cance of this physiological activator of plasminogen is to keep the urinary system free from the harmful effects of clotted blood.

1. Macfarlane, R. G., and Pilling, J., *Nature*, 1947, v159, 779; Macfarlane, R. G., and Biggs, R., *Blood*, 1948, v3, 1167.

2. Bjerrehuus, I., *Scand. J. Clin. Lab. Invest.*, 1952, v4, 179.

3. Müllertz, S., *Acta Physiol. Scand.*, 1952, v25, 93; Astrup, T. and Müllertz, S., *Arch. Biochem. Biophys.*, 1952, v40, 346.

4. Lassen, M., *Acta Physiol. Scand.*, in press.

5. Christensen, L. R., *J. Gen. Physiol.*, 1945, v28, 303.

6. Astrup, T., and Permin, P. M., *Nature*, 1947, v159, 681; Permin, P. M., *Nature*, 1947, v160, 571; *Acta Physiol. Scand.*, 1950, v21, 159.

7. Tagnon, H. J., and Petermann, M. L., PROC. SOC. EXP. BIOL. AND MED., 1949, v70, 359; Tagnon, H. J., and Palade, G. E., *J. Clin. Invest.*, 1950, v29, 317.

8. Lewis, J. H., and Ferguson, J. H., *J. Clin. Invest.*, 1950, v29, 1059.

9. Bendersky, J., *Arch. pathol. Anat. u. Physiol.*, 1890, v121, 554.

10. Bamberg, K., *Z. exp. Path. Pharmakol.*, 1909, v5, 742.

11. Abderhalden, R., *Ergebn. d. Enzymforschung*, 1950, v11, 1.

12. Abderhalden, E., and Buadze, S., *Fermentforschung*, 1931, v12, 465.

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Effect in Man of a New Indandione Anticoagulant.* (19984)

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Since anticoagulant drugs have become an accepted part of the physician's armamentarium there has been considerable stimulus to develop new drugs which give a better anticoagulant effect with less care and expense (1-4). The new anticoagulant drug which is the subject of this study, is an effort in this direction.

Derivatives of 1, 3 indandione were reported to induce hypoprothrombinemia in animals by Kabat, Stohlmann and Smith(5) and a number of clinical studies(6,7) have dealt with the potential usefulness of phenylindandione. A recent report(8) described the development of diphenylacetyl-1,3-indandione (Dipaxin)† in a survey of new indandiones. Correll *et al.* (8) indicate that Dipaxin possessed the unique ability to induce hypoprothrombinemia in rabbits in a quantity 1/200 the amount of Dicumarol necessary to induce an identical hypoprothrombinemia. This would suggest that Dipaxin is the most potent hypoprothrombinemic drug available. In order to evaluate the basic properties of this new agent in man and to determine if its potency offered any advantages for anticoagulant therapy the present investigation was undertaken.

Experimental. Prothrombin estimations were made by a diluted plasma technic involving a special heparin-oxalate collection fluid (9). The results are reported in per cent of a dried stable plasma standard which was adjusted to the mean of 20 normal individuals. Ac-Globulin was determined by a one-stage method using Ac-Globulin free plasma as substrate(10). About 75 subjects from the wards of the Los Angeles County General Hospital were used in the control studies in which they were given single doses of the drug; they were unselected as to age and sex. The acutely ill and those suffering from hepatic and renal disease or bleeding dyscrasias were omitted. An additional 35 patients who had indication for anticoagulant therapy received Dipaxin in therapeutic doses. Dipaxin (diphenylacetyl-1,3-indandione) was given orally in the form of 1 mg tablets.

Results. Effect of single doses. Plasma

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† A trademarked product furnished by Dr. H. F. Hailman, the Upjohn Co.

TABLE I. Effect of a Single Dose of Dipaxin on Prothrombin Levels in Man.

