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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uterine and extragenital subserous fibroids in the abdominal cavity.[1] No difference as yet has been found as to the localization and microscopical structure of fibroids induced by either of these estrogens.[2] On the other hand, stilbestrol has been shown to be more tumorigenic than free natural hormones (α-estradiol and estrone) and less tumorigenic than the esters of estradiol; with greater doses the tumorigenic action of stilbestrol was equal to that of similar doses of the esters of estradiol.[1] The greater tumorigenic action of stilbestrol, when compared with free estradiol, is probably due to the greater resistance against inactivation which the artificial estrogens offer in the body.[3] These properties of stilbestrol raised the question of the tumorigenic power and behavior of other artificial estrogens and similarly, the increased tumorigenic power of esterified natural female hormones led to a study of the effect of esterification on the fibromatogenic behavior of an artificial estrogen.

Experiments with Hexestrol. Forty-nine castrate female guinea pigs (290 to 630 g) were given thrice weekly subcutaneous injections of hexestrol[4] in olive oil, in the course of 3 months. Quantities injected varied between 0.05 and 80 γ per injection. The vagina remained open, and normal uterine weights were reached or surpassed with 0.3 to 0.6 γ per injection. Small nodules (tumoral seed) appeared on the spleen, stomach, diaphragm and abdominal wall, even with minute quantities of hexestrol (0.05 to 0.6 γ per injection). The microscopical structure of these nodules was typical of those obtained with other estrogens.[2] The tumoral seed became more conspicuous with 1 to 5 γ per injection. With 10 γ per injection, uterine fibroids of "class 1", according to our classification,[5] were elicited. With higher doses, a tumorigenic action, similar to that with the esters of estradiol, was produced (Fig. 1). A comparative survey of the results with hexestrol and other estrogens is given in Table I.

Notwithstanding the great individual variations noted with experimental fibroids, the table gives full evidence that not only is hexestrol more tumorigenic than the natural free hormones but also

[1] Lipschütz, A., and Vargas, L., Jr., *The Lancet*, 1940, **1**, 541.

[2] Lipschütz, A., and Vargas, L., Jr., *Cancer Research*, 1941, **1**, 236.

[3] Stroud, S. W., *J. Endocrinol.*, 1939, **1**, 201; Dingemanse, E., and Tsylowitz, R., *Endocrinology*, 1941, **28**, 450.

[4] Campbell, N. R., Dodds, E. C., and Lawson, W., *Nature*, 1938, **142**, 1121. We are indebted to Prof. E. C. Dodds for a generous supply of hexestrol.

[5] Lipschütz, A., and Vargas, L., Jr., *C. R. Soc. Biol.* (Paris), 1939, **131**, 27. Additional data, see Lipschütz, A., Bellolio, P., Chaume, J., and Vargas, L., Jr., PROC. SOC. EXP. BIOL. AND MED., 1941, **46**, 164.

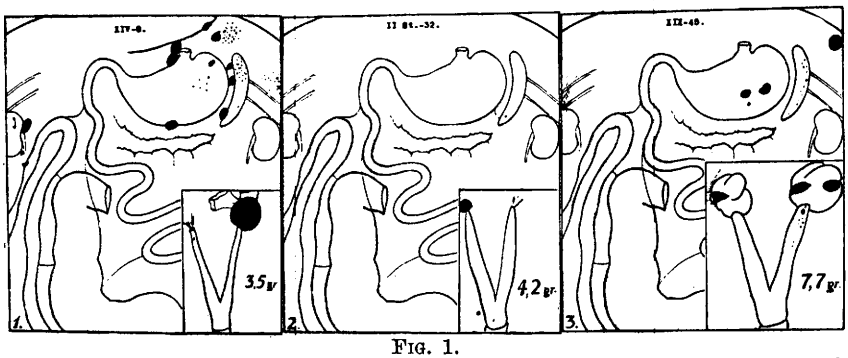

FIG. 1.

Castrate female guinea pig (355 g when castrated). 40 injections of 40 γ of hexestrol in the course of 88 days. Small uterine fibroid, large apical tumor of left uterine horn and multiple large abdominal fibroids. × 0.3. (XIV, 8).

FIG. 2.

Castrate female guinea pig (250 g when castrated). 47 injections of 40 γ of stilbestrol in the course of 114 days. Apical tumor of right uterine horn. Small subserous uterine and extragenital fibroids. × 0.3. (II. St. 32.)

FIG. 3.

Castrate female guinea pig (430 g when castrated). 48 injections of 20 γ of stilbestrol given as dipropionate in the course of 111 days. Small subserous uterine fibroids. Fibroids in the wall of tubar cysts. Large extragenital tumors. × 0.3. (XIX, 45.)

The tumoral effect in Fig. 1, 2 and 3 was classified as follows:

	Subserous or parametrial uterine tumor, class	Apical tumor, class	Tumor of dig. tract and abdom. wall, class	Splenic tumor, class	Total tumoral effect*
Fig. 1	0.5	3	3	2	8.5
" 2	0.5	2	0	0.5	3.0
" 3	1	2	2	0.5	5.5

*The sum of the 4 numerical classes.

more tumorigenic than stilbestrol. Hexestrol attains the tumorigenic action of the 2 esters of estradiol, even with 40 γ per injection. It is also remarkable that the initial conjunctive reaction (tumoral seed) can be found, though only exceptionally, with minute quantities of hexestrol coincident with, or even below, the hysterotrophic dose necessary to maintain a normal uterine weight. There was one case which, having received only 0.3 γ of hexestrol per injection, developed a small intramural fibroid in the uterine submucosa. Similar conjunctive reactions towards such minute quantities have as yet not been seen in this department with other estrogens, natural, esterified or artificial.

