Effect of obesity on conversion of plasma androstenedione to estrone in postmenopausal women with and without endometrial cancer

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The purpose of this study was to ascertain if a relationship exists between the transfer constant of conversion of plasma androstenedione to estrone ($[\rho]^{AE1}_{BU}$) and total body weight or excessive body weight in 50 postmenopausal women, of whom 25 had adenocarcinoma of the endometrium and 25 had no endometrial disease. The $[\rho]^{AE1}_{BU}$ ranged from 0.015 to 0.129 in these 50 women. The $[\rho]^{AE1}_{BU}$ in the women with endometrial cancer was 0.051 ± 0.006 (mean ± S.E.), whereas that in the women with no endometrial disease was 0.039 ± 0.004. These values are not significantly different ($p > 0.05$). The body weights of these 50 women ranged from 104 to 430 pounds. The weight of the patients with endometrial cancer was 234 ± 16 pounds (mean ± S.E.), and that for the women with no endometrial disease was 194 ± 12 pounds. A statistically significant correlation ($p < 0.001$) was found between $[\rho]^{AE1}_{BU}$ and body weight and between $[\rho]^{AE1}_{BU}$ and excessive body weight in both groups of women. Moreover, obesity and aging appear to act in concert to potentiate the conversion of plasma androstenedione to estrone in extraglandular sites since the $[\rho]^{AE1}_{BU}$ is considerably greater among obese postmenopausal women than among comparably obese premenopausal women. (Am. J. Obstet. Gynecol. 130: 448, 1978.)

EXTRAGLANDULAR ESTRONE formation, which occurs through the aromatization of plasma androstenedione, accounts for nearly all endogenous estrogen produced by postmenopausal women.[1-8] The rate of extraglandular estrone formation is determined by the availability of plasma androstenedione and by the extent of its aromatization. In postmenopausal women, nonendocrine tumors of the ovary with hyperplasia of the stroma are the most common cause of an increased production rate of androstenedione.[9, 10] However, the extent of aromatization of plasma androstenedione is known to be increased in a number of states which include hyperthyroidism,[11] aging,[12] and hepatic disease.[7, 13, 14]

In preliminary studies, we[5, 7, 15, 16] and others[17] found that the transfer constant of conversion of plasma androstenedione to estrone was greater in obese women than in nonobese women. Since extraglandular aromatization is the nearly exclusive mechanism of estrone production in postmenopausal women, including those with endometrial cancer,[5-8, 15, 16] and since obesity is a common constitutional feature of women with endometrial carcinoma, we sought to ascertain if excessive body weight is associated with an increase in extraglandular estrone formation in postmenopausal women. Moreover, we attempted to

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Table I. Transfer constant of conversion of plasma androstenedione to estrone in postmenopausal women with no endometrial disease

Subject (No. = 25)	*Race*	*Age (yr.)*	*Height (inches)*	*Weight (pounds)*	*Excessive weight (pounds)*	$[\rho]^{AEI}_{BU}$
A	Negro	51	58	104	0	0.016
B	Negro	81	59	105	0	0.015
C	Negro	52	60	130	10	0.024
D	Caucasian	53	63	140	10	0.033
E*	Caucasian	50	62	140	10	0.024
F†	Negro	56	62	151	21	0.024
G‡	Caucasian	63	61	160	40	0.027
H	Negro	83	62	160	35	0.038
I‡	Caucasian	55	59	163	50	0.021
J§	Caucasian	70	70	168	16	0.078
K§	Negro	57	61	178	50	0.030
L‡	Indian	51	59	185	75	0.023
M‖	Negro	67	61	188	60	0.034
N¶	Negro	73	59	195	85	0.044
O	Caucasian	72	67	195	52	0.048
P	Caucasian	69	60	200	80	0.057
Q	Caucasian	62	67	212	72	0.026
R	Caucasian	56	64	220	90	0.032
S#	Negro	72	64	220	95	0.029
T§	Caucasian	50	63	228	100	0.028
U§	Negro	61	64	230	100	0.037
V	Caucasian	61	60	232	112	0.039
W**	Caucasian	61	62	235	120	0.095
X†	Caucasian	67	62	360	245	0.066
Y†	Caucasian	57	64	363	233	0.093
Mean ± S.E.		62		194 ± 12	70 ± 12	0.039 ± 0.004

*Carcinoma of breast, pelvic metastases.

