were restricted to the epithelial germ regions of X-irradiated telogen hair follicles in mice supports the former view. Although it is quite possible that species differences exist in this regard, radiation technics utilized in our work afford a means for critical analysis of these apparently discordant viewpoints.

Summary. "Dopa oxidase" activity was absent in melanocytes of telogen hair follicles of non-irradiated mice. Following partial-body exposure to 200 r/week of X-radiation for 3 or 4 weeks, numerous dopa reactive dendritic cells were observed in the epithelial germ regions of irradiated quiescent hair follicles. Cells of the dermal papillae in irradiated and non-irradiated telogen hair follicles failed to exhibit "dopa oxidase" activity. The results thus support the view that melanocytes normally are restricted to the epithelial germ regions of hair follicles during telogen stage of hair growth cycle.

1. Kukita, A., *J. Invest. Dermatol.*, 1957, v28, 273.

2. Quevedo, W. C., Jr., Grahn, D., *Radiation Res.*, 1958, v8, 254.

3. Chase, H. B., *J. Morphol.*, 1949, v84, 57.

4. Chase, H. B., Montagna, W., Malone, J. D., *Anat. Rec.*, 1953, v116, 75.

5. Becker, S. W., *J. Invest. Dermatol.*, 1942, v5, 463.

6. Flesch, P., Rothman, S., *Science*, 1948, v108, 505.

7. Chase, H. B., Rauch, H., Smith, V. W., *Physiol. Zool.*, 1951, v24, 1.

8. Taylor, A. C., *J. Exp. Zool.*, 1949, v110, 77.

9. Danneel, R., Weissenfels, N., *Biol. Zbl.*, 1953, v72, 630.

10. Weissenfels, N., *ibid.*, 1954, v73, 399.

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Rabbit Endometrial Response to Intravenously Administered Progesterone. (24489)

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Spectrophotometric observations concerned with intravenously administered progesterone have revealed rapid clearance of the hormone from the ether soluble fraction of rabbit and human blood serum(1,2). The results were constant whether the vehicle in which progesterone was administered was saline, ethanol, propylene glycol or a mixture of ethyl carbamide, ethyl urethane and propylene glycol.* It has been suggested that disappearance of progesterone from the ether soluble fraction of blood serum resulted from tissue storage of this substance and continuing biological activity potential. It is, however, equally possible that rapid clearance of progesterone from blood serum resulted from rapid metabolism of the hormone. These experiments were planned to establish the biologic effectiveness of intravenous progesterone. Duration and intensity of tissue response to intravenous progesterone would indicate degree of storage and rate of destruction of the hormone.

Methods. Immature female rabbits, average weight 1200 g, were injected with 100 I.U. of estrogenic substance a day for 6 days.† Twenty-four hours after last injection of estrogen, intravenous progesterone as Proluton I. V., was administered into marginal ear vein of the rabbit. Twenty-four to 168 hours following intravenous injection, the rabbits were sacrificed. Ovaries were inspected and biopsied for evidence of activity. Uteri were removed and portions prepared for microscopic study. The Corner-Allen(3) progestational proliferation response and endometrial epithelial mitotic counts were utilized as evidence of luteoid activity within the endo-

* Progesterone dissolved in ethyl carbamide, ethyl urethane and propylene glycol was generously supplied by Schering, A. G. of Berlin, Germany as PROLUTON I.V.

† The estrogenic substance was generously supplied by Parke-Davis as THEELIN.

