THE USE OF VITAMIN K AND BILE IN TREATMENT OF THE
HEMMORRHAGIC DIATHESIS IN CASES OF JAUNDICE

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Osterberg, Ph. D., Division of Biochemistry: The presentation of this pre-
liminary report on the results of treatment has been prompted by inquiries
from members of the Staff and visiting physicians who were familiar with
our attempts to use vitamin K clinically.

Attempts to apply the theoretical considerations mentioned in previous
reports were met with numerous difficulties. The first of these concerned
a supply of the vitamin itself, which one of us (Osterberg) has discussed.

The Abbott Laboratories of North Chicago, Illinois, have assayed the
 crude extract obtained from the fish meal and reported that this material
was about ten times more effective in protecting chicks with a hemorrhagic
tendency than was the petroleum ether extract of alfalfa. The Abbott
Laboratories also have assayed for us certain other biologic materials to
determine their protective activity and in addition are attempting to pre-
pare vitamin K for us to use for the further study of its chemical com-
position. The details of these reports will be published later.

The second difficulty concerned dosage and methods of administration
of this vitamin. We did not know what dose might be required by man,
but by comparing the body weight and the weight of the intake of food of
man to that of a chick for which we knew the dose necessary to prevent
hemorrhage, we found that, theoretically, 23 mg. of our material should be
an adequate daily dose for man. However, we have been giving orally in
capsules 200 mg. daily, which is nearly ten times the calculated dose.
Greaves and Schmidt have demonstrated that bile salts serve as a carrier
for fat soluble vitamins across the mucous membrane of the intestine and
for this reason we have given in most cases either whole human bile or
rather large doses of bile salts (1,000 to 4,000 mg. of "Bilron Lilly" daily)
together with the extract containing vitamin K. Human bile was mixed
with pineapple juice and administered by mouth in doses of 75 to 150 c. c.
before each meal. To certain individuals the bile and the vitamin K were
administered through a tube directly into the stomach or duodenum.

Vitamin K and human bile or animal bile salts have been administered
to eighteen patients who had obstructive jaundice. In most of these eighteen
cases complete biliary obstruction and subsequent damage to the liver were present. In several cases the prothrombin time was not elevated greatly but vitamin K and bile salts were given as a prophylactic measure. An example of its prophylactic use was the case of a physician’s wife, who had a stricture of the common duct and jaundice. She had had a severe hemorrhage following a previous operation elsewhere for the relief of this condition. Although her prothrombin time was nearly within normal limits, vitamin K and bile salts were given as a precautionary measure. This patient went through her operative procedure at the Clinic without any abnormal bleeding and, although she later died from hepatic insufficiency, no abnormal bleeding was noted at necropsy.

The usual course in a case of obstructive jaundice in which there is a tendency to bleed is illustrated in figure 1a. In spite of repeated transfusions of blood the prothrombin time remained elevated until death. At necropsy a large amount of blood was found in the gastro-intestinal tract and in the peritoneal cavity.

The decrease in prothrombin time in three cases of obstructive jaundice following the administration of vitamin K and bile salts is given in
The rapid decrease in prothrombin time following this administration of vitamin K and bile salts is rather striking. In figure 2a a similar and even more dramatic case is represented graphically.

The next consideration was to determine the effect of administration of vitamin K alone on the prothrombin time. Vitamin K was given alone for nearly a week without any significant effect on the prothrombin time in one case (fig. 2b). The patient was not taking food by mouth. However, twenty-four hours after bile and vitamin K were administered together, there was a marked fall in the prothrombin time. These results illustrate well the virtual absence of absorption of sterols in the absence of bile from the intestine.

The remaining consideration was to determine the effect on the prothrombin time of bile alone. Dr. E. Starr Judd recognized early the empiric value of administering bile to patients who had jaundice and recommended this procedure as part of the routine preoperative and postoperative treatment particularly in cases of extensive biliary fistulas. Wangenstein of the University of Minnesota has noted also that the administration of bile to jaundiced individuals who have a tendency to hemorrhage appears to control bleeding satisfactorily. In one case in which the patient was eating heartily and the prothrombin time was nearly double the normal value, administration of human bile alone resulted in an immediate fall in the prothrombin time. The patient then underwent an operation following which there was no change in the prothrombin time nor was there any evidence of bleeding (fig. 3).

