CLINICAL SIGNIFICANCE OF PROTHROMBIN DEFICIENCY AND ITS TREATMENT

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The discovery of vitamin K has led to renewed interest in the mechanism of blood clotting, a field of study which for years has baffled many investigators. Indirect methods for the measurement of plasma prothrombin concentration have been developed, and as a result the clinical importance of prothrombin deficiency has also been brought under study. According to current ideas, plasma prothrombin, ionized calcium, and a tissue or platelet factor, thromboplastin, interact in the first phase of clotting with the formation of thrombin. Thrombin then acts upon plasma fibrinogen and fibrin is laid down. The process is known to be influenced by temperature, $p_H$, electrolyte pattern, and colloid content of the medium, as well as the concentration of the four primary clot factors. The nature and mode of action of the physiologic anticoagulants is as yet undetermined, but there is good reason to suppose that such substances exist and that their effect may be exerted against either or both of the two phases of clotting. The place of heparin in physiologic clot inhibition and the manner in which it acts are questions still unanswered, though the subject is being intensively investigated.

It has not been determined to what extent clotting is an enzyme reaction, and, indeed, the nature of the clotting mechanism must stand in clear relief before such intimate analysis will be possible. There can be no doubt, however, that the speed of clotting under physiologic conditions is directly related to the concentration of thrombin. The concentration of thrombin further depends on the concentration of prothrombin, though variables come into consideration at this point. The speed of formation of thrombin from prothrombin is influenced by concentration of thromboplastin, ionized calcium and antiprothrombic agents, and possibly by inherent "convertibility" of the individual's prothrombin,¹ ² a rather vague conception. The rapidity of clotting is obviously of the utmost importance in determining the hemostatic value of the process, but a neglected subject, of equal or greater importance, concerns the factors affecting the quality of the formed clot. Those who have worked with plasma clotting, in which the gross physical characteristics of the clot can be readily observed, know that the fibrin mass may be soft and jelly-like, tough and opaque, adherent or slippery, granular, friable, or noncontractile. These qualities are not necessarily related to the speed of clotting, but probably depend in part, at least, on the concentration and quality of the fibrinogen.

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Methods of Measuring Plasma Prothrombin Concentration.—Though knowledge of the coagulation reactions is incomplete, nevertheless, there can be no doubt about the clinical value of prothrombin determinations as performed by recently developed methods. As previously noted, these methods are indirect, for prothrombin cannot be isolated and weighed, or brought into definite measurable chemical combinations. The two methods which, in their original or modified forms, have been most widely used in this country are the two-stage titration method of Warner, Brinkhous, and Smith,5 4 and Quick's method of measuring clotting time of plasma in the presence of optimal concentration of calcium and thromboplastin.5 6 The first is more complicated, but results in better control of the variables and yields more precise data. The two-stage technic is preferable in investigative work, while Quick's method is more practical in controlling the administration of vitamin K clinically. Quick's method has been variously modified by using sodium citrate as the anticoagulant instead of sodium oxalate, by varying the amount of calcium chloride used in recalcification, by using thromboplastin from different sources, by serial dilution of the plasma, and by expressing the results in different terms. It should be borne in mind in using the Quick method that a linear relationship does not exist between prothrombin concentration and the plasma clotting time, and that it is, therefore, not permissible to convert clotting time directly into percentage of the normal control value. The "bedside method,"2 in which the determination is made on freshly drawn whole blood, thus obviating the use of anticoagulants and the centrifuge, in the author's experience, gives rather variable results, though it yields more significant information than does the ordinary determination of clotting time. Methods have been proposed for studying the prothrombin content of infants' blood which avoid the need for venepuncture by using small amounts of blood from a stab wound, and apparently such methods yield clinically helpful data.7 8

