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A Relationship Between Ovarian Norepinephrine and Breast Cancer in Humans.* (28609)

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In a recent study(1) on the distribution of norepinephrine and epinephrine in human tissues, it was observed by one of us (A.H.A.) that ovaries contained a relatively large amount of norepinephrine. Because of the postulated implication of this catecholamine in ovarian function(2), this observation was pursued further and it was found that the high levels of ovarian norepinephrine were associated with breast cancer.

Methods. Segments of ovaries were obtained from 38 patients, 12 of whom had breast cancer, at the time of surgery. (Table I). The catecholamine content of fresh tissue (designated as "normal" after gross examination by a pathologist) was determined by the aluminum oxide-trihydroxyindole procedure of Anton and Sayre(1); fluorescence was measured in the Aminco-Bowman Spectrophotofluorometer. Descending paper chromatography of the aluminum oxide extracted ovarian tissue was carried out on Whatman No. 3 using a solvent system consisting of butanol: acetic acid: water (4:1:5). The catecholamines were located by spraying the paper with a 5% aqueous solution of ethylenediamine, heating the paper at 100°C for 5 minutes and then examining the chromatogram under U.V. lite. Patients receiving catecholamines during the operation were excluded from this study.

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Results. There was a markedly significant elevation of norepinephrine in the ovaries of the breast cancer patients (Table I and Fig. 1). *All* of these patients had 0.50 μg or more of norepinephrine/g tissue whereas *90%* of the other patients had less than this amount. That the catecholamine extracted from the ovaries was indeed norepinephrine was established by means of paper chromatography in which the extract was compared to authentic norepinephrine. Only norepinephrine was detected on the chromatogram since the concentration of epinephrine (or other catecholamines) was below the sensitivity of the paper chromatographic procedure. Further verification of the identity of the extract was obtained by demonstrating that its fluorescence characteristics coincided with those of authentic norepinephrine (Fig. 2). Another intriguing finding was that the corpora lutea in these ovaries had negligible amounts of norepinephrine.

Discussion. It must be emphasized that an association between breast cancer and high levels of ovarian norepinephrine was the only correlation detected. Thus, when an attempt was made to relate ovarian norepinephrine levels to the patient's age, race, stage of pregnancy, phase of menstrual cycle, menopause, pathology (other than breast cancer), or degree of stress, *e.g.*, toxemia of pregnancy, no significant patterns or differences emerged (Table I). Also, the therapy, *e.g.*, drugs, ra-

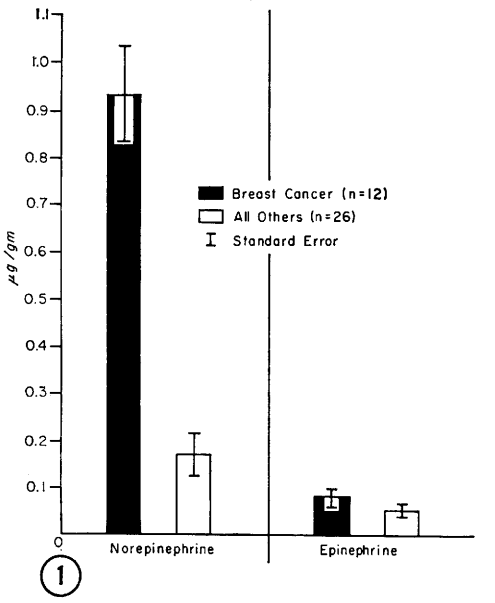
TABLE I. Pertinent Information on Patients Used in Study.

