tion and the finding mentioned before of a horse with completely normal thrombin generation, together with the reports of other authors indicate that horse, like man, presents various types of hemophilioid diseases. P. Barkhan (personal communication) has also observed different defects in the thromboplastin system of the various samples of horse plasma.

Summary. 1. The delayed thrombin generation in samples of horse plasma was made normal by 1) addition of normal human plasma, or 2) addition of reabsorbed heated human serum, or 3) addition of washed human or horse platelets, or 4) freezing of the horse plasma with its normal content of platelets. 2. These results indicate that the clotting defect of the horse plasma investigated is caused by lack of a factor similar to the Hageman factor. 3. Blood platelets, after washing or freezing, apparently substitute for the effect of the lacking plasma factor. 4. The coagulation defects in horse plasma apparently reflect various types of hemophilioid deficiencies.

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Comparison of Duration of Action of Progesterone and 17-α-Hydroxyprogesterone-17-n-Caproate. (23100)

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17-α-Hydroxyprogesterone(1), a progestationally ineffectual compound(2), has been esterified to yield 17-α-hydroxyprogesterone-17-n-caproate (HPC), a potent progestational substance(3). Junkmann(3) also demonstrated that when HPC was administered to rabbits in an ethyl lactate-castor oil vehicle, the progestational action was more prolonged than when progesterone was given in the same vehicle.

The present study was designed to verify Junkmann's findings and to determine the duration of action of HPC in benzyl benzoate-sesame oil, an oily vehicle more desirable for human therapy. Limited success has been reported previously by Plotz(4) in prolonging the activity of progesterone by vehicular alteration.

Materials and methods. Immature virgin female Flemish rabbits were primed with daily subcutaneous injections of 5 μg of estradiol in 0.5 cc of sesame oil for 6 days. Treatment was initiated on the morning of the seventh

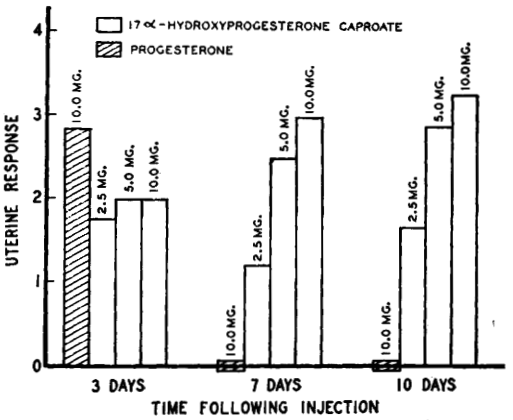

FIG. 1. Effect of progesterone and 17-α-hydroxyprogesterone caproate in ethyl lactate-castor oil on progestational changes in rabbit uterus (single subcutaneous inj).

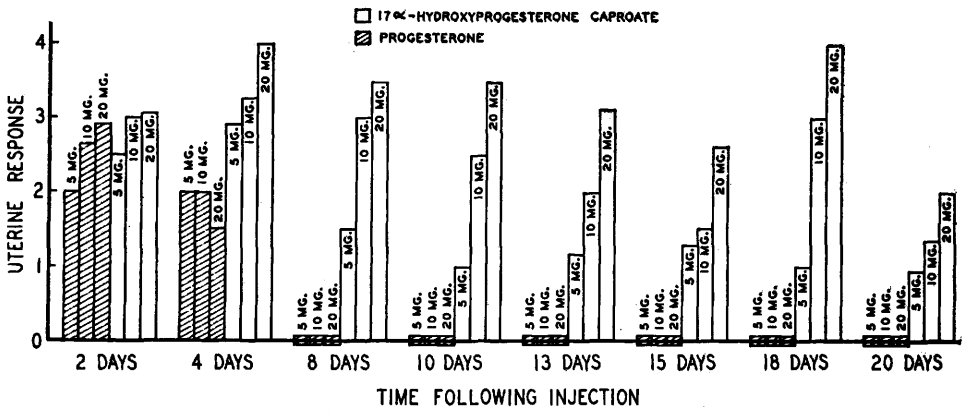

FIG. 2. Effect of progesterone and 17-α-hydroxyprogesterone caproate in benzyl benzoate-sesame oil on progestational changes in rabbit uterus (single subcutaneous inj).

day. In one study 10 mg of progesterone, or 2.5, 5 or 10 mg of HPC in ethyl lactate-castor oil,* or the vehicle alone was given in 1 cc as a single subcutaneous injection. Estradiol administration was continued daily at 0.5 μg for the duration of the study. In a second study an identical procedure was followed to evaluate benzyl benzoate-sesame oil† as a vehicle, but in this study 5, 10 or 20 mg of progesterone and similar doses of HPC‡ were administered. Groups consisting of 4 rabbits were sacrificed at intervals ranging from 2 to 20 days following the injection of the steroids, and vehicle-treated control animals received similar necropsy treatment. A uterine segment from each rabbit was fixed in Bouin's fluid and examined microscopically after hematoxylin-eosin staining. Simple estrogenic proliferation of the uterine mucosa was assigned an arbitrary value of 0, while the degree of progestational hyperplasia of the endometrium was estimated on a +1 to +4 basis(5).

Results. The progestational effect of a single progesterone injection was more pronounced at 3 days following administration than was the effect of HPC, when ethyl lactate-castor oil was used as the vehicle. Although progestational stimulation could not be detected 7 days after progesterone administration, the uterine response to HPC was greater at 7 days than at 3 days and was even more marked at 10 days. These data are in agreement with those of Junkmann(3), who reported similar activity after a single injection of HPC in the same oily vehicle, with maintenance of this effect beyond 13 days (Fig. 1). Only an estrogenic hypertrophy was seen in the control animals receiving vehicle alone.

When a single injection of progesterone was given in benzyl benzoate-sesame oil the uterine response was maximal at 2 days but showed signs of waning at 4 days, whereas the effect of HPC in this vehicle reached a peak at 4 days. Eight days following administration of progesterone in benzyl benzoate-sesame oil no progestational response was noted, while the response to HPC remained high. Thereafter, the progestational effect of HPC declined but was still apparent at 20 days (Fig. 2). Again no progestational response was seen in the vehicle-tested controls.

In comparing the data from Fig. 2 with those in Fig. 1 and those reported by Junkmann(3) it is apparent that an earlier peak response to HPC is obtained with benzyl benzoate-sesame oil than with ethyl lactate-castor oil. On the other hand, duration of activity of HPC in both vehicles is approximately the same.

* Composition in final solution: ethyl lactate 458 mg/cc; castor oil 424 mg/cc.

† 30% benzyl benzoate v/v; 70% sesame oil v/v; 0.5% chlorobutanol as a preservative.

‡ As Delalutin (Squibb), containing 125 mg of HPC per cc of 30% benzyl benzoate, 70% sesame oil and 0.5% chlorobutanol.

Similar studies of shorter duration were also carried out to evaluate the effectiveness of 17-α-hydroxyprogesterone as a progestational agent. A +2 progestational effect was noted with 50 mg of this compound, whereas no effect was demonstrated at 25 mg. This indicates that 17-α-hydroxyprogesterone is approximately 1/100 as active as progesterone *per se*.

Summary. 1. 17-α-hydroxyprogesterone-17-n-caproate (HPC) is an active progestational compound possessing prolonged activity, in confirmation of Junkmann(3). 2. Modification of the oily vehicle has resulted in an earlier peak response to HPC in virgin female rabbits, without affecting duration of action. 3. It has been verified that 17-α-hydroxyprogesterone is an extremely weak progestational agent.

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