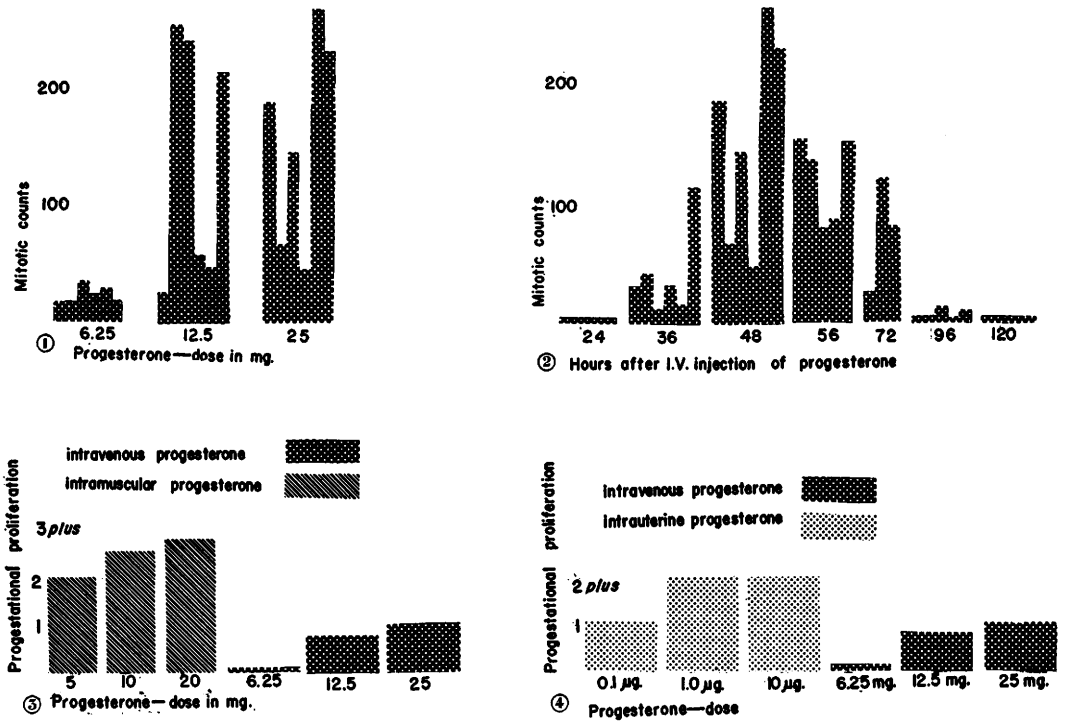

FIG. 1. Epithelial mitotic figure count per total cross section of the rabbit endometrium at 48 hr after a single intrav. inj. of progesterone.

FIG. 2. Epithelial mitotic figure count per total cross section of rabbit uterus induced by single intrav. inj. of progesterone.

FIG. 3. Comparison of Corner-Allen progestational proliferation induced in rabbit uterus by single intramusc. and intrav. inj. of progesterone; 48 hr after administration.

FIG. 4. Comparison of Corner-Allen progestational proliferation induced in rabbit uterus by single intrauterine and intrav. inj. of progesterone; 48 hr after administration.

metrium. Proliferation responses were recorded from 1+ to 4+. Mitotic counts are listed as total counts/cross section.

Results. Previous studies have shown that intravenous dose of 25 mg of progesterone, in rabbits of the size used, will produce saturation of rabbit blood serum with the hormone (2). The saturation concentration of 30 µg of progesterone/ml of blood serum is greater than the physiologic level of the hormone in the rabbit. Consequently, smaller than saturation doses of progesterone were administered in early phases of the study. Doses of 1 mg, 2 mg, and 5 mg produced no evidence of progestational activity either when judged by the Corner-Allen progestational proliferation index or the more sensitive epithelial mitotic count.

Total dosage levels of 6.25 mg, 12.5 mg and 25 mg of progesterone were used. Mitotic counts observed in animals receiving these dosage levels are shown in Fig. 1. The maximum mitotic figure count is obtained with 12.5 mg of progesterone. Doubling of this to the saturation dose makes no apparent difference in total mitotic figure counts. Injection of 6.25 mg of progesterone yields a minimum epithelial mitotic count.

