

Effect of Estrogens and Androgens on Growth of Mammary Fibroma in Rats.*

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That the growth of adenofibroma of the mammary gland of rats is restricted in the absence of the ovaries and that this restriction is prevented by estrogen administration has been demonstrated by Heiman and Krehbiel¹ and by Mohs.² However, with pure fibroma of the mammary gland no such effect has been previously reported.

This paper concerns a transplantable mammary fibroma, the growth of which is strongly affected by variations in the estrogen level in the body of the host. Occurring spontaneously in the mammary gland of an old female rat this pure fibroma has survived 10 transplant generations over a period of 3 years.

To test the effect of variations in the estrogenic and androgenic hormone levels the tumor was implanted subcutaneously in the inguinal region of rats of 6 different groups as follows: (1) females, (2) castrate females, (3) estrogen-injected castrate females, (4) males, (5) castrate males, and (6) estrogen-injected castrate males. Castration was done 2 weeks before tumor implantation. The estrogen used was Amniotin† in oil and it was injected in 6 rat-unit doses every other day starting 2 days before tumor implantation and continuing to the end of the experiment 4 to 6 months later. At 2-week intervals the tumors were measured with calipers and the mean of the greatest and smallest diameters recorded.

The results (Table I) show that both the success of implantation and the rate of growth of the successful implants were definitely greater in the "estrogen-present" groups (normal females and estrogen-injected castrates) than in the "estrogen-absent" groups (normal males and untreated castrates) the ratio being 2.5:1 in regard to success of implantation and 3:1 in regard to rate of growth.

The finding that in normal males fibroma behaves the same as in castrates of both sexes indicates that the testes have little or no effect

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¹ Heiman, J., and Krehbiel, O. F., *Am. J. Cancer*, 1936, **27**, 450.

² Mohs, F. E., to be published in *Am. J. Cancer*.

† Amniotin was kindly furnished by Dr. John Anderson of E. R. Squibb and Sons.

TABLE I.
Effect of Estrogenic and Androgenic Hormones on Transplantability and Growth Rate of a Pure Fibroma of the Mammary Gland of the Rat.

Hormonal status	No. implanted	Positive		Growth rate mm/week
		No.	%	
Estrogen present				
Normal female	89	38	42.7	3.81
Estrogen-injected castrate female	30	13	43.3	2.14
" " " male	32	19	59.3	3.24
Estrogen absent				
Normal male	59	11	18.6	1.89
Castrate female	41	9	21.9	1.83
" male	35	6	17.1	1.53

on the transplantation or growth of this tumor. However, in 9 castrate females and in 10 castrate males given 250 gamma of testosterone propionate‡ biweekly for 4-5 months this fibroma grew successfully in 44.4% and 90% of the rats respectively. Though the number of testosterone-injected animals is insufficient to justify definite conclusions the data show that, if anything, androgens enhance fibroma growth. This conforms with the findings of Selye, *et al.*,³ and others that androgens stimulate rather than retard mammary growth in rats.

The greater transplantability and greater growth rate of fibroma in the estrogen-injected castrate males as compared to the estrogen-injected castrate females (59.3% cf. 43.3%) parallels a similar finding previously reported for adenofibroma. It has been tentatively suggested on the basis of work in progress that this phenomenon is due to the greater ease of liberation of mammogenic hormone from the male anterior pituitary as compared to the female.

Malignant connective tissue tumors of the mammary gland, however, lose the ability to respond to hormones. Thus in 2 sarcomas arising in the midst of transplanted adenofibromas no sex difference was found upon transplantation (62.8% of 43 females grew the sarcomas while 65.6% of 64 males had positive implants).

The responses of mammary fibroma to hormonal influences are essentially the same as have been previously demonstrated for benign mammary adenofibroma. In view of the close relationship which the benign tumors of the mammary gland proper have been shown to bear to one another⁴ it is probable that all will respond similarly to hor-

‡ Testosterone propionate was supplied by Dr. Erwin Schwenk of the Schering Corporation.

³ Selye, H., McEuen, C. S., and Collip, J. B., *Proc. Soc. Exp. Biol. and Med.*, 1936, **34**, 201.

⁴ Mohs, F. E., *Proc. III Internat. Cancer Cong.*, Atlantic City, September, 1939.

monal effects. Being benign these tumors retain the capacity to respond to the hormones which affect the normal mammary gland.

Summary. The transplantability and rate of growth of a pure mammary fibroma were markedly enhanced by the presence of physiological levels of estrogens in the host rats. Physiological levels of androgens, however, had no demonstrable effect on this tumor. The tumor-stimulating effect of estrogen injections was greater in male castrates than in female castrates. With the onset of malignancy the connective tissue tumors lose their responsiveness to hormonal influences.

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Destructive Effects on Carcinoma of Colchicine Followed by Distilled Water.*

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While studying the enhanced effects of X-rays on transplanted Flexner-Jobling carcinoma following injections of colchicine into the host (paper in press), distilled water injected into the tumors some 15 hours after administration of the drug was used as a control for comparison with the effects of the irradiation. The results are summarized in Table I. Since colchicine alone has a retardative but only occasionally a lethal effect on some tumors¹ it is evident from the tabulation that the subsequent treatment with distilled water was unexpectedly destructive. F.-J. tumors injected with distilled water alone, in 47 rats, showed approximately the same percentage of recoveries as the spontaneous regressions and recoveries in our present strain of rats when the implants are left to grow for 3 weeks and only those regarded as "takes" which have increased to at least 1 cm in diameter; namely, between 3 and 4% (6 of 157 rats). Such 3-week growths were the only kind used in the present experi-

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¹ Ludford, R. J., *Arch. f. exp. Zellforsch.*, 1936, **18**, 411; Clearkin, P. A., *J. Path. and Bact.*, 1937, **44**, 469; Lits, F. J., Kirschbaum, A., and Strong, L. C., *Am. J. Cancer*, 1938, **34**, 196; Guyer, M. F., and Claus, P. E., *Proc. Soc. Exp. Biol. and Med.*, 1939, **42**, 565.