13056

Comparative Effect of Vitamin K and Whole Blood on Prothrombin Deficiency of Newborn Infant.

H. C. WILLUMSEN, H. E. STADLER AND C. A. OWEN. (Introduced by E. D. Plass.)

From the Departments of Obstetrics and Gynecology, and Pediatrics, State University of Iowa, Iowa City, Iowa.

The etiologic importance of a plasma prothrombin deficiency in the bleeding tendencies of obstructive jaundice, biliary fistula, and severe liver damage has been receiving prominent attention.

In 1937, it was first shown[1] that the bleeding in hemorrhagic disease of the newborn is a manifestation of prothrombin lack. Recent investigators[2-14] have reported a physiological depression of the plasma prothrombin during the first few days of life in the majority of infants. The infant's prothrombin is essentially normal at birth but falls to 20-50% of normal within the next few days and returns to its original level by the fifth to seventh day. Chart 1 illustrates the curves obtained in 3 normal infants. When this depression is extreme, infants may have a hemorrhagic tendency (melena, hematemesis, etc.).[5-9]

It should be noted that the various one-stage methods used for prothrombin determinations[15-17] measure not only prothrombin con-

1 Brinkhous, K. M., Smith, H. P., and Warner, E. D., *Am. J. M. Sc.*, 1937, **193**, 475.

2 Waddell, W. W., Guerry, D., Bray, W. E., and Kelley, O. R., PROC. SOC. EXP. BIOL. AND MED., 1939, **40**, 432.

3 Owen, C. A., Hoffman, G. R., Ziffren, S. E., and Smith, H. P., PROC. SOC. EXP. BIOL. AND MED., 1939, **41**, 181.

4 Quick, A. J., and Grossman, A. M., PROC. SOC. EXP. BIOL. AND MED., 1939, **41**, 227.

5 Waddell, W. W., and Guerry, D., *J. A. M. A.*, 1939, **112**, 2259.

6 Nygaard, K. K., *Acta obstet. et gynec. Scandinav.*, 1939, **19**, 361.

7 Dam, H., Tage-Hansen, E., and Plum, P., *Ugesk. f. laeger*, 1939, **101**, 896.

8 Dam, H., Tage-Hansen, E., and Plum, P., *Lancet*, 1939, **1**, 1157.

9 Quick, A. J., and Grossman, A. M., *Am. J. Med. Sc.*, 1940, **199**, 1.

10 Bray, W. E., and Kelley, O. R., *Am. J. Clin. Path.*, 1940, **10**, 154.

11 Kato, K., and Poncher, H. G., *J. A. M. A.*, 1940, **114**, 749.

12 Macpherson, A. I. S., McCallum, E., and Haultain, W. F. T., *Brit. M. J.*, 1940, **1**, 839.

13 Fitzgerald, J. E., and Webster, A., *Am. J. Obstet. and Gyn.*, 1940, **40**, 413.

14 Kove, S., and Siegel, H., *J. Pediat.*, 1940, **17**, 448.

15 Quick, A. J., *Am. J. Physiol.*, 1936, **114**, 282.

16 Ziffren, S. E., Owen, C. A., Hoffman, G. R., and Smith, H. P., PROC. SOC. EXP. BIOL. AND MED., 1939, **40**, 595.

17 Kato, K., *Am. J. Clin. Path.*, 1940, **10**, 147.

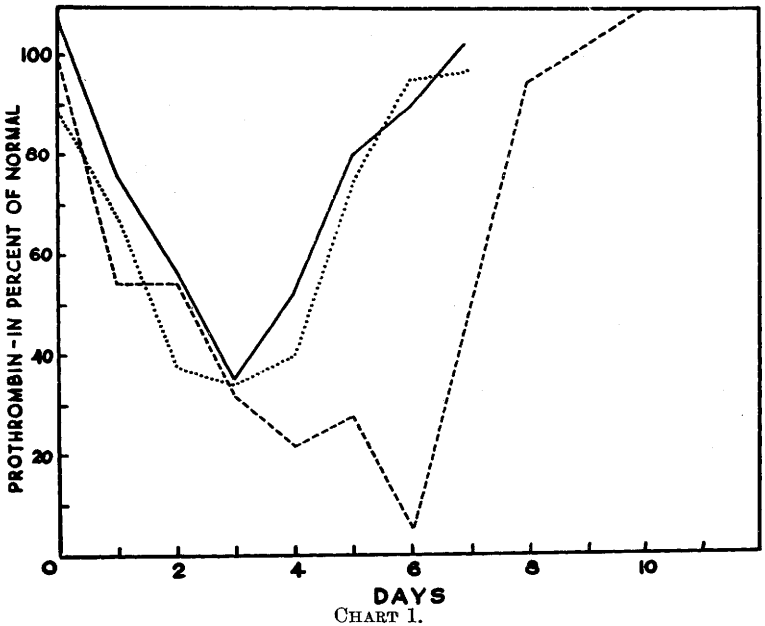

CHART 1.
Daily prothrombin levels in 3 normal newborn infants.

centration but also the rate of prothrombin conversion to thrombin. Inasmuch as this conversion rate is variable and can at times compensate for a low prothrombin,[3, 16, 18, 19] the methods employed furnish a more reliable index of a possible bleeding tendency than does the more complex 2-stage test[20] which measures only prothrombin concentration.