†Postmenopausal bleeding: proliferative endometrium or cystic hyperplasia.

‡Carcinoma of cervix, Stage I or II.

§Ovarian serous cystadenocarcinoma, Stage I.

‖Acute cholecystitis.

¶Pelvic liposarcoma.

#Benign teratoma of ovary (adult type), hyperplasia of ovarian stroma, atrophic endometrium, and diabetes mellitus.

**Compensated congestive heart failure.

ascertain if extraglandular aromatization is greater in obese, postmenopausal women with endometrial cancer than in similarly obese, postmenopausal women with normal endometria. In the present study, we measured the transfer constant of conversion of plasma androstenedione to estrone in 50 postmenopausal women weighing from 104 to 430 pounds. Twenty-five of these women had endometrial cancer, and twenty-five had normal endometria.

Materials and methods

Extent of conversion of plasma androstenedione to estrone. Each subject received an intravenous infusion of a tracer dose of 10 μCi of (6,7-^{3}H)–estrone and 25 μCi of (4-^{14}C)–androstenedione. The extent of conversion of plasma androstenedione to estrone was computed from the relationship of the ^{3}H:^{14}C ratio of the infused tracers to the ^{3}H:^{14}C ratio of the urinary metabolite estrone which was isolated from a three-six-day urine collection, following hydrolysis of urinary glucuronides with β-glucuronidase by methods previously described in detail.[2, 18] The fraction of the administered (4-^{14}C)–androstenedione converted to (^{14}C)-estrone, i.e., $[\rho]^{AE1}_{BU}$, was computed as follows: $[\rho]^{AE1}_{BU}$ = ^{3}H:^{14}C ratio of infused tracers ÷ ^{3}H:^{14}C ratio of urinary estrone (glucuronide).

This computation gives the fraction of infused (4-^{14}C)–androstenedione metabolized in the same manner as the in vivo internal standard (^{3}H)-estrone. It is emphasized that this calculation does not give the fraction of injected (4-^{14}C)–androstenedione excreted as a (^{14}C)-labeled urinary metabolite of estrone but, rather, reflects the fraction of plasma androstenedione converted to estrone in the tissue sites of aromatization.

Subjects. The race, age, height, body weight, excessive body weight for height, $[\rho]^{AE1}_{BU}$, and medical status of the 25 postmenopausal women with no endometrial disease and of the 25 postmenopausal women with en-

Table II. Transfer constant of conversion of plasma androstenedione to estrone in postmenopausal women with endometrial cancer

Subject (No. = 25)	*Race*	*Age (yr.)*	*Height (inches)*	*Weight (pounds)*	*Excessive body weight (pounds)*	$[\rho]^{AEI}_{BU}$
1*	Caucasian	47	68	135	0	0.026
2†	Negro	62	58	135	23	0.015
3	Caucasian	49	60	143	23	0.016
4*	Caucasian	65	67	159	20	0.022
5*	Caucasian	72	63	159	29	0.100
6	Caucasian	62	60	170	50	0.059
7	Negro	73	62	173	43	0.028
8	Latin	52	60	180	50	0.038
9	Caucasian	62	64	186	56	0.031
10	Caucasian	50	63	190	60	0.016
11	Negro	64	62	193	63	0.064
12	Negro	68	62	195	65	0.025
13*	Negro	78	61	211	91	0.049
14*	Caucasian	65	64	216	81	0.053
15	Caucasian	63	63	255	125	0.043
16	Negro	67	62	259	129	0.048
17*	Negro	69	59	276	161	0.124
18	Negro	63	65	279	144	0.042
19	Negro	62	63	280	150	0.054
20	Caucasian	60	61	281	161	0.042
21*	Caucasian	65	65	282	147	0.103
22	Negro	57	65	296	166	0.056
23*	Negro	59	63	358	238	0.129
24	Caucasian	47	62	420	305	0.080
25*	Negro	51	68	430	280	0.125
Mean ± S.E.		61		234 ± 16	106 ± 16	0.051 ± 0.006

*Compensated congestive heart failure.
†Diabetes mellitus.

dometrial cancer are presented in Tables I and II, respectively. Each subject was ambulatory during the study. Several of these women were receiving antihypertensive agents (none received spironolactone) and/or digitalis or oral hypoglycemic medications before and during these studies, but none had received estrogen treatment for at least four weeks prior to the initiation of this investigation.

