

The 17-Monocaprylic Ester of Estradiol—A Highly Active Tumorigenic Estrogen.*

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The 17-caprylate of α -estradiol has been shown to be more tumorigenic than the monobenzoate and dipropionate esters.^{1, 2} This finding has led us to examine quantitatively how greatly the tumorigenic action of estradiol is enhanced when it is esterified with caprylic acid. When 200 γ of free estradiol are injected thrice weekly in the course of 3 months into a castrate female guinea pig, there is little or no fibrous reaction: 400 γ per injection, or a total of 16 to 20 mg of free estradiol, are necessary to induce in a 3-month period a definite tumoral reaction.³ We therefore investigated the amount of the caprylic acid ester necessary to cause a similar reaction.

When 1 γ of estradiol given as the monobenzoate or dipropionate ester† was injected thrice weekly (a total of 37 to 38 γ in the course of 3 months) no fibroids, tumoral seed on the spleen, or fibrous strands in the mesentery were visible to the naked eye. Microscopical investigation revealed minute mesometrial fibroids in one out of 10 animals (Fig. 1).

Of 17 animals which received the caprylic acid ester, uterine tumors visible to the naked eye were found in 2 which received during a 3-month period 18 and 41 injections of 1 γ respectively. No stress can be laid as yet on these 2 findings since the microscopical structure of these 2 tumors was unlike the experimental fibroid in

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¹ Jedlicky, A., Lipschütz, A., and Vargas, L., Jr., *C. R. Soc. Biol. (Paris)*, 1939, **130**, 1466.

² Lipschütz, A., Belloio, P., Chaume, J., and Vargas, L., Jr., *Proc. Soc. Exp. Biol. and Med.*, 1941, **46**, 164.

³ Lipschütz, A., Rodríguez, F., and Vargas, L., Jr., *C. R. Soc. Biol. (Paris)*, 1939, **130**, 939.

† 1 γ of estradiol is contained in 1.38 γ of the monobenzoate, in 1.41 γ of the dipropionate and in 1.46 γ of the monocaprylate.

