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Vitamin K Requirement of the Newborn Infant.*

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(Introduced by H. P. Smith.)

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During the first week of life the plasma prothrombin level of infants commonly falls to dangerously low levels.[1-4] The fall can be minimized or entirely prevented by prophylactic administration of vitamin K to the infant after delivery[4-8] or to the mother prior to delivery.[4, 6] When the treatment is given directly to the infant, a dosage of 1 mg of synthetic vitamin is usually employed. We agree that this is probably the proper dosage, but we shall show that it exceeds the minimal daily requirement almost 1000-fold. In view of this, we wish to suggest that a reasonable intake of milk, artificially supplied, may furnish enough vitamin K to meet the minimal needs of the normal infant, and that synthesis of the vitamin by intestinal bacteria may not be so important as commonly assumed.

In the present studies we administered 2-methyl-4-amino-1-naphthol (Synkamin) intramuscularly as a source of vitamin K activity. Treatment was of 3 types: (1) Maintenance therapy, consisting of small daily injections of the vitamin; (2) Prophylactic therapy, consisting of a single dose administered shortly after birth; (3) Curative therapy, in which case a single dose was given after depletion had already become established.

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The Synkamin used in these studies was kindly furnished by Parke, Davis and Company.

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Table I shows the results of maintenance therapy with vitamin K, along with the results obtained in 6 untreated controls. In the latter, the prothrombin usually reached its lowest level on the third or fourth day. The treated cases show that within the range of 0.5-2.0 μg of vitamin, daily, there is some variation in the response, but at 2 μg, and at still higher levels, the fall is minimal or entirely absent.

Table II shows the effect of a single injection of the vitamin, given within the first few hours of life. When the dosage is 5 μg or less, the prothrombin level eventually falls, but the fall is not so profound as when no vitamin is given. At the level of 10-20 μg, the prothrombin level is reasonably stable, and when the dose is

TABLE I.
The Daily Maintenance Requirement for Vitamin K.*

Case No.	Daily dose vit. K μg	Plasma prothrombin levels† first day %	second day %	third day %	fourth day %	fifth day %	sixth day %	seventh day %	
1	0	116	74	58	36	53	80	90	
2	0	88	68	38	38	41	87	96	
3	0	108	42	37	31	48	81	95	
4	0	102	58	32	21	40	61	98	
5	0	86	58	25	27	23			‡
6	0	100	31	18	10	8			‡
7	0.05	108	83	65	60	72	100		
8	0.1	128	110	71	62	64	84		
9	0.2	114	103	75	68	80	106		
10	0.5	114	107	83	110	110	123		
11	0.5	97	103	92	100	116	123		
12	0.5	115	98	91	100	112	112		
13	0.5	75	63	73	64	82	85		‡
14	1.0	94	86	76	93	92	102		
15	1.0	115	100	103	110	112	118		
16	1.0	78	95	107	105	95	102		
17	1.0	104	92	88	93	97	102		
18	1.0	110	107	110	117	109			‡
19	1.0	87	92	95	115	100			§
20	2.0	97	83	80	90	102	112		
21	2.0	97	102	110	107	112			‡
22	2.0	108	92	95	94	93			§
23	5.0	96	89	101	111	106	100		
24	10.0	94	89	103	107	102	104		

*Synkamin solution was diluted with normal saline to provide the indicated dosage. Injections were made into the gluteal muscles.

†Prothrombin determinations were made by a micro-adaptation of the "bedside test" (Ziffren, S. E., Owen, C. A., Hoffman, G. R., and Smith, H. P., PROC. SOC. EXP. BIOL. AND MED., 1939, **40**, 595).

When glucose was given, a 10% solution was employed and a total of 200-400 cc were administered. The infants, so treated, received neither colostrum nor milk during the period of study. Those infants which received "no colostrum" were given neither sugar nor milk.

‡Glucose daily.

§No colostrum.

TABLE II.
The Prophylactic Treatment of Infants with Vitamin K.

Case No.	Vit. K given first day only μg	Plasma prothrombin levels					
		first day %	second day %	third day %	fourth day %	fifth day %	sixth day %
25	1	98	100	89	55	78	89
26	2	108	92	57	27	57	83
27	5	96	107	93	73		
28	5	125	91	88	102	104	
29	10	103	98	95	99	94	
30	20	89	89	100	102	98	95
31	20	114	114	103	78	100	118
32	50	112	110	110	116	118	113
33	100	110	100	102	105	97	98
34	1000	97	101	108	105	103	108

Prothrombin determination and vitamin K administration were carried out as in the experiments given in Table I.

still larger the fall in prothrombin is no longer apparent. From these data it is evident that the total vitamin K requirement for the first 5 days of life is definitely higher when the vitamin is given in a single dose at the beginning of the period than when given in the form of small daily injections. The experiments show, moreover, that a certain amount of storage is possible, but that considerable "wastage" does occur.

