in attempting to stop the locally cooled heart. This failure is probably related to the use of scopolamine prior to surgery.

Conclusions. 1. Total circulatory occlusion alone does not slow the rate of the normothermic or hypothermic heart. 2. Intracoronary acetylcholine will profoundly decrease the cardiac rate in the occluded heart. The duration of this effect is short at normal body temperatures but quite prolonged during hypothermia (24-27°C). 3. Intracoronary atropine readily reverses the acetylcholine effect on the heart. 4. Cardiac slowing or arrest affords an added protection to the hypothermic heart during total circulatory occlusion.

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Rectal Administration of Warfarin (Coumadin) Sodium. Sodium [3(2-acetonyl-benzyl)-4 hydroxycoumarin]. (22382)

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Considerable experience has accrued with the use of warfarin sodium, the salt of 3-substituted - 4 - hydroxycoumarin, administered orally and intravenously in anticoagulant therapy(1-6). The drug is effective when given by either route and produces a significant prolongation of the prothrombin time in 12 to 16 hours, usually reaching therapeutic levels in 20 to 24 hours. A single dose usually reaches and maintains therapeutic levels in anywhere from 1 to 7 days and achieves a peak effect in 2 days. However, there are occasions when it may be desirable to use another route of administration if feasible. Both methods have their limitations, and rectal administration of the drug would be advantageous under certain circumstances. Experience with the rectal administration of bishydroxycoumarin (Dicumarol) has been limited to that of Meyer and Spooner(7). They reported an occasional significant decrease in the coagulability of the blood which was irregular, however; hence the route proved impractical.

Experience with the use of warfarin (Coumadin) sodium suppositories in 23 patients is the basis for this report. The suppositories contained 100 mg in a polyethylene glycol base.*

Methods. Preliminary studies were performed on 3 groups of patients to determine the latent period and the hours required to achieve the therapeutic level of 25 to 17 seconds (20 to 40% of normal). All prothrombin determinations were made by the one-stage method of Quick with the use of Difco thromboplastin (rabbit brain). Prothrombin times were determined for group A patients 12 and 18 hours after receiving suppositories. Group B patients had prothrombin determinations at 24 and 30 hours, and groups C and D patients at 18 and 24 hours. In each group daily prothrombin times were subsequently measured until they returned to normal or the patient was discharged from the hospital. It soon became apparent that the latent period was more than 12 hours and less than 18 hours, and, consequently, most of the patients had initial prothrombin determinations at 18 and 24 hours. The 19 patients comprising ex-

* Supplied by Endo Pharmaceutical Co., Richmond Hill, through the courtesy of Dr. Samuel M. Gordon.

TABLE I. Effect of a Single 100 mg Warfarin Sodium Suppository.

Patient	Age	Sex	Latent period (hr)	Therapeutic range		Peak effect (days)	Return to normal (days)
				Hr to achieve	Duration (days)		
1A	34	♀	18	24	3	2	6
2	41	♀	18	"	3*	3	4*
3	62	♀	?	36	2	3	6*
4B	43	♂	?	24	2	2	4
5	63	♂	?	"	—	—	—
6C	16	♀	24	"	2	2	3*
7	18	♀	18	"	2	2	4*
8	41	♀	18	"	4	2	6
9	49	♀	18	> "	1	2	6
10	54	♀	24	> "	3*	4	4*
11	56	♀	18	"	3	2	4*
12	61	♀	18	> "	1	2	4
13	72	♀	18	"	6	3	8*
14	27	♂	18	"	2	2	4
15	32	♂	18	"	1	1	4
16	32	♂	18	> "	1	2	3*
17	38	♂	18	"	5	3	6*
18	42	♂	18	> "	3	3	4*
19	53	♂	18	18	3	2	6
20D	63	♀	18	24	2	2	?
21	76	♀	18	"	2	2	?
22	48	♂	18	18	3	2	?
23	60	♂	18	"	?	?(2)	?