Dose, mg	Control	Prothrombin level (in %) Days 1*	2	3	4	5	6	7	8	9
.5	120	123	110	125						
1	107	110	103							
2	122	111	105	113						
4	123	105	93	126						
6	129	113	103	103	130					
8	145	106	86	97	93	106				
10	116	85	78	85	85					
15	131	90	79	77	74	67	90	88	100	
20	121	93	55	55	59	71	72	79	84	83

Each line of figures is an avg of results observed in 4 to 8 patients.

* Actually represents the prothrombin level about 14 hr after drug rather than 24 hr, the drug usually being given at 6 PM, the blood sample withdrawn the following 8 AM.

prothrombin levels were measured at daily intervals in patients given single doses of Dipaxin and these results are summarized in Table I. Six patients receiving only 0.5 or 1.0 mg of the anticoagulant did not show a measurable decrease from the initial level. However, the prothrombin of 4 of 5 patients given 2 mg Dipaxin was slightly but significantly reduced, and a hypoprothrombinemia was established in all of 4 patients given 4 mg Dipaxin. With increasing quantities of Dipaxin a more intense hypoprothrombinemia was established which persisted longer. With a dose of 20 mg prothrombin concentrations were reduced to 55% by the second day and they remained at that level until about the fifth day (Table I). A greater variability in individual response was obtained than is evident in Table I because the figures reported are the average response of a number of patients. A moderate to almost complete resistance to Dipaxin was experienced in one individual in the groups receiving 6, 15 and 20 mg.‡ In most human subjects given 8 mg or more a detectable hypoprothrombinemia was present within 12 hours, and it was well established in 24 hours. By 48 hours the maximum effect was almost always attained and the hypoprothrombinemia would plateau at about this level for the duration of its effect.

Effect of vit. K upon Dipaxin hypoprothrombinemia. Correll *et al.*(8) have reported that vit. K_1,§ but not a synthetic vit. K preparation, rapidly restored Dipaxin-induced hypoprothrombinemia in rabbits. Similar studies were performed in human subjects by attempting to inhibit a hypoprothrombinemia before its initiation or to restore to normal a well-established hypoprothrombinemia. Seven patients were given a single dose of 20 mg Dipaxin and simultaneously a dose of 150 mg of a water soluble vit. K analogue, Synkayvite,‖ was given intramuscularly. The vit. K was then given daily in the same dose until normal prothrombin levels were restored. A protocol of the results in one patient who served as his own control is given in Table II as also is the summary of the data on all the patients treated in the same manner. When 100 mg vit. K_1 was given intravenously to 6 patients with well-established hypoprothrombinemia normal prothrombin levels were rapidly reestablished within 24-48 hours. Two illustrative protocols are included in Table III. Ordinarily normal prothrombin levels would not be reattained for 2 to 5 days. Thus it would appear that vit. K readily counteracts the hypoprothrombinemia induced by Dipaxin.

Use of Dipaxin as a therapeutic anticoagulant. In different regimens Dipaxin has been administered to 35 patients to provide anticoagulant therapy for acute myocardial infarction, suspected infarctions, myocardial insufficiency, pulmonary embolism and thrombophlebitis. In several instances heparin was given during the first 24-48 hours until hypoprothrombinemia was established. Initial studies to obtain basal hypoprothrombinemia (15-30% of normal) utilized first and second day doses of 6 and 4 mg; 6 and 6, 8 and 6, 8 and 8, 10 and 0, 10 and 5, and 10 and 6 mg. With a few exceptions, these conservative doses did not satisfy the

‡ Since the present approach consisted of the administration of a fixed dose to all individuals in a group regardless of weight it appeared that a lesser hypoprothrombinemia was induced in obese or very heavy persons.

§ Mephyton, a trademarked product of Merck & Co., Rahway, N. J., which is 2-methyl-3-phytyl-1,4-naphthoquinone.

‖ A trademarked product of Abbott Laboratories, North Chicago, Ill., which is 2-methyl-1,4-naphthohydroquinone diphosphoric ester tetra sodium salt.

TABLE II. Protocol of Effect of Synthetic Vitamin K (Synkayvite) on Hypoprothrombinemia Induced by Dipaxin in Humans.