Experiments with Dipropionate of Stilbestrol.‡ All quantitative

‡ Dipropionate of stilbestrol was at our disposition only in an oily solution manufactured by Messers Bayer (local branch). The solution (B-Cyren, "fuerte") contains 2.5 mg of dipropionate per ml. One mg of stilbestrol is contained in 1.42 mg of dipropionate.

TABLE I.
454 Castrate Female Guinea Pigs Injected with Natural and Artificial Estrogens, Thrice Weekly, in the Course of 3 Months.

Quantity per injection, γ	Estradiol and estrone 91 animals*	Stilbestrol 48 animals†	Hexestrol 56 animals‡	17-benz. and 3-17-prop. of estradiol 218 animals§	Diprop. of stilbestrol 41 animals
.05-.6	0	0	±	0	0
1	0	0	±	±	•
2	0	•	•	•	•
3-4	0	±	±	•	±
5	0	±	±	1	1
10	0	+	1	1	1
20	0	•	2	5	5
40	0	1	4	4	4
80	0	5	5	5	5
100	±	5	•	•	•
250-300	+	4	•	6	•
400-500	4	5	•	•	•

*Rodríguez, F., *Public Med. Exp.* (Chile), 1940.
†See 1 and unpublished results.
‡Results of Palma, J., *Public Med. Exp.* (Chile), 1940, No. 6 included.
§Iglesias, R., *Public Med. Exp.* (Chile), 1938; Bellolio, P., *ibid.*, 1939; Murillo, R., *ibid.*, 1940; Lipschütz *et al.*, PROC. SOC. EXP. BIOL. AND MED., 1941, **46**, 164; and unpublished work. Different animals treated for less or more than 3 months also are included in this column.
Explanation of signs:
0 = no visible macroscopical reaction.
± = only initial reaction (fibrous strands; tumoral seed).
+ = only small fibroids not reaching "class 1."
1, 2 etc. = fibroids of class 1 or more; the *average* "total tumoral effect" is given.
• = no data available.

and timing conditions were identical with those in the foregoing experiments. Table I indicates that the tumorigenic power of stilbestrol is enhanced by esterification (see also Figs. 2 and 3). With doses of 10 to 80 γ per injection, the dipropionate of stilbestrol is probably equal to the highly tumorigenic 17-caprylate of estradiol.[6] Dodds, *et al.*,[7] state that esterification of stilbestrol favors a protracted action. According to our former results, estrogens acquire tumorigenic faculties when a stable threshold folliculinaemia is maintained for a sufficiently long time,[8] and this is probably facilitated by esterification.

[6] Lipschütz, A., Vargas, L., Jr., Baeza-Rosales, H., and Baeza-Herrera, H., PROC. SOC. EXP. BIOL. AND MED., 1941, **46**, 76.

[7] Dodds, E. C., Goldberg, L., Lawson, W., and Robinson, R., *Nature*, 1938, **211**, 142.

[8] Lipschütz, A., *Libro de Homenagem Prof. A.e.M. Ozorio de Almeida*, Rio de Janeiro, 1939, p. 413; Lipschütz, A., and Vargas, L., Jr., *C. R. Soc. Biol.* (Paris), 1939, **130**, 9; Lipschütz, A., Rodríguez, F., and Vargas, L., Jr., *Endocrinology*, 1941, **28**, 664.

Summary. Uterine and extrauterine fibroids can be induced in the guinea pig by a prolonged treatment with hexestrol. Like stilbestrol, hexestrol also is more tumorigenic than the free natural follicular hormones (estrone and estradiol). The tumorigenic power of hexestrol is even greater than that of stilbestrol. The tumorigenic power of stilbestrol is, like that of estradiol, greatly enhanced by esterification.

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Effects of Roentgen Irradiation upon Linear Rate of Flow in Cutaneous Lymphatics of Humans.

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The effects of irradiation upon the function of lymphatics is of clinical as well as experimental significance. Many clinicians believe that irradiation therapy can be used to obstruct lymphatics and thereby reduce the ease of metastasis of malignancy. Sufficient physiological observations necessary to evaluate the opinion are lacking. Teneff and Stoppani[1] employing thorium dioxide and India ink for visualization found evidence of changes in lymph circulation of the subcutaneous tissues of dogs and guinea pigs only when large doses of X-ray sufficient to produce destruction of cells were used. Hodes and Griffith[2] using the thorium dioxide method of Menville and Ané[3] failed to find any significant interference with lymph flow in the subcutaneous lymphatics even with doses as large as 2,200 r. Accordingly, the observations to be described were initiated in an attempt to learn some of the effects of roentgen irradiation upon the cutaneous lymphatics of humans.

Seven white adults (19 to 57 years of age) who were receiving roentgen therapy for various clinical states were selected as subjects. The linear rate of flow in the cutaneous lymphatics of 12 different skin areas were studied 45 times by the colloidal dye method of McMaster.[4] The subjects rested quietly for about 30 minutes in the

[1] Teneff, S., and Stoppani, F., *Radiol. med.*, 1935, **22**, 768.

[2] Hodes, P. J., and Griffith, J. Q., *Radiology*, 1941, **37**, 203.

[3] Menville, L. J., and Ané, J. N., *J. A. M. A.*, 1932, **98**, 1796.

[4] McMaster, P. D., *J. Exp. Med.*, 1937, **65**, 347.