Occurrence of Prothrombin Deficiency.—An examination of the known facts of vitamin K metabolism suggests clinical and experimental states in which the normal rôle of this accessory food factor may be disturbed. Vitamin K occurs naturally as a fat-soluble substance or substances, rather widely distributed in leafy green vegetables and in certain animal tissues. Its proper absorption, like that of other fat-soluble vitamins, depends on the presence of sufficient amounts of bile salts in the small intestine. Absorption from the colon probably does not occur. After absorption from the intestine vitamin K conditions, in some as yet unknown manner, the formation of prothrombin by the liver. Prothrombin is a constituent of the plasma globulin, and apparently both vitamin K and prothrombin are not stored to any significant extent in the body. From this one might expect prothrombin deficiency as a result of insufficient intake of vitamin K, lack of bile salts in the intestine with or without jaundice, impaired absorption of nutrients from the intestine as in diarrheal states, and defective digestion and absorption of fat due to lack of pancreatic enzymes. In addition, prothrombin deficiency might, theoretically, be based on impaired liver function from intrinsic liver disease, with conse-
quent failure in utilization of vitamin K. Prothrombin deficiency has in fact been encountered clinically in most, if not all, of these circumstances.

It was discovered early in the investigation of vitamin K that a number of the common bacteria, such as *E. coli*, *Staphylococcus aureus*, *B. subtilis*, the *Mycobacterium tuberculosis* synthesize the substance. Bacterial synthesis of vitamin K was further found to take place normally in the intestine of mammals and fowls, presumably distal to the mucosal areas in which absorption occurs. In the production of K-avitaminosis in chicks by dietary restriction, Almquist and Stokstad found it necessary to keep the chicks from access to their droppings, as otherwise deficiency did not develop. These points may be of significance in relation to the occurrence of hypoprothrombinemia in the newborn before the intestinal bacterial flora has been established, though the mechanism is not entirely clear.

Prothrombin deficiency is commonly present in obstructive jaundice, and in this condition poor absorption of vitamin K and impairment of hepatic synthetic power may be present in combination. In a group of 50 cases of obstructive jaundice, which have come under the author's observation at the Massachusetts General Hospital, the plasma prothrombin concentration was invariably reduced before treatment, the average value in the cases of calculous obstruction being 65 per cent, and in the cases of carcinomatous obstruction 45 per cent. In every case, the prothrombin value improved after administration of vitamin K parenterally or vitamin K and bile salts orally, though the patients with calculous obstruction responded better, probably owing to greater hepatic functional reserve. In a group of 112 patients with obstructive jaundice operated upon at the Massachusetts General Hospital during the six-year period, 1931 to 1936 inclusive, 15 per cent died of massive postoperative hemorrhage. In the author's experience, the proper use of vitamin K before and after operation, together with adequate nutritional therapy, has entirely eliminated this hazard, even in patients with severe liver damage and initial prothrombin concentrations below 10 per cent.

It has been shown that an immediate postoperative reduction in plasma prothrombin concentration is the rule after operation for obstructive jaundice. The reduction may be as great as 30 or 40 per cent, and occurs most commonly within the first four days, from which the need for having the preoperative prothrombin value well above the hemorrhagic zone is apparent. The depression may follow spinal or local anesthesia, and probably is due to the hepatic trauma and blood loss of operation, as well as absence of prothrombin reserves. After operations for conditions other than obstructive jaundice, and in patients without liver disease, postoperative hypoprothrombinemia does not seem to occur. In the early experiences with the clinical use of vitamin K, when only the crude alfalfa meal extracts and bile salts were available for oral treatment, the author observed two instances in which patients refused to take the material after operation for obstructive jaundice. The interesting point was that following the resultant massive wound hemorrhage a further reduction in plasma prothrombin concentration immediately
occurred, from which one is led to believe that hemorrhage may be a contribu-
tory factor in exhausting a depleted plasma prothrombin content.

Prothrombin deficiency may occur in acute hepatitis, such as "catarrhal
jaundice," though usually the reduction is moderate. The hypoprothrombin-
emia is not proportionate with the jaundice, and this gives the determina-
tion value in the differential diagnosis of jaundice from intrahepatic disease
and from extrahepatic block. In the progression of acute hepatitis to acute
yellow atrophy or liver failure, however, the plasma prothrombin concentra-
tion falls to values in the hemorrhagic range, which is below 40 per cent.16
Cirrhosis of the liver may be accompanied by moderate reduction in plasma
prothrombin concentration, and in patients with bleeding esophageal varices
the value may be less than 40 per cent. It is reasonable to suppose that in
such cases the clotting defect may be a contributory factor and may lead to
gross rather than microscopic bleeding from a lesion exposed to constant
trauma.

