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Failure of Thyrotropic Pituitary Hormone to Prevent Spontaneous Mammary Cancer in Mice.

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(Introduced by E. T. Engle.)

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Since Lacassagne proved that mammary carcinoma can be induced in mice by means of estrogens, workers in several laboratories have sought to discover what rôle, if any, pituitary hormones play in the development of this disease. The close relationship of ovary and pituitary gland in other biological processes makes this kind of research reasonable.

Cramer and Horning, in the laboratory of the Imperial Cancer Research Fund in London, gave a series of female mice of the RIII strain thyrotropic pituitary hormone subcutaneously, and reported[1] that they were able to prevent the development of mammary carcinoma in this strain by this means. They used a watery solution of pituitary hormone, sold under the trade name of *Ambinon.** It contained, according to biological assay, 150 guinea pig units of thyrotropic hormone and 50 units of gonadotropic hormone per cubic centimeter. This preparation was injected twice weekly in doses of 0.1 cc into the subcutaneous tissues of the mice. Only 19 mice were used. Their treatment was begun when they were 2 months of age. It was still being continued when Cramer and Horning wrote their report about a year later. At this time none of the mice had developed mammary carcinoma, and the authors felt justified in concluding that the development of the disease had been prevented by the hormone. Although these female mice had been kept with males, none of them had littered during the period of treatment. In a control series of 22 untreated female mice, which although kept with males had borne no litters, Cramer and Horning observed 11, or 50%, develop mammary carcinoma.

We have been able to repeat this experiment on a somewhat larger scale, using the same strain of mice and the same preparation of pituitary hormone. The RIII strain of mice has been bred by brother and sister matings in our laboratory since 1935, when we obtained 6 members of the strain directly from Lacassagne in Paris.

1 Cramer, W., and Horning, E. S., *Lancet*, 1938, **1**, 72.

* Purchased from the N. V. Organon Co., Oss, Holland.

Our control material now includes some hundreds of animals. The pituitary hormone was purchased from the same firm that supplied the London authors. We realized that the preparation was not a very pure one, containing as it did 50 units of gonadotropic hormone in addition to 150 units of thyrotropic hormone per cubic centimeter. Since we were trying to repeat the London authors' experiment we had no choice except to employ it.

We treated a total of 33 mice. Of these 29 survived for at least 6 months, the lower age limit for the development of spontaneous mammary carcinoma in our control series. The treatment was begun when the mice were just under 2 months of age, 0.1 cc of the hormone being given twice weekly. It was continued for fifteen months. At the end of this time 13 mice remained alive. Our supply of hormone being exhausted, and its failure to prevent mammary carcinoma being apparent, the treatment was discontinued. All of the mice in the series are now dead and we are able to present the complete data. The fate of the 29 mice is shown in Table I.

Among these 29 treated mice that survived 6 months, 16 therefore

TABLE I.

Mouse No.	Age (months) treatment began	No. Litters	Age (months) treatment ended	Age (months) death	Mammary carcinoma
801	1.6	0	9.7	9.7	0
803	1.7	2	14.5	14.5	+
805	1.6	0	16.3	27.0	0
807	1.5	3	11.3	11.3	+
809	1.6	0	14.7	18.0	0
815	2.1	1	15.7	16.4	+
817	1.9	0	15.5	25.4	0
819	1.8	0	8.9	8.9	0
821	1.9	1	15.1	15.1	+
823	1.9	0	16.7	31.3	0
825	1.8	0	14.8	19.3	0
827	1.7	0	15.8	15.8	+
829	1.6	0	14.6	16.9	+
831	1.7	0	7.2	7.2	0
833	1.2	0	10.8	10.8	+
835	1.4	2	14.6	29.2	0
837	1.3	2	15.5	15.5	+
841	1.5	0	14.5	17.0	0
843	1.4	1	14.3	19.8	+
847	2.0	1	16.1	26.0	0
849	1.5	0	16.1	20.8	0
851	2.1	3	10.5	10.5	+
853	1.4	3	10.5	10.5	+
855	1.7	2	9.4	9.4	+
857	1.6	0	13.9	24.0	0
859	1.6	2	8.5	8.5	+
861	1.7	2	10.3	10.3	+
863	2.0	1	12.9	12.9	+
865	1.8	0	9.8	9.8	+

developed mammary carcinoma. This tumor incidence is not significantly different from that for our untreated, unbred controls, and slightly lower than that for our untreated bred controls. In the light of our knowledge that breeding increases the incidence of spontaneous mammary carcinoma in this strain of mice this result might be expected, for the breeding record of this group of *Ambinon*-treated mice was intermediate. Only 14 of the 29 bore litters, averaging 1.8 litters each. In our untreated control series of bred females 128 of the 140 that survived 6 months bore litters, averaging 5.5 litters each. Our conclusion must be that the treatment with *Ambinon* prevented, to some extent, pregnancy in our mice, and therefore lowered slightly the incidence of mammary carcinoma. It certainly did not abolish the disease as Cramer and Horning claimed.

