from the rest of the leech body. A comparable quantitative relationship is found to exist between head and body extracts when tested for another property, *e. g.*, their power to spread in the rabbit skin. 3. The parallelism in the strength of various extracts, as regards both mucolytic activity and spreading power, supports the view that the "mucinase" and the leech spreading factor may be identical. 4. A mucoprotein has been prepared from normal rabbit skin. 5. The viscosity of a skin mucoprotein solution is rapidly and considerably reduced by the action of leech extracts. 6. The effect of leech extracts on the skin mucoprotein *in vitro* suggests that their ability to spread through the skin may be due, at least in part, to their power to cause hydrolysis or depolymerisation of the same or a similar compound *in vivo*.

11304

Effect of Synthetic Vitamin K Compounds on Prothrombin Concentration in Man.

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The effectiveness of preparations of vitamin K in correcting hypoprothrombinemia has been demonstrated by numerous investigators.[1] Following the discovery of the antihemorrhagic activity of certain naphthoquinones,[2] several synthetic crystalline compounds were made available for clinical use in man. Butt, *et al.*,[3, 4] administered 2-methyl-3-hydroxy-1,4-naphthoquinone (phthiocol) in doses of 25 to 50 mg intravenously to 9 patients with obstructive jaundice or disease of the liver; and 1,4-dihydroxy-2-methyl-naphthaldehyde in doses of 5 to 10 mg intravenously to 10 patients with obstructive jaundice. These preparations were effective in shortening the prolonged prothrombin time as calculated by the method of Quick. No untoward reactions were observed.

* Assisted by a grant from the Christine Breon Fund.

1 Quick, A. J., *Am. J. Med. Sci.*, 1940, **199**, 118.

2 Almquist, H. J., and Klose, A. A., *J. Am. Chem. Soc.*, 1939, **61**, 1293.

3 Butt, H. R., Snell, A. M., and Osterberg, A. E., *Proc. Staff Meet. Mayo Clin.*, 1939, **14**, 497.

4 Snell, A. M., and Butt, H. R., *J. A. M. A.*, 1939, **113**, 2056, footnote 41.

We have studied the effectiveness of 3 synthetic naphthoquinones—2-methyl-3-hydroxy-1,4-naphthoquinone (phthiocol), 2-methyl-1,4-naphthoquinone, and 4-amino-2-methyl-naphthol-hydrochloride—in 26 patients, 11 having obstructive jaundice, 11 chronic diseases of the liver, 2 acute diseases of the liver, 1 non-tropical sprue, and 1 gastro-colic fistula. The prothrombin concentration was determined by the method of Quick.[5] All determinations were made in duplicate.

Phthiocol† was administered intravenously in doses of 50 to 300 mg of a 0.5% solution. 4-amino-2-methyl-naphthol-hydrochloride‡ was administered intravenously in doses of 5 to 30 mg of a 0.1% solution. Gelatin capsules containing 0.6 mg of 2-methyl-1,4-naphthoquinone‡ dissolved in corn oil were administered orally in daily doses of 3.6 to 13.2 mg. The total daily dose was divided into 3 equal parts and given after meals. With the exception of Case 25, 100 mg of desoxycholic acid was given with each 1.2 mg of 2-methyl-1,4-naphthoquinone. Bile salts were not used in Case 25 nor given to those patients who received the intravenous preparations.

Results. A. *Obstructive Jaundice.* (Table I.)

The prothrombin concentration before treatment varied from 3% to 45%, and 24 hours after treatment from 60% to 130%. The duration of the significant effect produced by the intravenous compounds lasted in some cases as long as 7 days. The administration of 50 mg phthiocol (Case 10) elevated the prothrombin concentration to 50% in one hour, 60% in 4 hours, and 100% in 24 hours. After the intravenous administration of 10 mg of 4-amino-2-methyl-naphthol-hydrochloride (Case 6), the prothrombin concentration was elevated to 30% in 1 hour, 50% in 4 hours, 75% in 8 hours, and 100% in 24 hours. In Case 1 the prothrombin concentration was maintained at 100% for 3 months on a daily oral dose of 0.6 mg of 2-methyl-1,4-naphthoquinone. The relatively poor response observed in Case 4 may have been due to a severe diarrhea from which this patient suffered. In Case 6 following exploratory laparotomy, a rapid diminution in the prothrombin concentration was observed.

