the unknown causative "agent" of leukemia, and consequently the disease appears later in life and in a more chronic form. With an increased life expectancy metabolic differences might be expected to delay the onset of neoplastic change.

Concerning the incidence of leukemia in males as compared with females, in both hybrids and the pure F stock there was no significant difference in either the total incidence or the age distribution. Although administration of estrogens results in an increased incidence of leukemia in low leukemia stocks,[6] there is no evidence that sex hormones play a role in the spontaneous appearance of leukemia in strain F mice. Fifty-six strain F mice were gonadectomized at weaning age (34 males and 22 females). When no mouse was older than 525 days of age 17 of the castrate males and 10 of the 22 spayed females had developed leukemia. Gonadectomy did not alter the incidence of leukemia in either sex; the castrate atrophy of the male and female accessory sex organs indicated that the adrenal glands were not an extragonadal source of appreciable amounts of sex hormone.

There was no evidence for the existence of a leukemia "milk influence." Previous experiments on foster-nursing in this strain[7] indicated that a maternal influence, as for mammary cancer, is not operating.

[6] Gardner, W. U., Kirschbaum, A., and Strong, L. C., *Arch. Path.*, 1940, **39**, 1.

[7] Kirschbaum, A., and Strong, L. C., PROC. SOC. EXP. BIOL. AND MED., 1942, **51**, 404.

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Comparative Fibromatogenic Action of Ovarian and Urinary Estrogens.*

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So far all estrogens, natural or artificial, free or esterified, have been shown to induce abdominal fibroids when continuously administered to female guinea pigs for a certain time.[1,2] The urinary estrogen, estriol, also has been found to be fibromatogenic[3] though less so than estradiol or estrone, whereas with equilenin fibromatogenic action was insignificant[4] even when quantities twice or thrice those of estrone were absorbed. On the other hand, great increase of uterine weight and formation of endometrial polyps was also obtained with equilenin under these experimental conditions.[4] Equilenin has also been found to be less active than estrone in eliciting mammary adenocarcinoma in mice.[5]

One might tentatively suggest that presence of hysterotoxic and epitheliotoxic actions in the absence of fibromatogenic ones in the

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[1] Iglesias, R., Tesis Universidad de Chile, 1938, *Public. Med. Exp.* (Chile), No. 1; Lipschütz, A., and Iglesias, R., *C. R. Soc. Biol* (Paris), 1938, **129**, 519; Lipschütz, A., and Vargas, L., *Lancet*, 1939, **1**, 1313.

[2] Lipschütz, A., *J. Am. Med. Assn.*, 1942, **120**, 171; *Cold Spring Harbor Sympos.*, 1942, **10**.

[3] Szabó, E., *Rev. Chil. Hig. y Med. Prev.*, 1940, **3**, 127.

[4] Thibaut, R., Tesis Universidad de Chile, 1941, *Public. Med. Exp.* (Chile), No. 7; Lipschütz, A., Thibaut, R., and Vargas, L., *Cancer Research*, 1942, **2**, 45.

[5] Lacassagne, A., *Ergebn. d. Vitamin-u. Hormonforsch.*, 1939, **2**, 259.

TABLE I.
Ninety-one Castrated Female Guinea Pigs with Subcutaneously Implanted Small Pellets of Ovarian Estrogens and Big Tablets of Urinary Ones. Necropsy at 90 days after implantation.