* These patients were all discharged before the prothrombin times had returned to normal. In patients 2A and 10C prothrombin times were still in the therapeutic range.

perimental groups A, B, and C had diseases ranging from asthma to muscular dystrophy. Three patients had diabetes mellitus. In 6, the primary diagnosis was that of a functional illness. All these patients were in relatively good physical condition and had no evidence of renal or hepatic disease. The group D patients were those in whom a maintenance oral dose of warfarin sodium was subsequently continued. Two of these patients had intracranial thromboses, one a peripheral thrombophlebitis, and one an acute myocardial infarction. No data are available on the time required for the prothrombin times to return to normal in these patients.

Results. The results for the individual patients are shown in Table I.

The latent period was less than 18 hours in most cases. Initial prothrombin determinations were made on the 2 patients in group B at 24 hours, at which time the therapeutic range had already been obtained. Patient 3-A exhibited no alteration in the prothrombin time in 12 and 18 hours; however, when the prothrombin time was next determined at 36 hours, the therapeutic level had been reached. In 2 of the remaining 20 patients there was a 24-hour latent period.

A therapeutic level of 20 to 40% prothrombin was achieved in the majority of patients within 24 hours. In 5 of the 6 patients requiring more than 24 hours to reach this level, the prothrombin concentration was 50% or less. Patients 1-A and 2-A did not have prothrombin determinations at 24 hours; however, their prothrombin times at 18 hours were elevated to such a degree that it may be assumed that a therapeutic level was reached in 24 hours. In 3 patients the therapeutic range was achieved in 18 hours; 2 of these patients were acutely ill. Once reached, the therapeutic level was usually maintained for 2 to 3 days, the same duration as that following a single oral or intravenous dose of warfarin sodium.

The peak effect was obtained in about 2⅓ days. In only one instance (15-C) did it occur within 24 hours. This suggests the advisability of giving the first maintenance dose after 48 hours, provided the prothrombin concentration is not less than 20%.

The data presented do not suggest that age,

sex, or weight has any marked effect on the patient's response to the drug. These patients weighed from 38½ to 100 kg. Three patients (1-A, 9-C, and 19-C) weighed less than 45 kg, and in none of these was the prothrombin time excessively prolonged (maximum prolongation 26 seconds or 19%). It is advised, however, that if the patient weighs less than 45-50 kg the initial dose for routine use should be 1 mg/kg, with earlier adjustments being made in maintenance doses as indicated. Three patients (11-C, 12-C, and 15-C) weighed more than 80 kg and demonstrated a satisfactory response to the drug. The usual precautions against giving large initial doses in the acutely and chronically ill, in the early postoperative period and in the presence of significant liver (including acute congestion) and/or renal disease, must be observed with suppositories as well as other modes of administration. Patient 23-D was one in whom more caution in initiating therapy should have been taken. However, patient 22-D had an acute myocardial infarction and associated acute hepatic engorgement without an excessive response to the 100-mg suppository.

Vit. K_1 was administered to 2 patients. In patient 5-B, 50 mg of K_1 (Mephyton+) was given intravenously 30 hours after the suppository (prothrombin time 23 sec.), and a normal prothrombin time was observed 18 hours later. This was done because the patient was to have a bronchoscopic examination the following day. Forty-two hours after patient 23-D received the suppository, the prothrombin time was 80 seconds. Twenty milligrams of Mephyton+ administered intravenously resulted in a prothrombin time of 13 seconds (control, 12 seconds) 24 hours later. Interestingly, although the prothrombin concentration was less than 4%, no side effects occurred, and microscopic hematuria was not present. In no other instance was the prothrombin concentration brought below 10%; in only 3 other patients was it reduced to less than 15%. Although urinalyses were not routinely done, in no patient was hematuria observed.

We have not attempted to maintain any patient on rectally administered warfarin sodium, since the oral route has proved satisfactory. However, reasonably accurate divisions of the suppositories could be prepared for this purpose.