It has been shown that the prothrombin level of the infant can be stabilized by the administration of 1 mg of the vitamin to the mother prior to delivery.[9] Since the prophylactic requirement of the infant is 10 to 20 μg, it follows that at least 1-2% of the vitamin given to the mother must pass into the fetal circulation. That this much should reach the fetus is not surprising when one recalls that the weight of the infant is about 5% as great as that of the mother. One is tempted to postulate a simple physical partition of the injected vitamin between the mother and fetus.

Fig. 1 deals with curative rather than with the prophylactic dosage. The vitamin, given intramuscularly in one dose, was supplied on the second, third, or fourth day, while the prothrombin level was low. The response to 0.5 μg or less was slow and was incomplete. At the level of 1 μg the response was maximal, though still rather slow. With larger doses, 5 to 1000 μg a maximal response is usually obtained in as short a period as 8 to 10 hours.

In a number of cases prothrombin determinations were made within the first 60 minutes after injection of the vitamin. However,

[9] Bohlender, G. P., Rosenbaum, W. M., and Sage, E. C., *J. A. M. A.*, 1941, **116**, 1763 (literature cited).

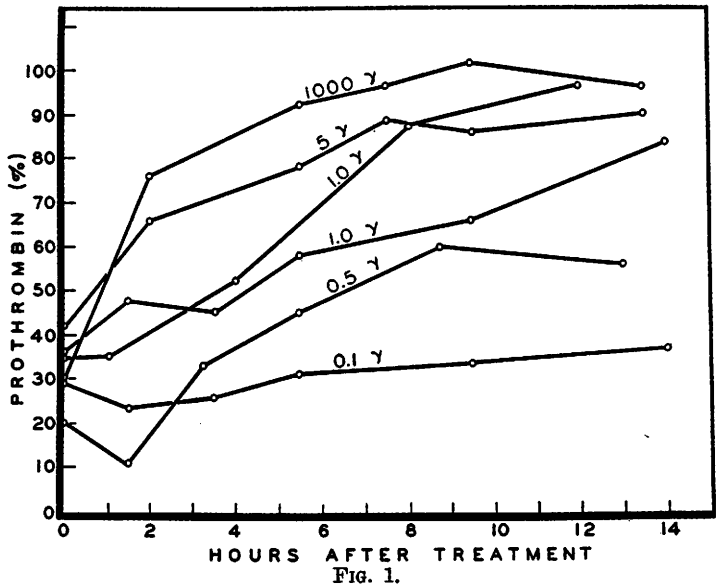

FIG. 1.
The curative dose of vitamin K.

no detectable response was observed in this short interval. The initial delay in response is evidently associated with metabolic processes, not with sluggish absorption of the vitamin from the site of intramuscular injection, for data already published[10] show a similar delay where the vitamin is given intravenously in 1 mg doses.

Most workers now agree that the fall in prothrombin during the first 4 days of life is soon followed by a rise. It is significant that this rise develops as soon as the supply of breast milk becomes abundant; in fact Salomonsen[11, 12] showed that the fall could be prevented by simply giving 30-60 cc of cow's milk during the first few days of life. Milk does not contain large amounts of vitamin K, and Salomonsen believed that the main role of the milk consists in providing a culture medium for intestinal bacteria which then produce the vitamin K in necessary quantities. Others[3] had already suggested the importance of bacteria, but without placing special emphasis on the role of milk. However, on finding that the vitamin K requirement of the newborn infant is extremely low, we suspected at once that the milk may of itself contain adequate amounts of preformed vitamin K. In testing this possibility we fed milk

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powder as a curative procedure to infants on the third or fourth day of life. We found that 5-10 g, given in water, gave a prothrombin response equivalent to 0.5-1.0 μg of the synthetic vitamin. If the dried milk be extracted with ether, a dose several times as large is required to give the same response. The ether-soluble extract from 10-15 g of dried milk is more than adequate to give this response.

Colostrum is consumed in small quantities during the first 3 days of life, and evidence indicates that it does contain small amounts of vitamin K. In 2 cases (19 and 22 of Table I), nursing problems were such that the infants received water, but neither colostrum nor glucose. Several others, shown in Table I, received glucose, but no colostrum. There is some variation in results, but the general trend is toward lower prothrombin levels. We believe that the colostrum contains enough vitamin K to account for this small difference.

Summary. The vitamin K requirement of the newborn infant is shown to be extremely low (approximately 1 μg of synthetic vitamin a day). Milk contains enough preformed vitamin K to meet this minimal requirement.

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Absence of Supplementary Relationships in Requirements for Pyridoxin and Essential Fatty Acids.*

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A number of investigators[1-8] have been concerned with the question of a possible supplementary relation existing between pyridoxin and the essential fatty acids.

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