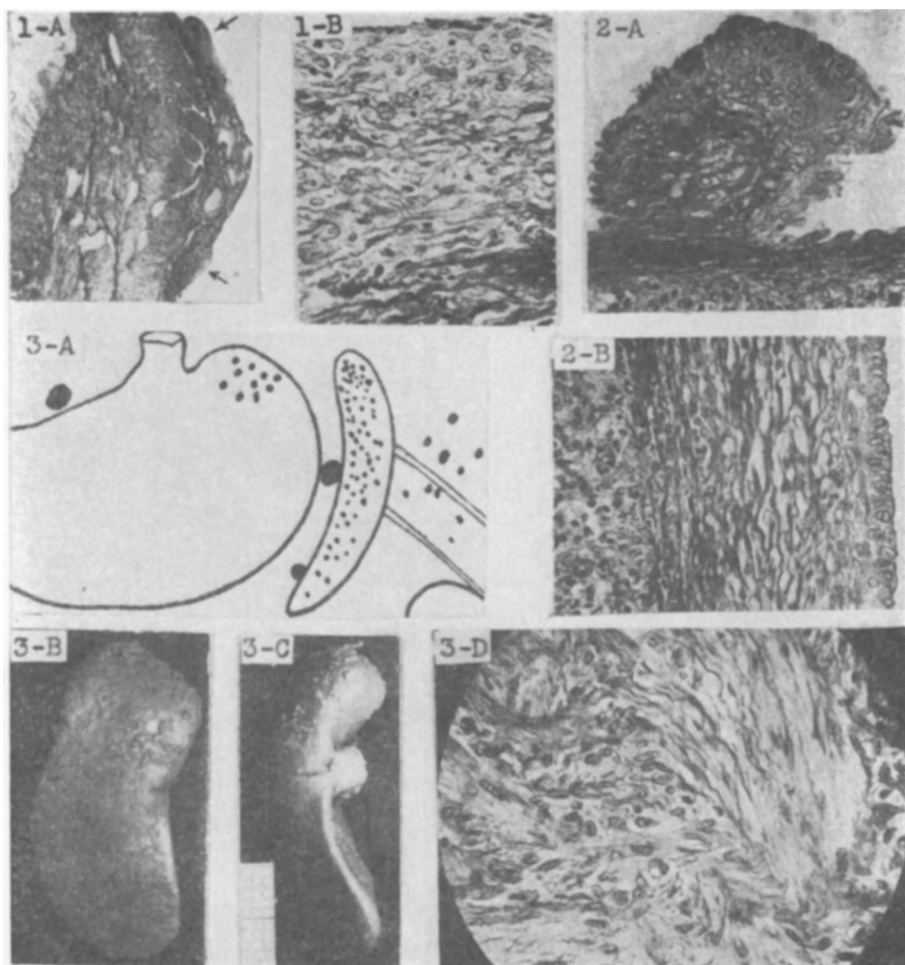


FIG. 1. Two minute fibroids near the mesometrium, discovered only at microscopical examination. Animal received 37 injections of 1 γ of estradiol (monobenzoate) in the course of 85 days. A. $\times 10$. Arrows indicate fibroids. B. $\times 200$. Peripheral part of minute fibroid. Note spindle shaped cells (fibroblasts?) and flattened cells on the surface. Fibrous tissue nearer to the center (VI, 5).

FIG. 2. A. $\times 200$. Small excrecence on the spleen produced by 10 injections of 1 γ of estradiol (in form of the 17-caprylate) in the course of 21 days. Cells rich in protoplasm at the periphery and sclerotic tissue nearer to the center. Capsule of the spleen thickened. Cells of peritoneal mesothelium increased. B. $\times 200$. Same animal. Fibrous patch of greater extension on the spleen. Cells rich in protoplasm at the periphery, and below them, spindle shaped cells separated from one another by thick fibers (XVII, 12-B).

FIG. 3. A. Diagram to show localization and size of fibroids produced by 38 injections of 2 γ of estradiol (in form of the 17-caprylate) in the course of 88 days. Splenic and gastric fibroids. Tumoral seed on spleen, stomach and abdominal wall. B and C. $\times 1.4$. Dorsal view of the spleen of the same animal, with tumoral seed and tumor in the hilum (XXI, 13). D. $\times 200$. Fibroid in the hilum of the spleen. Abundance of cells, fibrous strands and probably also smooth muscle fibers (XXI, 11).

TABLE I.
Ten Castrate Female Guinea Pigs Treated with Subcutaneous Injections of the
17-caprylate of Estradiol During 3 Months.

Quantity* of estradiol inj. thrice weekly γ	No. of inj.	Total No. animals	No. of animals with some kind of conjunctive reaction	No. of animals with tumors size class 1 or over	Avg "total tumoral effect"
2	38	5	4	2	2.3
3	38	5	5	5	2.5

*The weight of estradiol is given. 1 γ of estradiol is contained in 1.46 γ of the caprylic acid ester.

general. Tumoral seed on the spleen (Fig. 2) and other parts of the abdominal cavity was found after use of the caprylate in 10 out of 46 animals which received 10 to 40 injections of 1 γ in the course of 21 to 93 days. One may indeed question how far the tumoral seed is to be identified with experimental fibroids in general.

The results are very different when 2 to 3 γ of the caprylic ester per injection were given (Table I). Not only a tumoral seed on the spleen but also splenic and other fibroids were produced (Fig. 3) with a total amount equivalent to only 76 γ of estradiol and injected in the 3-month period. With this minute quantity of estradiol administered as the 17-caprylate the tumoral reaction is much more considerable than with 5 or even 10 γ of the monobenzoate or dipropionate per injection.² The tumorigenic action of 2 γ of the caprylate is also enormously superior to that of 200 γ of free estradiol.^{3, 4} *Under the given timing conditions (3 injections weekly) the tumorigenic action of free estradiol is enhanced by esterification with caprylic acid from one to two hundred times.* On the contrary, the hysterotropic or "physiological" dose³ of free estradiol is certainly no more than 10 times that of the 17-caprylate. This gives full evidence that esterification, especially with caprylic acid, confers upon estradiol under certain timing conditions greater tumorigenic potency. When roughly expressed in figures the tumorigenic quotient, or $Q_{\text{tum}} = \frac{\text{tumorigenic dose}}{\text{hysterotropic dose}}$ is for the 17-caprylate less than 20 ($Q_{\text{tum}} = <2/0.1$), and for free estradiol more than 200 ($Q_{\text{tum}} = >200/<1$).

Summary. The conjunctive tumorigenic action of α -estradiol is so greatly enhanced by esterification with caprylic acid at position 17 that under certain timing conditions it becomes 100 to 200 times greater than that of free α -estradiol. With 38 injections of the 17-caprylate of estradiol given in the course of 3 months and equivalent to a total of 76 γ of estradiol, typical experimental abdominal fibroids can be induced.

⁴ Rodríguez, F., *Public Med. Exp.* (Chile), 1940.