Histological study of the adrenals, ovaries, uterus, mammary glands, and mammary carcinomas when they developed, in these treated mice showed no abnormality which we have not found in the tissues of our control animals. In this strain of mice certain changes in the endocrine glands, which might be called degenerative, occur spontaneously. The thyroids were studied with special care, but the only difference between those of the treated animals and the controls that could be made out was a slightly greater cellularity of the glands in some of the former. The pituitary showed no gross changes in the treated mice. We were not able to carry out adequate histological study of this organ.

The statistical data for the treated animals and our controls is given in Table II.

Since 1938, when Cramer and Horning published their report of the carcinoma *inhibiting* effect of anterior pituitary, and we under-

TABLE II.

	Mice treated with thyrotropic hormone	Unbred control mice	Bred control mice
Total number surviving 6 mo.	29	94	140
Developed mammary carcinoma	16 or 55.2% ± 9.23%	49 or 52.2% ± 5.15%	103 or 73.6% ± 3.72%
Mean age at death of those with carcinoma	13 mo. ± .79	16.44 mo. ± .73	12.15 mo. ± .36
Median age at death of those with carcinoma	12.1 " ± .98	16.5 " ± .91	11.3 " ± .45
Standard deviation of age at death of group with carcinoma $\left(\sqrt{\frac{\Sigma d^2F}{N} - b_x}\right)$	3.15 " ± .56	5.12 " ± .52	3.67 " ± .25

Note: All corrections are standard deviations.

took to verify their findings, Loeb and his associates[2] have reported that the same organ, when transplanted subcutaneously, causes the carcinoma rate to be *increased.* We have not attempted any transplantation experiments, but our data concerning the results of subcutaneous injection of the hormone may apply to some extent to Loeb's new interpretation of anterior pituitary function. Cramer[3] has presented an elaborate theory of the genesis of mammary carcinoma in which the pituitary takes an important rôle as an antagonist of the disease. His theory would appear to be premature.

Summary. Long continued subcutaneous injection of an anterior pituitary preparation which contained thyrotropic hormone and some gonadotropic hormone did not definitely affect the incidence of mammary carcinoma in female mice of the RIII strain.

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Typhus Rickettsia Isolated from Mice and Mouse-Fleas During an Epidemic in Peiping.*

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It is now generally recognized that "endemic" or murine typhus has its reservoir in rats and is transmitted to man by rat-fleas, particularly *Xenopsylla cheopis.*[1, 2] However, in South Queensland, Australia, circumstantial evidence strongly incriminates mice, rather than rats, as the reservoir, although actual proof of infection among these rodents or their ectoparasites is as yet lacking.[3, 4] Lépine and Lorando,[5, 6] in Athens, examining rats as well as mice trapped in the premises where cases of typhus had occurred, found that whereas rats were frequently infected with typhus Rickettsia, mice were

2 Loeb, L., and Kirtz, M. M., *Am. J. Cancer,* 1939, **36**, 56.

3 Cramer, W., *Am. J. Cancer,* 1940, **38**, 463.

* We are indebted to Dr. A. B. D. Fortuyn for identification of the species of mice and to Dr. H. F. Hsü for that of fleas.

1 Biraud, Y., and Deutschman, S., *League of Nations Epidem. Rep.,* 1936, **15**, 99.

2 Zinsser, H., *Am. J. Hyg.,* 1937, **25**, 430.

3 Wheatland, F. T., *Med. J. Australia,* 1926, **1**, 261.

4 Strickland, C., *Far East. Assn. Trop. Med. Trans. Ninth Congress,* 1927, **2**, 517.

5 Lépine, P., *Compt. rend. Soc. de biol.,* 1934, **117**, 848.

6 Lépine, P., and Lorando, N., *Bull. Soc. path. exot.,* 1936, **29**, 285.