Dr. H. P. Smith, Professor of Pathology, University of Iowa, and his associates, whose extensive studies on prothrombin have been cited, have informed us that they have independently carried out similar studies on animals and on patients who had jaundice and have obtained substantially similar results, which will be published in the near future. Dr. Smith has used a petroleum ether extract of alfalfa meal as his source of vitamin K. He has devised a very accurate method for determining quantitatively the level of prothrombin in the blood, and in the near future we expect to adopt this method at the Clinic.

SUMMARY AND CONCLUSIONS

We have, at present, data which suggest that vitamin K is present in normal human feces in rather large amounts and in smaller amounts in the liver; it apparently is not present in human bile but it is present in acholic stools. These suggestions together with the clinical data mentioned warrant certain hypotheses. It appears that the normal organism obtains vitamin K either directly from ingested food or by the putrefactive action of the intestinal flora on this food. The sterols (vitamin K) are then, with the aid of bile, absorbed by the intestine and have some effect on the prothrom-
bin content of blood or on the activity of the prothrombin in the phenomenon of clotting.

Concerning the mechanism by which vitamin K affects prothrombin, we have no data. Schönhedayder\textsuperscript{26,27} has demonstrated that vitamin K is present in the prothrombin of the normal chick but absent or inactive in the chick which has hemorrhagic disease. In conjunction with Drs. Bollman and Mann, we are now carrying out experiments to determine the presence of vitamin K in human prothrombin and other biologic materials.

From a clinical standpoint, certain facts seem fairly well established. The administration of vitamin K together with bile or bile salts to patients who have jaundice has reduced elevated prothrombin times to within normal limits and in certain cases probably has prevented hemorrhage or has had a definite inhibitory effect on actual bleeding. The administration of bile alone to an individual who was ingesting an adequate diet has resulted in a shortening of the elevated prothrombin time. The administration of vitamin K alone, when bile is absent from the intestinal tract, has had little or no effect in decreasing the elevated prothrombin time in one individual. We realized that much more data must be collected before any definite conclusions may be drawn and that the whole problem is one of extraordinarily complexity. No doubt many other sources of vitamin K will be discovered and more simple methods for elevating the level of prothrombin in the blood will be described. However, a considerable experience will be required to establish a routine for the use of vitamin K and bile salts in preoperative and postoperative care, and to determine the clinical value and the limitations of this type of treatment. Results so far obtained, however, encourage us to believe that the prevention and control of the hemorrhagic diathesis of the jaundiced patient may be attained in the not too distant future.

**DISCUSSION**

J. L. Bollman, M. D., Division of Experimental Medicine: Most normal animals have a large excess of prothrombin in their blood. It has been shown that normal plasma contains about 200 times the amount necessary to produce sufficient thrombin to clot fibrinogen within a few seconds. The amount present in the blood remains quite constant under a wide variety of dietary and other experimental conditions. Warner, Brinkhous and Smith found that prothrombin removed by extensive bleeding was rapidly replaced in the blood. Severe infection or formation of abscesses did not alter the level of prothrombin. Some definite inhibition of prothrombin liberation in the plasma is indicated by the rapid fall of prothrombin in the plasma following acute chloroform or phosphorus poisoning and its return to normal levels as the liver is restored to normal. This fact seems to indicate that the liver is concerned with the formation or destruction of prothrombin. For vitamin D, Heymann has shown that much larger amounts are necessary to prevent rachitic changes in rats when the liver is injured by carbon tetrachloride or by biliary obstruction. It is quite probable that the amount of vitamin K required to maintain the level of prothrombin might also be increased in the presence of impairment of the liver.
Chicks which have been deprived of vitamin K present an impressive picture. The coagulation of their blood is greatly delayed and there are numerous dark areas of subcutaneous hemorrhage on the entire body. Less than 1 mg. of the as yet partially purified vitamin K in about one month's diet will prevent the occurrence of hemorrhage and allow the chickens to appear normal, or will restore the chicks to normal once the condition has been allowed to develop. It requires but little imagination to think of this small amount of substance being altered in its activity by conditions which affect the liver.

