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Absorption of Estradiol and its Esters from Subcutaneously Implanted Tablets in the Guinea Pig.*

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Deanesly and Parkes made use of their ingenious method of subcutaneously implanted tablets to study the question of the rate of hormone absorption. Emmens[1] has recently communicated important results on the comparative rate of absorption of estrogens and androgens and their esters in the rat.

In the course of our work on the fibromatogenic action of a prolonged treatment with estrogens in the guinea pig, we have applied the method of Deanesly and Parkes with most satisfactory results.[2] In this way, we also became interested in the rate of absorption of different hormones. In the present paper, we shall give the results obtained in 52 female guinea pigs with 3 estrogens: free estradiol, dipropionate of estradiol and 17-caprylate of estradiol. Our results (Table I) which confirm those of Emmens, present new relevant details and render it possible to compare the rate of absorption in two different species.

The range of weight of the disc-shaped tablets, or their fragments, was the same in all 3 groups, and range of surface was very likely the same. This is important because absorption is related to the surface. There was considerable scattering of percentage of absorption in each of these three groups (fifth row of Table I and Fig. 1), but it is remarkable that the range of scattering of percentage of absorption coincided with the range of weight of tablets in the respective group (fourth row of Table I, figures in parentheses). The smaller or the thinner a tablet, the greater the surface in relation to the weight and the greater also the percentage of absorption.

The average absorption of estradiol was 20% in 73 days, or 0.28% per day (sixth row of Table I). The caprylate tablets lost 6.1% in 74 days or 0.08% per day. The corresponding figures of Emmens

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1 Emmens, C. W., *Endocrinology*, 1941, **28**, 633.

2 Lipschütz, A., and Vargas, L., Jr., *The Lancet*, 1939, **1**, 1313.

TABLE I.

(1)	(2)	(3)	(4)	(5)		(6)	Avg. absorption calculated as *free* estradiol		
Group	No. of animals	Duration of exp. days	Avg wt of tablet, mg	Avg absorption mg	Avg absorption %	Avg absorption per day, %	Total, mg	Per day, γ	Per day per mm², γ
Free estradiol (series XXVII, No. 21-37)	17 (310-740 g)*	73	21.2 (12-34)*	4.25 (1.7-6.9)*	20.2 (10-38)*	.28	4.25	58	1.2-1.4
Dipropionate of estradiol (series XXX, No. 1-21)	16 (315-855 g)	70	16.9 (12-28)	5.49 (3.2-7.6)	32.5 (23-46)	.46	3.93	56	1.1-1.6
17-caprylate of estradiol (series XXXI, No. 2-25)	19 (430-725 g)	74	19.2 (14-27)	1.21 (0.8-1.7)	6.1 (4.6-7.8)	.08	0.83	11	0.2

*Figures in parentheses indicate range.

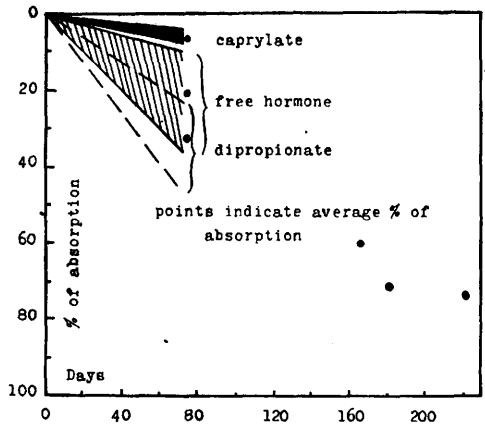

FIG. 1.

Percentage of absorption from subcutaneously implanted tablets of estradiol, and dipropionate and 17-caprylate of estradiol in 52 castrate female guinea pigs. Scattering curves of percentage of absorption and average percentage of absorption in the course of 70 to 74 days. Percentage absorption of dipropionate in three females in the course of 168 to 222 days reaching 74%.

in the rat were 0.26 and 0.08% per day in 91 days. Though there were differences in weight and shape of the tablets used in guinea pigs and rats, the rate of absorption coincided in the two species.

The average percentage of absorption of the dipropionic ester was 32% in 70 days or 0.46% per day in our guinea pigs, and 0.3% in the rat.[1] Though there is a considerable gap between these two figures, both indicate that the dipropionic ester of estradiol behaved differently as to its rate of absorption from the caprylate and, as shown by Emmens, also from the remaining known esters.

The tablets of estradiol and its dipropionate were disc-shaped. The diameter was 7 mm, and thickness was about 1 mm. A central notch allowed for easy breakage into 2 more or less equal halves. The weight of one half was 25 mg, and the surface was somewhat less than 50 mm^2. Since several fragments were smaller or thinner (average weight only 21 and 17 mg respectively instead of 25, see Table I), the average surface must have been less than 50 mm^2 but certainly no less than 42 and 34 mm^2 respectively (2 mm^2 per 1 mg). The diameter of tablets of caprylate was 5.25 mm and the thickness about 1 mm. The surface of a tablet of 20 mg was somewhat more than 50 mm^2. In the last row of Table I, absorption is calculated per square millimeter and day; even when allowance was made for error in the calculation of the average surface (42 to 50 mm^2 for estradiol, 34 to 50 mm^2 for dipropionate) the results were not altered significantly. An average of 1.2 to 1.4 γ of estradiol was

absorbed daily per square millimeter of a tablet of free estradiol. A similar quantity of estradiol was available daily from one square millimeter of a tablet of dipropionate (1.1 to 1.6 γ), *i. e.*, the rate of absorption was, in our experiments, so greatly enhanced by combination with propionic acid that a tablet of dipropionate gave up per day and per square millimeter the same number of molecules of estradiol as a tablet of the free hormone. On the contrary, five to six times less was absorbed daily per square millimeter of a tablet of caprylate. This would explain why dipropionate of estradiol is so similar to estradiol in the estrous test in the rat whereas other esters are much less estrogenic.[3]

Summary. The rate of absorption of free estradiol, and dipropionate and caprylate of estradiol from subcutaneously implanted tablets has been studied in the *guinea pig*. The average percentage absorption per day was very similar to that found by Emmens in the *rat*. Average percentage absorption from 17-caprylate tablets was 3 times less than that from tablets of free estradiol. On the contrary, average percentage of absorption from dipropionate tablets was greater than from estradiol tablets. Combination of estradiol with two molecules of propionic acid so greatly enhanced the percentage absorption in the guinea pig that the number of molecules of estradiol available from one square millimeter of a dipropionate tablet became similar to that available from one square millimeter of a tablet of the free hormone.

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Conjunctive Tumorigenesis Elicited by Different Artificial Estrogens.*†

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As with *natural* follicular hormones, free or esterified, a prolonged treatment with an *artificial* estrogen, such as stilbestrol, will induce

3 Miescher, K., Scholz, C., and Tschopp, E., *Biochem. J.*, 1938, **32**, 725.

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