Drug	Control	Prothrombin levels (%) Days 1‡	2	3	4	5	6	7	8	9	10	11	12
20 mg Dipaxin*	90	100	28	22	21	24	29	45	80	74	78	80	100
" " " + 150 mg vit. K daily (I.M.)*	100	88	68	43	45	72	80	84	94	120			
Same (avg) †	108	64	78	85	112								

* In one patient compared with his own control. † Avg of 7 other patients.
‡ 14 hr ± after drug.

TABLE III. Effect of Dipaxin in Therapeutic Control of Patients Requiring Anticoagulant Therapy.

Patient	Diagnosis		Prothrombin level (in %) Days 1	2‡	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
J.	Arterial occlusion with gangrene		110	100	27	20	16	22	17	21	25	18	25	—	70	—	74	72		
		*	20					2		2			Off therapy							
G.	Myocardial infarction		110	52	22	19	22	25	—	26	38	39	40	34	27	32	20	26	26	
		*	10	5	2	1	2	2	2		3	2	6	3	3	4	2	2	2	
B.	Suspected myocardial infarction		100	49	33	21	21	36	48	52	43	28								
		*	8	6	7	2		3		10			Off therapy							
E.	Thrombophlebitis		120	77	49	31	39	45	43	42	100									
		*	15	10	4	4		6	4	†	Vit. K_1									
N.	Myocardial infarction		80	45	18	24	19	20	20	30	25	18	34	—	26	23	25	26	39	
		*	20	4		2	1	1	1	4	2		3		2	2	2	2	4	
M.	Thrombophlebitis		140	82	50	54	39	36	43	39	44	—	32	21	24	60	43	33	90	140
		*	20	10	5	5	3	3	5	4	4		4	2	0	6	4	3	†	Vit. K_1

* Dipaxin in mg. † Given vit. K_1, 100 mg i.v. ‡ 14 hr ± after drug.

desired goal of lowering the prothrombin below 50% by the 48th hour. However, when 20 mg was given initially to 12 patients, a satisfactory hypoprothrombinemia was established in 9 of these patients[r] within 48 hours. The prothrombin level at 24 hours usually gave no indication of the subsequent 24 hour fall. If, at 48 hours, the level was less than 50%, further therapy was withheld until the prothrombin level started to rise again. At this time, the following empirical program of determining dosage was used: with prothrombin levels of 50-75%, a dose of 8 mg was given; a level of 35-50% the dose was 6 mg; a level of 25-35% the dose was 4 mg; and maintenance of therapeutic levels of 15-25%, the dose was from 2 to 4 mg daily. It must be pointed out that these are generalizations based upon the average. Maintenance doses of Dipaxin were also established in six patients who were well-adjusted on Dicumarol therapy requiring levels of drug of 50-75 mg daily. The hypoprothrombinemia was easily maintained with an average daily dose of 3-5 mg of Dipaxin. Several representative protocols are given in Table III. It is apparent that a well-established hypoprothrombinemia being maintained with Dipaxin is dissipated very slowly so that as many as 3 to 6 days may be required for the return of pre-therapeutic prothrombin levels.

Effect on Ac-Globulin. The plasma Ac-Globulin was not decreased by Dipaxin.

Toxic phenomena. Dipaxin produced no uncontrollable hypoprothrombinemia or bleeding in any patient. Several patients complained of nausea with doses of 20 mg but this

[r] Two of these patients, both with myocardial infarctions and of average weight did not exhibit any hypoprothrombinemia when 20 mg Dipaxin was given. Only after this same dose had been repeated three times at intervals of several days was mild hypoprothrombinemia developed. This relative resistance is as yet not fully understood.

was thought to be attributable to the psychic effect of consuming 20 tablets at one time. No other gastric effects were noted. Observations of other objective criteria as the blood NPN, erythrocyte and leucocyte counts and liver function tests did not indicate that Dipaxin produced any change. No delayed toxic reaction was observed in any of the patients who were examined two months after the therapeutic regimen had been discontinued.