Waltman Walters, M. D., Division of Surgery: Dr. Snell and his coworkers have demonstrated: (1) that an increase in the prothrombin time of the blood is frequently associated with obstructive jaundice; (2) that a prolonged prothrombin time in cases of jaundice can be reduced to almost normal limits by administration of vitamin K and bile and (3) that in several cases of obstructive jaundice which came to operation and in which bleeding occurred subsequent to operation, the administration of vitamin K and bile controlled the hemorrhage.

Surgical considerations.—Prior to 1919 postoperative hemorrhage was a disturbing factor of the convalescence of patients operated on for obstructive lesions of the biliary tract. The incidence of postoperative hemorrhage in these cases decreased markedly after the introduction of preoperative transfusion of blood by Pemberton. Since 1921 when the intravenous injection of a solution of calcium chloride and glucose preliminary to, and subsequent to, operation was introduced, the incidence of postoperative hemorrhage in cases of jaundice has decreased further.

As a result of these measures as well as the institution of improved surgical methods, anesthesia, and so forth, and because of the recognition of a proper time for the institution of surgical procedures in cases of jaundice, the mortality rate has decreased in the Clinic to the extent that in 1936 209 patients who had jaundice were operated on with a mortality of 3.5 per cent. Of particular interest from the standpoint of the incidence of hemorrhage is the fact that it was found at postmortem examination to be the primary cause of death in only two of these cases (1 per cent). Other causes of death found at postmortem examination were bronchopneumonia which apparently occurred as a terminal event and pulmonary embolism.

The risk of operation in cases of biliary obstruction due to malignant lesions (and these for the most part are carcinoma of the head of the pancreas) varies from 10 to 14 per cent. In such cases jaundice is deeper, biliary obstruction more complete, and disturbance of the liver as evidenced by changes in its color, consistency, and its ability to excrete bile acids and bile pigment, is more marked. Microscopic examination of sections of the liver in such cases frequently reveals more marked changes in the parenchyma than in cases of benign lesions. The increased risk of surgical procedures in cases of malignant obstruction of the biliary tract producing jaundice may be due to these three factors and the effect of the malignancy per se. Many of the cases of hemorrhage taken from the postmortem
records and reported by Dr. Boland can be accounted for on the basis of the high incidence of hemorrhage in cases of malignant lesions.

Dr. Bollman has emphasized a very important point, namely, that one cause of decrease of the amount of prothrombin in blood is damage of the liver. Such disturbances of the liver and consequently the tendency of the patients to bleed are factors in surgical cases which must be taken into consideration in determining the effect of surgical relief of the obstruction as well as in evaluating any method used to increase the coagulability of the blood. On previous occasions attention has been called to the fact that a prolonged coagulation time in cases of jaundice indicates an abnormal disturbance of liver function with proportionate increase of the surgical risk. The effect of relief of biliary obstruction must be taken into account as the most important factor in increasing the coagulability of the blood and decreasing the tendency to bleed. It is a well-known fact that hemorrhage is less likely to occur in cases in which the biliary obstruction has been relieved surgically than in cases in which the biliary obstruction is not relieved. In the few cases in which biliary obstruction cannot be relieved, serious bleeding has occasionally occurred regardless of the administration of blood, calcium or glucose. It will be interesting to see whether the administration of vitamin K and bile will cause cessation of bleeding. In one case in which I recently performed a cholecystogastrostomy for carcinoma of the head of the pancreas, serious bleeding occurred on the day after operation. Apparent cessation of bleeding occurred a few hours after the administration of vitamin K and bile. During the postoperative period, however, the patient's serum bilirubin had rapidly decreased as a result of relief of obstruction.

REFERENCES

28. Smith, H. P.: Personal communication to the authors.
31. Wagensteem, O. H.: Personal communication to the authors.

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CORRECTION

In the article by Wollaeger and Keith on “Epigastric thrill and murmur in a case of cirrhosis of the liver with general vascular signs of arteriovenous fistula” in the Proceedings of the Staff Meetings of The Mayo Clinic, 13: 33-37 (Jan. 19) 1938, in the legend for figure 1 page 34 the “upper” and “lower” should be reversed. The upper should read “From a point 1 inch (2.5 cm.) to the right of the xiphoid process. Here the continuous murmur was not audible through a stethoscope and was not recorded on the tracing. Heart sounds are plainly recorded.” The lower should read “From the site of maximal intensity of the murmur over the xiphoid process. The small uniform vibrations at a frequency of about 90 per second are produced by the epigastric murmur. Heart sounds are superimposed.”