B. *Chronic Diseases of the Liver.* (Table II.)

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

† Made available through the courtesy of the Galen Company, Berkeley, California.

‡ Made available through the courtesy of Parke, Davis and Co., Detroit, Michigan.

TABLE I.
Obstructive Jaundice.

Case No.	Diagnosis	Compound administered	Dosage mg	Prothrombin concentration						
				Before treatment %	On day following institution of treatment					
					1 %	2 %	3 %	4 %	5 %	6 %
1	Metastatic carcinoma of common bile duct	2-methyl-1,4-naphthoquinone	3.6 daily	35	70	—	85	—	90	—
2	Stricture of common bile duct	"	5.4 "	40	75	95	100	—	—	100
3	Stone in common bile duct	"	3.6 "	40	80	90	—	85	100	—
4	Carcinoma of head of pancreas	"	5.4 "	45	60	70	60	—	—	—
5	Metastatic carcinoma of common bile duct	4-amino-2-methyl-naphthol-HCl	10	30	130	—	125	—	130	—
6	Carcinoma of head of pancreas	"	10	25	100	90*	50	55	50	—
7	Stone in common bile duct and multiple pyogenic abscesses of the liver	"	5	3	75	Patient died				
8	Metastatic carcinoma of common bile duct	Phthiocol	50	10	—	95	—	95	—	90
9	Carcinoma of ampulla of Vater	"	50	30	70	—	60	—	50	—
10	Stone in ampulla of gall bladder	"	50	40	100	110	90	90	—	75
11	Metastatic carcinoma of common bile duct	"	50 followed by 50 mg on 2d day	30	65	65	75	—	60	70

*Exploratory laparotomy on this day.

TABLE II.
Chronic Liver Disease.

Case No.	Diagnosis	Compound administered	Dosage mg	Prothrombin concentration: Before treatment %	On day following institution of treatment: 1 %	2 %	3 %	4 %	5 %	6 %
12	Portal cirrhosis	2-methyl-1,4-naphthoquinone	13.2 daily	50	40	—	40	45	40	35
13	" "	"	5.4 "	45	35	40	—	—	—	35
14	Banti's disease	"	5.4 "	30	35	30	—	35	35	—
15	Portal cirrhosis	4-amino-2-methyl-naphthol-HCl	30	50	50	—	50	—	—	50
16	" "	"	30	60	60	60	60	—	—	—
17	" "	"	30	25	50	65	60	50	50	‡
18	Primary carcinoma of the liver	"	10	30	50	45	‡			
19	Portal cirrhosis	Phthiocol	50	35	35	40	—	50	55	65
20	" "	"	50	40	45	45	45	50	40	40
20*	" "	"	300	45	40	35	—	45	—	40
21	Primary carcinoma of the liver	"	50	40	55	—	55	—	65	—
21†	" " " " "	"	50 daily	55	50	65	50	‡		
22	Portal cirrhosis	"	50 followed by 150 mg on third day	55	55	—	55	55	50	—

*21 days after first injection.
†11 " " " "
‡Patient died.

The prothrombin concentration before treatment varied from 25% to 60% and 24 hours after treatment from 35% to 60%. The maximum prothrombin concentration noted in any patient during the 6-day period following the institution of treatment was 65%. There was no significant rise in the prothrombin concentration following treatment in 8 of the 11 patients studied. There was a slight elevation in the prothrombin concentration in 3 cases. These patients were moribund and died within 24 hours of the last prothrombin determination. Large single doses (Cases 20 and 22), and repeated standard daily doses (Case 21) of phthiocol did not elevate the prothrombin concentration beyond that accomplished with a single standard dose. In Case 12, 3.6 mg of 2-methyl-1,4-naphthoquinone was given orally daily for 1½ months, and no significant variation in the prothrombin concentration was observed.