The time-honored treatment of hemorrhagic disease of the newborn is the administration of whole blood, either intravenously, intramuscularly or subcutaneously. The prophylactic and curative rôle of vitamin K in this disease was first reported in 1939[2] and is now well established. The purpose of this study was to compare the effect of vitamin K and of maternal whole blood on the prothrombin time of newborn infants.

Methods. Twenty-three healthy infants, 3 or 4 days old and weighing 2650 to 4900 g, were used. At this age the plasma prothrombin approaches its lowest level and remains depressed for at least one day.

Aqueous solutions of 4-amino-2-methyl-naphthol, a synthetic form of vitamin K, (Synkamin; Parke, Davis and Company), were

18 Schønheyder, F., *Am. J. Physiol.*, 1938, **123**, 751.

19 Brinkhous, K. M., *Med.*, 1940, **19**, 329.

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

administered orally, intramuscularly and intravenously, in doses of one milligram. This preparation may produce vomiting when given by mouth.

Maternal whole blood was given subcutaneously and intramuscularly in 15 cc doses and the same amount was administered intravenously after the addition of 2 cc of 2.5% sodium citrate solution. Each of 2 babies was given 7 cc of human serum by the intravenous route. The serum was obtained from whole blood which was allowed to clot spontaneously and then stand for 12 hours, when less than 1% of the original prothrombin remained.

Determinations of prothrombin levels were performed by a microadaptation of the "Bedside" test.[16] Capillary blood, obtained by heel puncture, was mixed with thromboplastin in a 10:1 ratio, on a clean glass slide. As in the "Bedside" test, prothrombin is recorded in percent of normal:

$$\frac{\text{clotting time of normal}}{\text{clotting time of patient}} \times 100.$$

Results. It will be noted in the charts that even when the age factor is constant there is considerable variation in the initial prothrombin level. As controls, several additional prothrombin determinations were made on the blood of 5 untreated infants with initial readings ranging from 40 to 65%. Invariably the values remained essentially constant during a 10-15-hour observation. We have assumed, therefore, that the initial reading for any infant established the prothrombin level for that baby, for the succeeding several hours.

Administration of synthetic vitamin K to 6 infants, regardless of route, resulted in a rapid rise in the prothrombin level (Chart 2). In every case the prothrombin values were at least 50% of normal within 3-4 hours and 70% in 6 hours.

Fifteen cubic centimeters of whole blood, when injected intravenously into 4 babies, raised the prothrombin level approximately to the point which would have been expected from the addition of the prothrombin contained in the added blood (Chart 3). This slight prothrombin elevation appeared shortly after the blood was introduced. Comparable quantitative increases in the plasma prothrombin following transfusions have been noted in adults.[19] In 2 infants whose prothrombin levels were 10% of normal at the time of transfusion, the values did not rise out of the "danger zone" (less than 40%) within the period of observation, but there was no bleeding. Vitamin K was injected intramuscularly into one of these