Estrogens implanted	Absorbed per day, avg. μg	Fibrous tumoral effect F.T.E. avg*	No. of animals	No. animals reaching avg F.T.E. of estradiol group	No. tumoral marks of classes 2 and 3 per animal
Alpha-estradiol	19	4.9	10	4	1.4
Estrone	12.5	3.2	27	8	0.9
Estriol	111	4.3	15	6	1.2
Equilenin	97	3.7	15	6	1.3
Alpha-dihydroequilenin	111	4.8	12	5	1.5
Beta-dihydroequilenin	136	1.7	12	2	0.5

* For the system of classification and units see Lipschütz and others.[6]

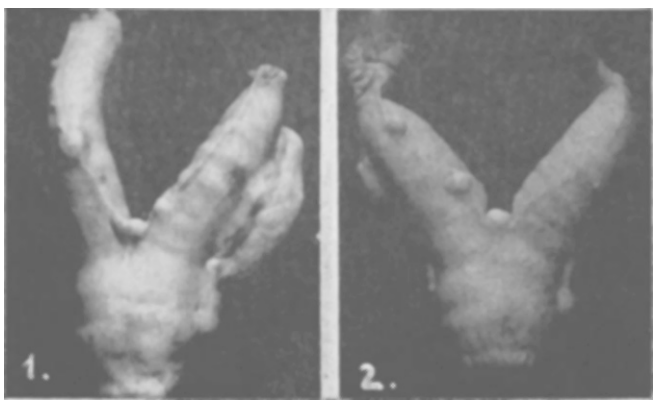

FIG. 1.
Uterus of guinea pig with subcutaneously implanted tablet of alpha-dihydroequilenin. Absorption of 136 μg per day in the course of 90 days. Subserous and parametrial tumors. Nat. size.
FIG. 2.
Absorption of 131 μg of beta-dihydroequilenin per day in the course of 90 days. Subserous and parametrial tumors. Nat. size.

guinea pig treated with equilenin could be due to the different thresholds upon which these different actions depend. If so, fibromatogenic action should be attained with equilenin as well as other less active estrogens, if sufficient quantities are continuously administered.

Comparative experiments were made with 6 different estrogens. Small pellets of estradiol or estrone of 1.6 mm in diameter weighing about 3.5 mg were used for subcutaneous implantation, as well as tablets of estriol, equilenin, alpha-dihydroequilenin and beta-dihydroequilenin§ of 5 mm in diameter weighing 20 to 43 mg. Under these experimental conditions absorption in the estriol-equilenin and dihydroequilenin groups was 5 to 10 times greater than in the estradiol-estrone group. All animals were sacrificed 90 days after subcutaneous implantation. Results are given in Table I.

The fibrous tumoral reaction with an average of 19 μg of estradiol was of the usual degree and the average reaction was reached in 4 out of 10 animals. A smaller reaction was

§ With a single subcutaneous injection of 50 μg of alpha- or beta-dihydroequilenin in oil full estrus was produced only in 2 out of 10 castrated rats; most of animals reached only proestrus. Unpublished work of R. F. Mello and C. Franke in this Department.

[6] Lipschütz, A., Bellolio, P., Chaume, J., and Vargas, L., PROC. SOC. EXP. BIOL. AND MED., 1941, **46**, 164.

obtained with only 13 μg of estrone. With 97 to 111 μg of estriol, equilenin and alpha-dihydroequilenin the result was in every respect equal to that with 19 μg of estradiol: there was the same average fibro-tumorous effect (F.T.E.), the same percentage of animals reaching the average F.T.E. of the estradiol group, and the same number of tumoral marks of classes 2 and 3 per animal. A slight reaction was obtained with beta-dihydroequilenin, but here again there were 2 animals with a F.T.E. = 5.5.

In our previous experiments no fibromatogenic action was seen when small quantities of equilenin were used; the present experiments show that the use of large quantities of equilenin will cause fibromas. A tentative conclusion is offered that the body tends to protect itself against the tumorigenic action of estrogens by the conversion of the more active substances (*e.g.*, estradiol, estrone) into less active ones (*e.g.*, estriol, equilenin). The differences in renal threshold for these substances may also be important.

Summary. Abdominal fibroids were induced in female guinea pigs with the natural urinary estrogen, equilenin, and two hydrogenated ones as alpha- and beta-dihydroequilenin. Estrogenic activity, even though it may be weak, is always concomitant with the fibromatogenic activity. Beta-dihydroequilenin has been shown to be the least fibromatogenic estrogen.