reduction of clotting factors. It should also be emphasized that frequently the defects are not of sufficient severity to cause hemorrhagic manifestations. In such cases, the diagnostic value of the studies may nevertheless be of the greatest value. For example, we have seen a prolonged Quick prothrombin time as the first premonitory sign of previously unsuspected metastatic disease in several patients.

An increased understanding of the clotting mechanism together with the development of simple assay techics for the various clotting factors has put accurate analysis of hemostatic abnormalities within the reach of any efficient clinical laboratory. Proper use of these methods will provide rewarding clinical information.

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Editorial: Clinical Implications of Acquired Blood Coagulation Abnormalities

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