The Corner-Allen progestational proliferation response of 32 test animals with saturation dose of 25 mg of intravenous progesterone was noted. The maximum observed response of 1+ progestational proliferation became apparent 48 hours after injection and remained so through 144 hours after injection. At 168 hours following intravenous administration of progesterone, the endometrium had returned to a resting state.

Mitotic figure counts in the same group of animals are illustrated in Fig. 2. The first evidence of increased endometrial mitotic activity was found at 36 hours after injection.

Maximum activity was found at 48 hours after intravenous injection with a gradual return to control levels at 96 hours after intravenous injection of progesterone.

In Fig. 3 progestational proliferation induced by single intramuscular injection of progesterone(4) is compared to proliferation following intravenous progesterone. These comparisons are at 48 hours after administration of the hormone. Saturation doses of intravenous progesterone are incapable of producing progestational proliferation of rabbit endometrium to a degree obtained with lesser amounts of intramuscular progesterone. Twenty-five mg doses of intravenous progesterone were capable of inducing an average progestational proliferation response in 6 animals to slightly above 1+. Five mg of intramuscular progesterone produced an average progestational proliferation response in the rabbit uterus of 2+ at 48 hours.

A final comparison of the efficacy of intravenous progesterone on rabbit endometrium utilizing the Corner-Allen progestational proliferation index is shown in Fig. 4. Here the effectiveness of intrauterine progesterone as compared to intravenous progesterone is shown. It was necessary to administer a saturation dose of 25 mg of intravenous progesterone to obtain the same progestational proliferation response to 1+ as found with 0.1 μg of intrauterine progesterone. It should be noted that maximum progestational proliferation of 4+ is rarely obtained with even larger doses of progesterone at 48 hours. Although the epithelial mitotic count is maximum at this point, the progestational proliferation response may require 72 to 96 hours for full development.

Discussion. Previously reported comparisons of relative efficacy of the several methods of progesterone administration have established that intramuscular administration of the hormone is approximately one thousand times(5,6) less effective in producing progestional proliferation than is intrauterine administration of progesterone. This marked difference in efficacy is the presumed result of inactivation of the hormone prior to its hematogenous transport to the endometrium. This biologic inactivation is delayed when the hormone is administered topically to the target tissue.

The current studies show that intravenous administration of progesterone is approximately twenty-five thousand times less effective than intrauterine administration of the hormone. Intravenous administration of the hormone is approximately 25 times less effective than the intramuscular route.

These comparisons establish the lessened biologic effectiveness of intravenous progesterone. Differences in effectiveness are usually the result of more rapid biologic inactivation either through absorption differences or circulation differences. Absorption of intravenously administered progesterone is instantaneous. Its lessened effectiveness is presumed to be the result of circulation of the hormone through the inactivating tissues prior to its arrival at the target tissue.

It appears that the previously reported rapid clearance of progesterone from the blood serum is not the result of tissue storage and continuing biologic effectiveness. It is the result of the rapid metabolism of the hormone and consequent lessened biologic effectiveness.

Summary. The biologic effectiveness of intravenously administered progesterone is approximately 25,000 times less than intrauterine administration of progesterone and 25 times less effective than the intramuscular route.

1. Haskins, A. L., Jr., PROC. SOC. EXP. BIOL. AND MED., 1950, v73, 439.

2. Rappoport, W. J., Goldstein, B., Haskins, A. L., *Obstet. and Gyn.*, 1958, v11, 49.

3. Corner, G. W., Allen, W. M., *Am. J. Physiol.*, 1929, v88, 326.

4. Kessler, W. B., Borman, A., PROC. SOC. EXP. BIOL. AND MED., 1957, v94, 820.

5. McGinty, D. A., Anderson, L. P., McCullough, H. B., *Endocrinology*, 1939, v24, 829.

6. Haskins, A. L., Jr., PROC. SOC. EXP. BIOL. AND MED., 1939, v42, 624.

Received October 6, 1958. P.S.E.B.M., 1958, v99.