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Routes of Administration of Materials Capable of Acting as Vitamin K.

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(Introduced by L. Reiner.)

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Present clinical and laboratory evidence indicates that vitamin K and many of the slightly water-soluble substances capable of acting as vitamin K are poorly absorbed from the intestinal tract under certain pathologic conditions such as ulcerative colitis, obstructive jaundice and other conditions tending to modify absorption or to restrict the production of bile salts. In the case of such interferences with the oral route, oil solutions have been injected intramuscularly. The percutaneous route, which has recently been found to be successful with such substances as stilbestrol still remained to be tested. The results of such a test are given in this paper.

Method. It was found that 2-methyl-1,4-naphthoquinone could be dissolved in warm anhydrous lanolin, liquid petrolatum, propylene glycol monostearate or solvents of similar nature. Two preparations were made, one employing anhydrous lanolin as the solvent, the other using propylene glycol monostearate. A series of graded doses, each contained in 0.25 g of material, were rubbed with the fingers into the skin beneath the wings of chicks which had previously been maintained on the Ansbacher[1] diet until clotting time, as measured by the Ansbacher[2] technic, was greater than 60 minutes. In order to insure thorough application, the rubbing was continued for a period of 5 minutes. As a further precaution, a small jacket was placed on each chick in order to prevent the possibility of the animal ingesting any vitamin K which might have escaped notice. During the application a certain undetermined portion of the material was absorbed by the ungloved fingers of the operator so that each animal actually received somewhat less than the specified dose.

Results. It was found that 2-methyl-1,4-naphthoquinone may be readily administered percutaneously. As little as 1 γ per chick reduced the clotting times of 11 out of 24 chicks to 10 minutes or less, 24 hours after dosing.

1 Ansbacher, S., PROC. SOC. EXP. BIOL. AND MED., 1940, **44**, 248.

2 Ansbacher, S., *J. Nutrition*, 1939, **17**, 303.

The nature of the solvent caused no discernible difference in results.

Additional data presented in Table I show that when the dose was increased, the percentage of animals cured increased, the relative clotting times decreased and that more than 5 hours were required to reach maximum effectiveness. The greatest percentage of cures was found at the 24-hour observation period. Although the peak of activity apparently is closer to the 24-hour period than either the

TABLE I.
Venous Blood Clotting Times in Minutes Following Administration of 2-Methyl-1,4-naphthoquinone.

Mode of administration	Dose per chick, γ	Hr after injection	Clotting time in min.						Cured %
Oral	2	5	2	3	2	3	2	2	100
		24	0.8	0.5	0.5	2	0.8	0.5	100
		72	2	2.5	1.8	4.5	6	0.5	100
		144	4	>60	>60	>60	>60	6	33
Intramuscular	2	5	2	1	2	1.5	4	3	100
		24	1	1	2.5	0.5	0.5	0.5	100
		72	0.5	3.5	3	3	1	1	100
		144	>60	>60	>60	8	>60	>60	17
Percutaneous	2	5	16.5	4	>60	>60	4	>60	33
		24	7.5	1.5	2	5.5	1.5	21	83
		72	4.5	>60	1.5	>60	7.5	18.5	50
		144	>60	>60	>60	>60	>60	>60	0
Percutaneous	4	5	>60	>60	4	3.5	>60		40
		24	1.2	2	2.5	2.2	7.2		100
		72	8	>60	3	1.5	>60		60
		144	>60	>60	>60	>60	>60		0
Percutaneous	8	5	2	1.5	>60	14	14		40
		24	6	0.8	2.5	1.5	1.2		100
		72	3.5	5	11.5	31	1		60
		144	>60	>60	22	1	4		40
Percutaneous	16	5	4	1.5	6.5	2	40.5		80
		24	4.5	1	0.5	0.8	3		100
		72	1.5	2	1.5	1.5	3.5		100
		144	3	6.5	>60	2	31		60
Percutaneous	32	5	0.5	0.3	0.3	2	0.3	0.3 0.5	100
		24	1	0.3	0.8	0.5	0.2	1 0.3	100
		72	2.5	1	*	1.5	0.5	1.5 3	100
		144	3	1.5		2	4	2 2	100

*Died.

Each series of 4 clotting times determined at 5, 24, 72 and 144 hours after dosing and arranged vertically represents a different chick.

Chicks whose blood clots within 10 minutes or less are arbitrarily classed as cured.

The 2-methyl-1,4-naphthoquinone was dissolved in corn oil for the intramuscular injections.

5-hour, the 72-hour or the 144-hour periods, marked activity persists for a long time. Even at the 2 γ dose, the majority of the animals still showed low clotting times at the end of 3 days while the largest dose was remarkable not only for the very low clotting times observed at the 5-hour and 24-hour periods but also for the fact that they were still very low at the end of 6 days. The results of oral and intramuscular injection are also given in Table I.

Summary. The percutaneous route affords a means of conveniently administering slightly soluble materials possessing vitamin K activity. Doses as small as 1 γ per chick successfully cured approximately 50% of a series of depleted chicks. Larger doses afforded protection for relatively long periods of time.

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Quantitative Effects of Implantation of Cattle Anterior Pituitary Powder on Gonads of Immature Rat.

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The use of subcutaneous or intramuscular "depots" for giving a more or less constant absorption of biological substances is a procedure of recognized value. Such slow, steady absorption should and perhaps does approach closely the same effect as glandular secretion within the body of the animal. This paper presents the results of the administration of cattle anterior pituitary powder* to rats by subcutaneous implantation.

The effect of implanting anterior pituitary powder on the ovaries of the rat was studied by Loeser[1, 2] and Janssen and Loeser.[3]

* The cattle anterior pituitary powder was furnished through the courtesy of the Geo. A. Breon and Co., Kansas City, Mo.

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1 Loeser, A., *Arch. Exp. Path. Pharm.*, 1930, **147**, 106.

2 Loeser, A., *Arch. Exp. Path. Pharm.*, 1930, **148**, 377.

3 Janssen, S., and Loeser, A., *Arch. Exp. Path. Pharm.*, 1930, **151**, 188.