Discussion. Dipaxin has a marked hypoprothrombinemic action in man and even in small doses its effect is relatively prolonged. Its effects appear to be relatively predictable and controllable and the hypoprothrombinemia appears to be corrected readily with vit. K. In the limited studies to date it has not produced any bleeding complications or other toxic phenomena. However, these advantages alone do not of themselves suggest that Dipaxin should supplant existing clinical agents.

The ideal hypoprothrombinemic anticoagulant for clinical use should be given orally. The hypoprothrombinemia should be produced rapidly and in a predictable manner involving simple management. Finally, upon withdrawal of therapy normal prothrombin levels should be rapidly restored. Dicumarol is the most widely used anticoagulant of this type and its disadvantages have not been eliminated by several newer anticoagulants (11,12). Dipaxin is considerably more effective in inducing hypoprothrombinemia than Dicumarol in the rabbit(8) and it appears to be roughly 15 to 25 times more active than Dicumarol in man. The general pattern of the curve of hypoprothrombinemia obtained with Dipaxin in man is very similar to that observed with Dicumarol. However, with the doses given, the rate of onset of hypoprothrombinemia appears to be less rapid as well as is the return to normal after withdrawal of the drug. These disadvantages obviously may weigh heavier than any advantage of being able to administer the agent in smaller doses. On the basis of this preliminary study it appears that Dipaxin should be added to the present list of useful anticoagulants. The present studies in man do not suggest that Dipaxin should replace Dicumarol but it is possible that after further trial in these and other clinics other advantages of this new anticoagulant may be revealed.

Summary. 1. A new anticoagulant, Dipaxin (diphenylacetyl-1,3-indandione), has been studied in man. This agent induces an effective hypoprothrombinemia in single doses of as little as 4 mg. It appears to be more potent on a weight basis than any other known agent. After single doses of 20 mg a marked hypoprothrombinemia was usually evident in 48 hours which persisted from 6 to 10 days. Its effects were usually reproducible and predictable. 2. The drug was successfully administered therapeutically. The recommended starting dose is about 20 mg. A schedule of dosages is given. The maintenance of adequate clinical hypoprothrombinemia was obtained with daily doses of 2 to 4 mg. Hypoprothrombinemia was readily overcome with vit. K, the natural vitamin being more effective than the synthetic. No bleeding or other toxic phenomena were encountered. 3. The advantages and disadvantages of Dipaxin as a clinically useful hypoprothrombinemic anticoagulant are briefly discussed.

1. Russek, H. I., Zohman, B. L., Doerner, A. A., Russek, A. S., and White, L. G., *Circulation,* 1952, v5, 707.

2. Nichol, E. S., *Ann. West. Med. and Surg.,* 1950, v4, 71.

3. Lilly, G. D., and Lee, R. M., *Surgery,* 1949, v26, 957.

4. Martorell, F., *Angiology,* 1952, v3, 185.

5. Kabat, H., Stohlman, E. F., and Smith, M. I., *J. Pharm. Exp. Therap.,* 1944, v80, 160.

6. Preston, F. W., O'Connor, W. R., Thompson, C. E., and Christensen, E. N., *Circulation,* 1952, v6, 515.

7. Blaustein, A., Croce, J. J., Alberian, M., and Richey, N., *Circulation,* 1950, v1, 1195.

8. Correll, J. T., Coleman, L. L., Long, S., and Willy, R. F., PROC. SOC. EXP. BIOL. AND MED., 1952, v80, 139.

9. Ware, A. G., and Stragnell, R., *Am. J. Clin. Path.,* 1952, v22, 791.

10. Lewis, M. L., and Ware, A. G., to be published.

11. Battle, W. D., Capps, R. T., Orth, O. S., and Meyer, O. O., *J. Lab. and Clin. Med.,* 1950, v35, 8.

12. Burke, G. E., and Wright, I. S., *Circulation,* 1951, v3, 164.

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