Discrepancies and technical difficulties occurred in 5 patients, 3 of whom are not included in this series. In 2 of these, defecation occurred soon after the suppository was inserted (1 within 15 minutes; the exact time of the other unknown). The prothrombin time was unaltered in the former patient and showed only a small and transitory change in the other. In the third patient, the suppository was very soft and incompletely inserted, and only a small and transitory prothrombin alteration ensued. In patients 9-C and 19-C a similar incident fortuitously occurred. In these cases, however, time permitted a second trial with a suppository that had been kept cool and firm in the refrigerator until just prior to use. As recorded in the table, the results in these re-trials were satisfactory. Accordingly, therefore, the condition of the rectum and the suppository, prior to the latter's administration, must be considered carefully.

Discussion. It appears that warfarin sodium in a polyethylene glycol base as a rectal suppository is absorbed with sufficient regularity so that its use is a practical method for administering a coumarin anticoagulant to lower the prothrombin to therapeutic levels. It is of particular value, obviously, in the treatment of a patient who is incapable of taking oral medication, for example, after cerebral thrombosis, or when intravenous administration is difficult or undesirable. Warfarin sodium suppositories make a worthwhile addition to our therapeutic armamentarium. It is possible that suppositories of 75 mg and less might be useful in allowing greater flexibility for this route of administration. It is our plan to test these smaller doses when they are made available.

Summary. Experience with rectal use of warfarin sodium in 23 patients has been recorded. In contrast to Dicumarol, the rectal administration of warfarin sodium is consistently effective. If certain precautions are taken, the rectal route appears to be as reliable as the oral or intravenous, and in some

circumstances it may be the route of choice.

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Radiophosphorus Uptake by Normal, Hyperplastic, and Tumorous Mammary Tissues of Mice.* (22383)

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The hyperplastic nodules of the mammary gland of high-cancer strains of mice have been the object of limited investigation over the past 15 years(1). In general, most of the available evidence points to these nodules as potential sites of tumor formation (hence preneoplastic), although it is important to emphasize that there seems to be a "family" of structures of varying morphology, and possibly of varying growth potential, which are described as hyperplastic nodules. As part of a comprehensive study of these nodules in the C3H/He mouse, we have been attempting to characterize them definitively, both morphologically and physiologically. The present study is concerned with an investigation of a general metabolic characteristic of hyperplastic nodules, based upon their uptake of radiophosphate (P^{32}). Phosphate, playing a key role in cellular metabolism, enters a wide variety of compounds within the cell, and to some extent the rate of incorporation of phosphorus may be used as an index of metabolic activity. In general, the rate of accumulation of phosphate is greater in actively metabolizing and growing cells and tissues(2).

The experiments reported here were designed to answer two questions: (a) Can normal, hyperplastic, and tumorous mammary tissues selected from a single mouse on the basis of their morphologic characteristics also be distinguished on the basis of their P^{32} uptake? (b) Can the relative P^{32} uptake of normal, hyperplastic, and tumorous mammary tissues be altered by varying the endocrine state of the mouse? The results obtained allow us to describe the hyperplastic nodule as a structure metabolically intermediate, as indicated by P^{32} uptake, between normal mammary tissue and frank mammary tumor.

Materials and methods. 81 multiparous female mice of the C3H/He strain, 8-11 months of age, were used in these studies. All mice bore spontaneous mammary tumors of various sizes. They were separated into groups and treated as follows (Table I): (1) 12 normal (untreated, non-pregnant); (2) 15 pregnant (14th-18th day); (3) 14 bilaterally ovariectomized (2 weeks before sacrifice); (4) 16 estrogen-treated (implanted with 2-3 mg pellets of estradiol 2 weeks before sacrifice); (5) 12 cortisol-treated (injected every 2 days with 0.5 mg hydrocortisone acetate in saline suspension beginning 2 weeks before sacrifice); (6) 12 androgen-treated (im-

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