Of special surgical interest is the group of cases in which toxic hepatitis,
jaundice, and massive hemorrhage follow operation for peritoneal infections,
such as perforative appendicitis, ruptured peptic ulcer, subdiaphragmatic
abscess, and pelvic abscess. These complications seem to be more common
when peritoneal sepsis is of gastro-intestinal origin, and determination of
plasma prothrombin concentration as well as serum protein concentration
should be routinely and periodically performed in the care of patients with
such infection.15 The reduction in plasma prothrombin may develop rapidly
and to an extreme degree. The resulting clotting defect may not only cause
massive hemorrhage from operative wounds, but may retard inflammatory
fixation and exudative confinement of the infection.

Reduction in plasma prothrombin concentration may be encountered during
the administration of sulfanilamide, sulfapyridine and sulfathiazole in the
treatment of infection. These drugs are known to exert a toxic effect on the
liver, and presumably the hypoprothrombinemia comes from depression of
liver function. Severe acute infections, however, may lead to reduction in
plasma prothrombin concentration in the absence of chemotherapy, and the
deficiency may be refractory to vitamin K treatment.16 Depression in plasma
prothrombin has been observed to precede jaundice as an early indication of
hepatitis in the chemotherapy of infections, and the determination should be
freely used in the control of such therapy. At the same time the importance
of nutritional measures directed at maintaining hepatic reserve, such as high
carbohydrate and high vitamin intake and blood transfusions, during the
management of chemotherapy is brought into focus.

Severe hypoprothrombinemia may develop in chronic external biliary fis-
tula, if the patient does not take adequate amounts of bile salts orally in
replacement. The author has seen near-fatal intracranial hemorrhage in two
patients who failed to take the prescribed amount of bile salts and vitamin K
following the surgical formation of external biliary fistula. The patients were
middle-aged women without arteriosclerosis or hypertension, and in both
there was much reduction in hepatic reserve. The prothrombin concentration at the time of hemorrhage was below 10 per cent, and the bleeding was readily controlled by giving vitamin K parenterally. In a third case of complete external biliary fistula of 14 months' duration, there was unaccountable absence of the bleeding tendency and only moderate reduction in plasma prothrombin, even though the patient had had no dietary or replacement therapy. In this connection, it is worth remembering that the bile drained through an external fistula in the presence of liver damage, may have a low bile salt content, and hence may have little value in digestion and absorption. The cholic acid content of such bile should be determined, or else refeeding of the bile should not be practiced. In any event, cholic acid derivatives in capsule or tablet form are much more easily taken than a bacteria-laden, nauseating liquid.

Some doubt exists as to whether prothrombin deficiency can occur in man purely on the basis of insufficient intake of foods containing vitamin K. Scarborough concluded from a study of 18 patients showing outspoken evidence of scurvy, beriberi, or pellagra that the prothrombin values in the plasma were normal as determined by Quick's method. On the other hand, Kark and Lozner, in studying four patients with clinical hypovitaminoses, found low plasma prothrombin values by a method of serial dilution of the unknown plasma with prepared prothrombin-free normal plasma. The question is rendered difficult by uncertainties as to liver function, bile salt excretion, and alterations in mucosal absorbing power in patients suffering from severe nutritional disturbances. In the author's experience, patients undergoing elective surgical operation and without clinical evidence of malnutrition frequently show moderately reduced plasma prothrombin values both by the method of Warner, Brinkhous, and Smith, and by Quick's method. For this reason normal control plasma must be selected with care. It remains to be shown, however, that a clinically significant degree of hypoprothrombinemia occurs in man purely from vitamin K lack.

Failure in absorption of vitamin K is to be expected in any condition in which the digestion and absorption of fat is seriously impaired. Idiopathic steatorrhea without evidence of liver disease may lead to spontaneous hemorrhage and hypocalcemic tetany from lack of vitamin K and vitamin D. Prolonged hyperactivity of the intestine may result in prothrombin deficiency from poor absorption of vitamin K, as in chronic ulcerative colitis. Following parenteral injection of vitamin K in this condition, improvement in prothrombin concentration and diminution in bleeding from colonic ulcers has been observed.