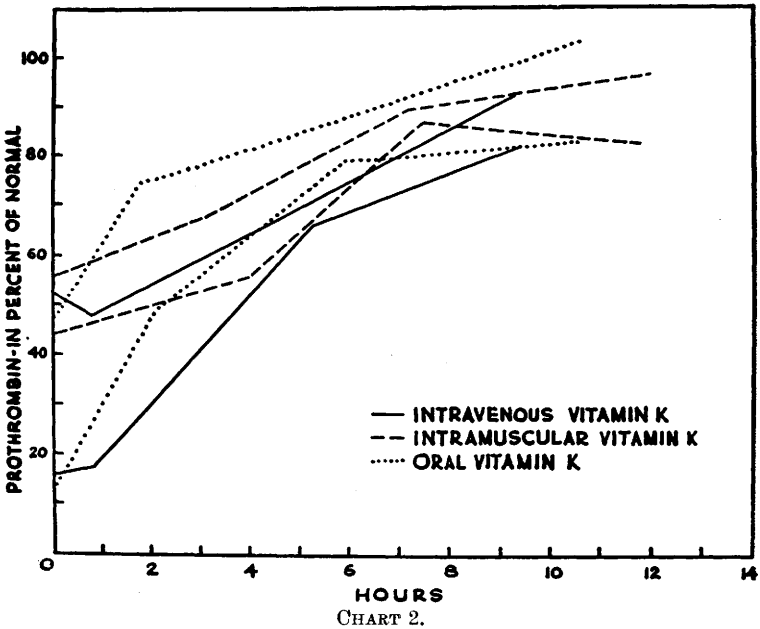

CHART 2.
Prothrombin levels in 6 infants after the administration of vitamin K.

2 infants 4 hours after the blood had been given; the prothrombin rose from 20% to 80% of normal in 8 hours (Chart 3).

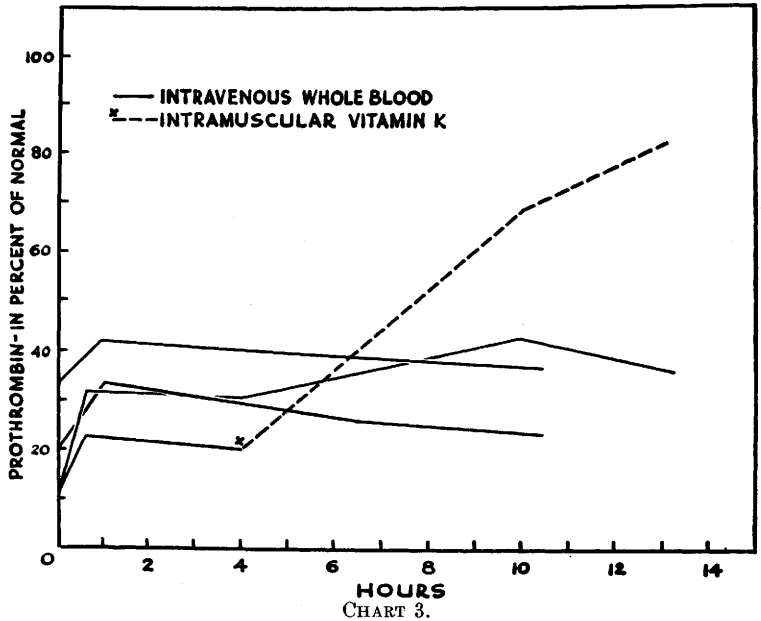

CHART 3.
Prothrombin levels in 4 infants after the injection of whole blood intravenously.

We were unable to demonstrate any prothrombin elevation when whole blood was injected subcutaneously or intramuscularly into 6 infants (Chart 4 shows representative cases).

That no "stimulating" action is present in the serum portion of blood is indicated by the lack of prothrombin elevation following intravenous injection of prothrombin-free serum into 2 infants (Chart 4).

Discussion. Vitamin K, given orally or parenterally, causes a rapid rise in the plasma prothrombin level of newborn infants with hypoprothrombinemia whether there is a hemorrhagic tendency or no clinical manifestation of the depressed prothrombin level. Whole blood has a slight additive effect when injected intravenously. Satisfactory treatment with adequate blood transfusions (30-50 cc) has the disadvantage of requiring such specialized technical proficiency that it is frequently not available when needed. Moreover, some time is lost by the need for cross-matching. Injections of blood, other than intravenously, have no effect on the clotting time within 12-15 hours, as measured by plasma prothrombin levels.