C. *Acute Diseases of the Liver.* Case 23 (acute cholangeitis, acute hepatitis, and *B. coli* septicemia) received oral daily doses of 3.6 mg of 2-methyl-1,4-naphthoquinone. The prothrombin concentration before treatment was 70% and on the following 6 days it was 65%, 50%, 75%, 80%, 80% and 90%. The relative refractivity and the nature of the response of this patient appeared to be conditioned by the severity of the illness. Case 24 (acute yellow atrophy of the liver) received 50 mg of phthiocol intravenously. The prothrombin concentration before treatment and 8 hours later was 20%. This patient died 12 hours after the last test.

D. *Gastrointestinal Diseases.* Case 25 (non-tropical sprue) received daily oral doses of 3.6 mg of 2-methyl-1,4-naphthoquinone Bile salts were not given. The prothrombin concentration before treatment was 30%, and on the following 6 days it was 55%, 75%, 70%, 70%, 70%, and 75%.

Case 26 (gastro-colic fistula) was treated with 4-amino-2-methyl-naphthol-hydrochloride and phthiocol. The prothrombin concentrations were as shown in Table III.

TABLE III.

Days	Prothrombin conc., %	Days	Prothrombin conc., %	Days	Prothrombin conc., %
1*	50	9	60	21§	70
2	75	10	60	22	80
4	55	11	60	23	70
5†	60	12‡	70	25	85
6	55	13	70	28	70
7	75	14	70	36	65
8	75	19	60	43	55

*Single intravenous dose of 10 mg 4-amino-2-methyl-naphthol-hydrochloride.
† " " " " 20 " 4-amino-2-methyl-naphthol-hydrochloride.
‡ " " " " 30 " 4-amino-2-methyl-naphthol-hydrochloride.
§ " " " " 50 " phthiocol.

Summary. Three synthetic vitamin K compounds were administered to 26 patients with hypoprothrombinemia. Following treatment the prothrombin concentration: (1) was markedly elevated in 11 patients with obstructive jaundice, (2) was not elevated in 8 and only slightly elevated in 3 patients with chronic diseases of the liver; (3) was not elevated in 1 patient, and after an initial delay was elevated in 1 patient with acute diseases of the liver; (4) was moderately elevated in 2 patients, one with non-tropical sprue, and the other with gastro-colic fistula. When considered in terms of the dosages employed, there were no significant qualitative differences in the relative effectiveness of the three compounds. No untoward reactions were observed except that the patients receiving large doses of 4-amino-2-methyl-naphthol-hydrochloride complained of slight burning pain at the site of injection.

11305 P

Effect of Posterior Pituitary Extract on Concentration of Urine Secreted during Osmotic Diuresis in Rabbit.*

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When 10% sucrose is infused rapidly into the circulation of anesthetized rabbits, there follows the rapid elimination of a large amount of urine, having a sugar concentration approaching that of the infusion fluid, and almost keeping pace with it as to rate. The injection of posterior pituitary extract during this diuresis results in a further acceleration of rate. This has been shown to be due to an increase in glomerular filtration.[1] If from the calculated filtration, using the amount of sucrose in plasma and urine for making the calculation, there be subtracted the amount of urine actually eliminated, there is obtained a figure which represents the amount of filtrate reabsorbed during the passage through the tubules. During this phase of increase in filtration from pituitary extract, there not only is no decrease in absorption, but there may actually be a slight increase. During this pituitary "diuresis" the sugar content of urine falls

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1 Nelson, E. E., *J. Pharm. Exp. Therap.*, 1934, **52**, 184.