There is abundant evidence now on record indicating the importance of prothrombin deficiency as a factor in hemorrhagic disease of the newborn. Brinkhous, Smith, and Warner observed a uniform reduction in the plasma prothrombin levels in the newborn and throughout infancy. During the first 11 days, values ranging from 26 to 44 per cent of normal were found, and thereafter there was a gradual rise until a nearly normal level was reached at the end of ten and one-half months. Maternal
prothrombin values, before and after delivery, were normal. As determined by Quick's method, plasma prothrombin in the newborn is apparently less commonly found reduced, though prolongation of the prothrombin time can often be demonstrated from the first to the sixth day. The discrepancy in the findings by the two methods has led to the suggestion that the available prothrombin in the newborn has a higher "convertibility" than in the adult, which would tend to compensate for the deficiency in the newborn. Mounting clinical evidence leaves no doubt as to the existence of profound hypoprothrombinemia in the newborn with hemorrhagic disease, and the response to the parenteral administration of vitamin K is dramatic and lifesaving. The rapidity of response suggests that the cause of the deficiency is lack of vitamin K rather than primary hepatic dysfunction, though the pathogenesis of the condition requires further study. Of similar significance is the finding that plasma prothrombin values in the newborn are much higher than average if the mother is given vitamin K before delivery, and this is true even if the maternal plasma prothrombin concentration is normal before the administration of vitamin K.

Hemorrhagic states into the etiology of which prothrombin-lack does not enter are thrombocytopenic purpura, hemorrhagic retinitis, aplastic anemia, leukemia, polycythemia vera, hemophilia, and multiple congenital telangiectases. In any case of bleeding of doubtful etiology, the prothrombin concentration of the plasma should be determined, but if the value is within normal limits no benefit is to be expected from vitamin K therapy.

Effects of Prothrombin Deficiency.—It should be borne in mind that the extent of hemorrhage resulting from tissue trauma depends on the summation of opposing reactions. The cross-sectional area of the wound in the vascular bed, the size and contractility of the vessels laid open, the mobility and temperature of the part, the force of the blood pressure, and the richness of the local tissue thromboplastin supply are variables independent of the quality of the circulating blood, which, nevertheless, influence the success of the hemostatic process. From these considerations, it is clear that the clinical manifestations of prothrombin deficiency may be expected to vary greatly. Given absolute freedom from injury, no demand would be made on the hemostatic defenses, and complete absence of plasma prothrombin might pass unnoticed. The patient with obstructive jaundice and severely reduced plasma prothrombin concentration may get along without serious hemorrhage until surgical incision is made in the abdominal wall, as was repeatedly shown in clinical experience before the discovery of vitamin K. Likewise, the danger of hemorrhage from a lesion constantly exposed to trauma, such as duodenal ulcer, ulcers of chronic ulcerative colitis, and esophageal varices becomes greater as the clotting mechanism is crippled by lowering of plasma prothrombin concentration.

It is of interest to consider the reported sites of hemorrhage following operation in patients with obstructive jaundice treated before vitamin K was discovered. This is the group of patients in whom prothrombin deficiency is
most constant and severe, for a combination of etiologic factors is at work, such as lack of bile salts in the intestine, intrinsic liver damage, infection and, often, inadequate dietary intake. Bleeding into excoriated skin, nosebleeds, and bleeding from gums were not unusual. Severe postoperative bleeding, however, occurred into the wound, the gastro-intestinal tract, the peritoneal and pleural cavities, skeletal muscles, the urinary passages, and sometimes into the uterine canal. Hemoptysis and hemarthrosis were rare.

In a group of untreated patients with obstructive jaundice which came under the author’s observation during the past three years, tests for blood in the stools were frequently positive. In nine of 22 patients with calculous obstruction of the common duct, and in 13 of 22 with neoplastic obstruction the guaiac test on the stools was strongly positive, and the test became negative under vitamin K therapy before operation, coincident with improvement in plasma prothrombin concentration. No ulcerations were visible in roentgenologic studies of the gastro-intestinal tract, so one is led to suppose that the bleeding was from small excoriations of the mucosa.