Summary. Observations made upon a group of 3- and 4-day-old infants, who showed the expected hypoprothrombinemia, indicate

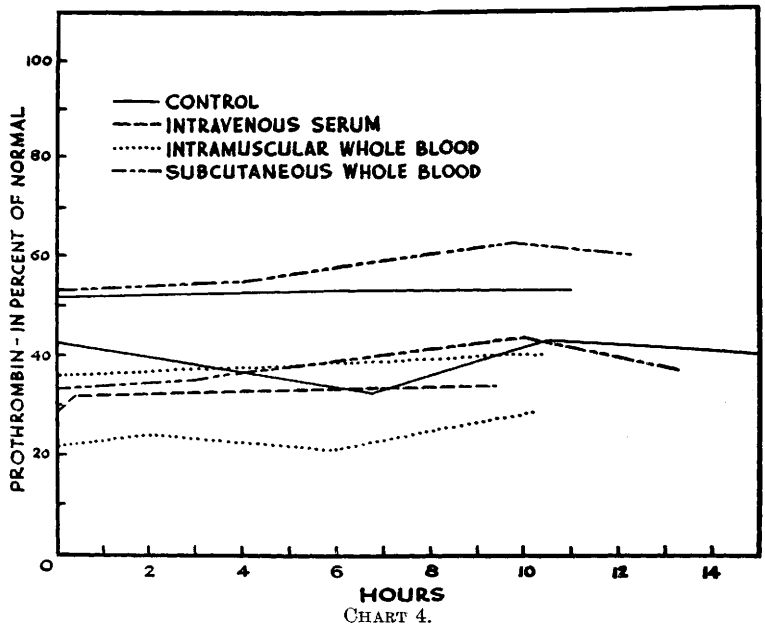

CHART 4.

Comparative effect of whole blood administered intramuscularly and subcutaneously, and of human serum injected intravenously, on prothrombin levels of normal infants.

that maternal whole blood, regardless of the mode of administration, is not as effective as vitamin K in raising the plasma prothrombin level. Because of the known relationships of reduced prothrombin levels to hemorrhagic disease of the newborn, it is suggested that treatment with vitamin K, which produces very rapid and significant elevations of the prothrombin, will prove much more effective than injections of maternal blood.

13057

Differential Cell Counts of Ant. Lobe of Pituitary Glands of Rats Showing Diabetic Traits.

MOLLIE A. GEISS. (Introduced by B. K. Harned.)

From the Department of Pathology, Woman's Medical College of Pennsylvania, Philadelphia, Penn.

Recent reports[1-5] on studies of a strain of rats with diabetic traits have presented evidence of hyperfunction of anterior lobe of the pituitary gland. The purpose of this investigation was to study the anterior lobe of the pituitary gland of this strain by the method of cell enumeration. No critical cytological study was done.

Material and Methods. The pituitary glands of 15 sexually mature male rats of the "diabetic" strain, and of an equal number of a "non-diabetic" strain matched in sex, age and weight, were studied. The average age of the "diabetic" rats was 233 days; of the controls, 212 days. The average weight of the "diabetic" rats was 451 g; of the controls, 347 g. The glands were not weighed. They were fixed in Bouin's solution modified according to Gomori,[6] whose method for fixing pancreatic islets was followed. The whole gland was embedded in paraffin at 57°C. Serial sections were cut in the coronal plane at 5 microns and all sections were mounted. The sections were stained by Mallory's Acid Fuchsin-Aniline Blue method as modified by Crooke and Russell.[7] We found that better results were

1 Cole, Versa V., and Harned, B. K., *Endocrinology*, 1938, **23**, 318.

2 Harned, B. K., and Cole, Versa V., *Endocrinology*, 1939, **25**, 689.

3 Cole, Versa V., and Harned, B. K., PROC. SOC. EXP. BIOL. AND MED., 1939, **42**, 738.

4 Harned, Ben K., and Cole, Versa V., *Science*, 1940, **92**, 361.

5 Cole, Versa V., Harned, Ben K., and Keeler, Clyde E., *Endocrinology*, 1941, **28**, 25.

6 Gomori, G., *Am. J. Path.*, 1939, **15**, 498.

7 Turner, O. A., *J. Lab. and Clin. Med.*, 1939, **24**, 997.