Patient	Age	Menopause	Race	Diagnosis	Ovarian catecholamines, μg/g NE	E
M. L. R.	18	No	C	Term pregnancy	.330	.100
C. T.	30	"	C	" "	.040	.020
E. B. F.	38	"	C	" "	.080	.030
B. R. H.	22	"	W	Gangrene appendix, pregnant	.000	.170
C. M. S.	23	"	C	Hypertension, 4 days post partum	.150	.050
J. N. L.	26	"	W	Stillborn, epileptic	.043	.014
V. G.	18	"	C	Eclampsia, 3rd trimester	.065	.048
L. B.	40	"	W	Therapeutic abortion, 1st trimester	.810	.300
R. T.	48	"	W	Adenocarcinoma of endometrium	.240	.074
R. L. P.	65	Yes	C	" " "	.005	.022
H. D.	44	No	W	Adenomyosis of uterus	.004	.009
B. A. R.	26	"	W	Atypical endometrial hyperplasia	.000	.060
O. K. H.	30	"	W	Endometrial hyperplasia	.110	.008
B. G. R.	30	"	W	" "	.310	.064
R. J.	39	"	C	Fibromyomata of uterus	.090	.090
E. M. D.	47	"	C	" " "	.030	.022
Q. E. W.	52	Yes	C	" " "	.360	.020
R. M. K.	59	"	W	Thecoma of ovary	.014	.012
J. E. P.	33	No	W	Ovarian cyst, benign	.050	.050
R. B.	24	"	C	Carcinoma of ovary	.320	.012
F. B. C.	29	"	W	Carcinoma of cervix	.050	.020
E. B.	30	"	W	" " "	.090	.030
B. E. M.	33	"	C	" " "	.160	.060
L. M. B.	34	"	W	" " "	.140	.010
N. H.	44	"	C	" " "	.030	.030
D. L. K.	44	Yes	W	" " "	.820	.040
J. R.	30	No	W	Breast cancer	.540	.067
G. L.	40	"	C	" "	1.230	.260
B. R. W.	40	"	W	" "	.670	.006
E. M. S.	43	"	C	" "	.590	.062
H. M. T.	45	"	W	" "	.950	.000
M. E. S.	45	"	W	" "	.500	.020
G. E. T.	63	Yes	W	" "	1.500	.180
L. W.	66	"	W	" "	1.040	.176
L. T.	67	"	W	" "	1.250	.110
E. B.	68	"	C	" "	.500	.030
V. E. G.	69	"	W	" "	1.020	.078
H. L. H.	70	"	W	" "	1.400	.000

diation, mastectomy, given to the breast cancer patients prior to and during the oophorectomy did not appear to influence the results obtained.

It is of interest to speculate that the high level of norepinephrine in ovaries may be pathognomonic of breast cancer. Thus, the assay for catecholamines in the laboratory correlated with the diagnosis in about 90% of the cases without prior knowledge of the condition of the patient. Urinary catecholamines were determined in only 2 of the breast cancer patients and no significant differences from normals were detected. This observation agrees with the results of von Euler *et al* from 4 breast cancer patients(3). However, in the light of our findings, a more detailed study of urine will be made with the view of evolving a biochemical diagnostic procedure for this malignancy.

The data presented here suggest that this may be another quantitative biochemical difference associated with cancer(4). Whether these high levels of norepinephrine reflect an aberrant ovarian activity which may be a factor in the hormonal involvement of ovaries in breast cancer remains to be clarified. If such a relationship does exist, then the way might be open to explore the use of drugs which interfere with adrenergic function as



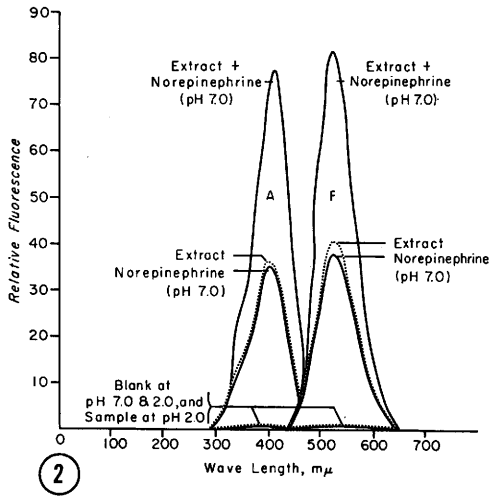


FIG. 1. Norepinephrine and epinephrine in human ovaries.

FIG. 2. Fluorescence characteristics of ovarian extract and authentic norepinephrine. A, activation spectrum with a peak at 407 mμ; F, fluorescence spectrum with a peak at 520 mμ. Norepinephrine was present at 0.172 μg/ml. Reactions carried out at pH 7.0 and 2.0 (see reference 1 for details of method).

adjunct therapy in this disease.

The patients with breast cancer will be followed to see whether there is any relationship between the amount of norepinephrine found in their ovaries at the time of oophorectomy and how well they respond to this operation. Also, an attempt will be made to extend this observation to animals with mammary cancer and to see whether drugs will influence any differences that may be found.

Summary. Of a wide variety of human female disorders, breast cancer was found to be associated with high levels of ovarian norepinephrine. Whether this observation indicates that norepinephrine contributes to an altered ovarian activity as a factor in the hormonal involvement of ovaries in breast cancer remains to be seen.

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