Petechial hemorrhage is uncommon in prothrombin deficiency, though small hemorrhages into cutaneous abrasions produced by scratching are frequently present in patients with obstructive jaundice. Numerous and large ecchymotic areas were observed over the trunk in a patient with idiopathic steatorrhea and plasma prothrombin values below 15 per cent. Epistaxis and bleeding from the gums may occur in prothrombin-lack. Reference has already been made to two patients with chronic external biliary fistula who had severe intracranial hemorrhages as a result of neglecting bile salt and vitamin K therapy. The author has seen hemoptysis from lung abscess and uterine hemorrhage from hyperplastic endometritis associated with plasma prothrombin concentrations of 65 to 75 per cent, but the importance of the hypoprothrombinemia in such cases is open to question. A group of 30 patients with chronic pulmonary tuberculosis were found to have moderate hypoprothrombinemia, but the values were no lower in the patients having hemoptysis. Bleeding into the urinary tract is rare in prothrombin-lack in the absence of adequate local causes, but such clotting deficiency may perhaps occasionally be a contributory factor.

A consideration, possibly of great importance, is the rôle of plasma prothrombin in resistance to infection. The thrombosis of lymphatics and capillaries at the boundary of an inflammatory process and the coagulation of plasma exudate in the region presumably would be impaired by prothrombin deficiency, although the direct conversion of fibrinogen into fibrin by bacterial or inflammatory products might operate in compensation. When large blood vessels become involved in advancing necrotizing infections, the rapid formation and organization of a firm thrombus in response to endo-arteritis is of lifesaving importance.

The characteristic peritoneal reaction to trauma is capillary dilatation and transudation of plasma, with the formation of a plastic exudate. The surgeon’s suture line after gastro-intestinal operation is quickly sealed over in this
manner, thus initiating fibroblastic healing, and at the same time preventing bacterial leakage. The efficiency of this reaction, on which the safety of abdominal surgery depends, probably is influenced by various factors, but of unquestionable importance is the plasma content of prothrombin and fibrinogen. The formation of excessive peritoneal adhesions after peritoneal trauma may arise in factors which exaggerate this vital protective process.

Hyperprothrombinemia.—The possible occurrence of hyperprothrombinemia, either spontaneously or in response to vitamin K therapy, has been subjected to study. In examining normal individuals and a large number of patients with a variety of diseases, the author has seen only three instances in which the plasma prothrombin concentration, as determined by a slightly modified two-stage method, was above 110 per cent. In one of these patients dehydration was present, as evidenced by elevated plasma protein concentration, and this was adequate explanation for the hyperprothrombinemia. The other two patients were afflicted with a tendency to recurrent thromboses of peripheral veins without any satisfactory explanation. It is possible that in the latter patients a hyperactive clotting mechanism was of pathologic importance. There appears to be no danger of producing hyperprothrombinemia from administering excess of vitamin K and, of course, it is generally true of vitamin therapy that many times the effective dose can be taken without harm. The author has given convalescent surgical patients with normal prothrombin values up to ten times the effective oral dose of vitamin K without ill effects and without elevating the plasma prothrombin concentration above 100 per cent.

Prothrombin Determination as a Liver Function Test.—Since plasma prothrombin is formed chiefly if not entirely in the liver, it is not surprising that factors interfering with hepatic function result in depression of the plasma prothrombin concentration. Experimental and clinical evidence indicates that reduction in the prothrombin value may be an early and sensitive index of decline in hepatic reserve. After chloroform anesthesia in patients or in animals, the first detectable sign of the hepatotoxic action of the drug is a sharp reduction in plasma prothrombin concentration. In patients with hypoprothrombinemia, the improvement in the prothrombin value following a single adequate dose of water-soluble vitamin K given parenterally may be used as a liver function test. In patients with liver failure and prothrombin deficiency massive doses of vitamin K given parenterally or orally with bile salts may be without benefit, though complete absence of response indicates extremely severe hepatic change. Intercurrent infection, such as pneumonia or cholangitis, may produce immediate lowering of plasma prothrombin concentration in a patient receiving a daily adequate dosage of vitamin K. The lability of plasma prothrombin concentration makes it important to determine the value frequently and regularly in the management of cases of obstructive jaundice.

