

definitely the slow, deep rhythm described by Gruber,² and ascribed by him after electrocardiographic studies to the development of ventricular ectopic beats interspersed with long compensatory pauses.

After the administration of a minimal narcotic dose, 4 of the dogs were carried along as nearly as possible at the level of abolition of corneal and joint reflexes by saline-diluted fractional doses (0.003-0.005) of pentothal sodium as indicated. There was a progressively longer narcotic effect after each successive administration. In each case, death followed an unwarned sudden drop of blood pressure to the base line, sometimes before respiration had ceased. The suddenness of the blood pressure fall and the previous appearance of ectopic ventricular contractions suggest the development of ventricular fibrillation.

It is of interest that in cats with 2 or 3 repeated minimal anesthetic doses intraperitoneally, respiration continued for as long as 2 to 5 days before the unconscious animals finally died.

Summary. The first undesirable effect of a single sublethal dose of pentothal sodium is sudden cessation of respiration. Repeated administration of small amounts, sufficient to maintain light anesthesia, suddenly produces signs of heart muscle poisoning. There seems to be a definite cumulative action. Whether this is due to damage of liver tissue, or whether the drug is changed into simpler, larger dose, and longer acting forms (diethyl-barbiturate?) we are not prepared to suggest. The longer the administration is continued, the more does the threat seem to shift to the more fatal circulatory side.

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Bleeding Tendency of Obstructive Jaundice: Prothrombin Deficiency and Dietary Factors.*

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Hawkins and Whipple¹ have described in bile fistula dogs a bleeding tendency which is prevented by feeding whole bile. Hawkins and Brinkhous² showed that the bleeding is due to a prothrom-

² Gruber, Charles M., *J. Pharm. and Exp. Therap.*, 1937, **60**, 143.

* Aided by a grant from the Committee on Scientific Research of the American Medical Association, and more recently by a grant from the John and Mary R. Markle Foundation.

¹ Hawkins, W. B., and Whipple, G. H., *J. Exp. Med.*, 1935, **62**, 599.

² Hawkins, W. B., and Brinkhous, K. M., *J. Exp. Med.*, 1936, **63**, 795.

bin deficiency. That low prothrombin values may occur in obstructive jaundice has been suggested by Quick, Stanley-Brown and Bancroft.³ We wish to report our experience with human cases of obstructive jaundice and of biliary fistula.

The prothrombin titration method is one which we have described previously.⁴ Many of our jaundiced cases showed no bleeding tendency, and in them the prothrombin level was usually above 50% of normal. If the prothrombin level is below 35% one often encounters bleeding from mucous membranes or hemorrhage at operation or from the wound afterward. A subsequent rise in the prothrombin level is associated typically with cessation of bleeding. In 2 cases, for example, spontaneous hemorrhage occurred with prothrombin values of 33 and 16% respectively. Recovery from the hemorrhagic tendency in these was associated with a prothrombin rise to 92 and 66%.

The restoration of bile to the intestinal tract results in a gradual rise in the prothrombin level. This is shown in cases where the obstruction is suddenly released, or in cases where bile is fed by mouth. In one case the patient was bleeding, with a prothrombin level of 10%. Then there was spontaneous and practically complete relief of the obstruction and the bleeding tendency ceased a few days later. At the end of 2 weeks the prothrombin had risen to the 89% level. In another case in which there was a biliary fistula of 4 months' duration, bleeding from a recent operative incision occurred. The prothrombin level was 27% of normal. The bile which drained from the fistula was then fed by mouth. With this therapy the prothrombin gradually rose to 89% of normal over a period of 7 weeks. Bleeding ceased after the prothrombin had risen above the 30% level.

These patients undoubtedly suffer from disturbances in the digestion and absorption of fats. This difficulty is probably overcome, at least in part, by restoration of bile to the intestinal tract. In "hemorrhagic chick disease," due to a deficiency in the fat-soluble anti-hemorrhagic vitamin, low prothrombin values have been reported.^{5, 6} Alfalfa, as shown by Almquist and Stokstad,⁷ is rich in this vitamin. We have followed the prothrombin level in human cases in

³ Quick, A. J., Stanley-Brown, M., and Bancroft, F. W., *Am. J. Med. Sc.*, 1935, **190**, 501.

⁴ Warner, E. D., Brinkhous, K. M., and Smith, H. P., *Am. J. Physiol.*, 1936, **114**, 667.

⁵ Dam, H., Schönheyder, F., and Tage-Hansen, E., *Biochem. J.*, 1936, **30**, 1075.

⁶ Quick, A. J., *Am. J. Physiol.*, 1937, **118**, 260.

⁷ Almquist, H. J., and Stokstad, E. L. R., *J. Biol. Chem.*, 1935, **111**, 105.

which bile feeding was supplemented with a fat soluble extract of alfalfa meal. The residue of a petroleum ether ("Skellysolve A") extract of 200-400 gm. alfalfa meal was emulsified in human bile, or, in some cases, in 2% sodium taurocholate solution, and fed daily. In a number of patients given this alfalfa-bile mixture, the rise in prothrombin was very rapid, even with persistence of jaundice. If bleeding had existed, it soon ceased. In 3 cases of obstructive jaundice, the prothrombin level before therapy was 43, 20, and 37%. Alfalfa with bile or bile salts was given for 6, 8, and 6 days respectively. At the end of the period, the prothrombin values had risen to 86, 107, and 102%. The rise in these cases is considerably faster than with simple bile feeding.

In these cases, whole blood clotting time and Duke's bleeding time were usually within normal limits despite considerable reduction in plasma prothrombin. Significant prolongations were found only when the prothrombin was at very low levels and bleeding was imminent or actually present.

The data presented show that the bleeding tendency in cases of obstructive jaundice and of biliary fistula is due to a low plasma prothrombin level. The importance of bile in the intestinal tract is shown by the return of the prothrombin to normal levels when bile is restored to the intestine. The fact that the prothrombin rises with greater speed when an alfalfa extract is fed along with bile suggests that Vitamin K is concerned. However, this vitamin deficiency disease has not been produced in normal mammals by feeding deficient diets.

Summary. 1. The bleeding tendency in cases of obstructive jaundice and biliary fistula is due to a prothrombin deficiency. 2. With restoration of bile to the intestine the prothrombin gradually returns to normal and the bleeding ceases. 3. Feeding of alfalfa extract, rich in Vitamin K, in addition to bile, causes a more rapid return of the prothrombin to normal.