Treatment of Prothrombin Deficiency.—Before the isolation and identification of the chemical nature of vitamin K in 1939, only crude extracts obtained
from spinach, alfalfa meal, putrefied fish meal, etc., were available for use in treatment. The crude extract was given orally with bile salts, and the efficacy of the therapy is attested to by many clinical and experimental data. Through the efforts of Dam,31, 32 Almquist,33, 34, 35 Doisy and his colleagues,36, 37 Fieser38, 39 and others, a number of 1,4-naphthoquinone derivatives have been shown to have high vitamin K potency when given in chemically pure form. Vitamin K activity is found in various naturally occurring mono- or di-alkyl 1,4-naphthoquinone compounds, including vitamin K₁ derived from spinach and vitamin K₂ from putrefying fish meal. One of the most potent vitamin K substances studied to date is 2-methyl-1, 4-naphthoquinone, and there is a growing tendency to express the value of other materials in terms of this substance, rather than in the uncertain and variable units proposed earlier by different investigators.

The known naturally occurring vitamin K substances are fat-soluble, and clinical needs led to a search for water-soluble substances which could be more easily administered. A number of water-soluble, highly potent compounds have been identified, as recently described by Fieser, Tishler, and Sampson.40 These substances can be injected in aqueous solution, or they can be given orally, and they are absorbed from the gastro-intestinal tract in the absence of bile salts.41 All the known fat-soluble and water-soluble compounds with vitamin K activity have low toxicity, as shown by extensive studies on small animals and in the clinic.

The following methods are available in the administration of vitamin K to patients:

1. Crude extracts may be given by mouth, together with bile salts.
2. Synthetic fat-soluble vitamin K (2-methyl-1,4-naphthoquinone) may be given by mouth together with bile salts.
3. Synthetic fat-soluble vitamin K in oil may be sterilized and injected intramuscularly.
4. Synthetic water-soluble vitamin K may be administered by mouth.
5. Synthetic water-soluble vitamin K may be sterilized and injected subcutaneously, intramuscularly, or intravenously.

In most instances where the fat-soluble synthetic preparation or the crude extracts are given by mouth, bile salts also should be administered, for even in the absence of jaundice the absorption of the fat-soluble material from the intestines may be facilitated by additional quantities of bile salts.16 An adequate daily dose is 2 to 4 mg. of 2-methyl-1,4-naphthoquinone or an equivalent amount of one of the other preparations, and it has been found that much larger doses are of no avail if no improvement in the prothrombin concentration follows doses of this size. If bile salts are also being given 1 to 2 Gm. per day is sufficient. In patients with severe liver damage, the author prefers to give vitamin K parenterally and avoid the administration of bile salts. In urgent need, as in the presence of active hemorrhage, vitamin K should be administered parenterally, and the response occurs within a few hours. For patients
who are vomiting, or in whom uncertainty as to absorption exists, the parenteral route should be used.

In the author’s experience, hypoprothrombinemia refractory to vitamin K treatment may be encountered in two groups of patients. As already noted, liver function may be reduced to such a point that vitamin K is not properly utilized no matter how generous the supply, or how it is administered.18, 45, 46 There is also a group of patients with chronic, severe sepsis, such as pyelonephritis, osteomyelitis, or subdiaphragmatic abscess, in whom prothrombin deficiency of moderate degree may exist, and in these patients the deficiency may not respond to vitamin K therapy. In such conditions, blood transfusions are in order, and fresh rather than “bank” blood should be used.42, 49 The average blood transfusion of 500 cc. may be expected to effect a transitory rise in the adult patient’s plasma prothrombin concentration of about 10 per cent.26, 12

Since the formation of plasma prothrombin is a function of the liver, it should be borne in mind that an essential part of treatment of prothrombin deficiency consists in the measures known to influence liver function favorably.44 A high intake of carbohydrate and the proper kind of protein is important, as well as a high vitamin intake. The fluid and electrolyte needs of the patient must be carefully met. In connection with surgical operation, the proper choice of time and anesthesia, and the division of the necessary surgical trauma by two-stage procedures in certain cases are matters for careful consideration, if depleted hepatic reserve is not to be fatally overtaxed.

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