Among the 25 postmenopausal women with no endometrial disease (Table I), 10 were considered to be normal postmenopausal women; five had nonendocrine ovarian neoplasms; three presented with postmenopausal uterine bleeding but were found to have proliferative endometrium or cystic hyperplasia of the endometrium; three had Stage I or II squamous cell carcinoma of the cervix; one had acute cholecystitis; one had a retroperitoneal pelvic liposarcoma; one had severe cardiovascular disease with compensated congestive heart failure; and one had disseminated carcinoma of the breast with metastases to the ovaries.

In the 25 postmenopausal women with adenocarcinoma of the endometrium (Table II), the neoplasia was confined to Stage I disease in all women. Nine of these women had severe hypertension and/or compensated congestive heart failure and were receiving digitalis and/or antihypertensive medications. One subject had adult-onset diabetes which was treated with oral hypoglycemic medication. The other subjects of this group were considered normal except for obesity and endometrial cancer.

Each category of subjects was essentially composed of the same racial proportions. Excessive weight was considered to be that amount of body weight which exceeded the upper limit of ideal weight for height and medium body frame, as determined from actuarial data prepared by the Metropolitan Life Insurance Company.

Analysis of data. The curves for the regression lines describing the relationship between $[\rho]^{AEI}_{BU}$ and body weight were computed by the least-squares fit of the exponential function $y = ae^{bx}$, where $y > 0$. This equation was linearized with the transformation $\ln y = \ln a + bx$, and the coefficient of correlation was determined for each line. The regression lines were evaluated by a two-way analysis of variance (Fig. 1).

Results

Tritium:carbon-14 ratios of urinary estrogen metabolites following the administration of (6, 7-^{3}H)–estrone and (4-^{14}C)–androstenedione. The $^3H:^{14}C$ ratios of urinary estrone, estradiol, and estriol obtained following the administration of (6,7-^{3}H)–estrone and

(4-^{14}C)-androstenedione to the 50 women of this study are presented in Table III. The amount of excessive body weight and days of urine collection in each subject are also presented in Table III. In all subjects, the ^{3}H:^{14}C ratio of estriol was at least 85 per cent of that of estrone; in 12 subjects, the ^{3}H:^{14}C ratio of estriol was 115 per cent or greater than that of estrone. The ^{3}H:^{14}C ratio of estradiol was 85 per cent or less than that of estrone in only two subjects and was 115 per cent or greater than that of estrone in only two subjects. The isotopic ratios of estrone, estradiol, and estriol were similar in the other subjects. It has been shown that the ^{3}H:^{14}C ratios of urinary estrone, estradiol and estriol are similar following the intravenous infusion of (^{3}H)-estrone and (^{14}C)-androstenedione in women, provided complete urine collections are obtained over a sufficient time to allow complete urinary excretion of the metabolites of (^{3}H)-estrone and (^{14}C)-estrone.[19] However, the urinary excretion of radiolabeled estrone is faster than that of estriol in obese subjects and the computation of $[\rho]^{AE1}_{BU}$ is accurately computed from the ^{3}H:^{14}C ratio of urinary estrone if radiolabeled estrone excretion is complete, irrespective of the completeness of excretion of radiolabeled estradiol or estriol.

The extent of conversion of plasma androstenedione to estrone in postmenopausal women weighing 104-430 pounds. The transfer constant of conversion of plasma androstenedione to estrone among the postmenopausal women with endometrial cancer, 0.051 ± 0.006 (mean ± S.E., Table II), was not different from that found in the postmenopausal women without endometrial cancer, 0.039 ± 0.004 (Table I). The women with endometrial cancer had 1.5 times more excessive body weight than did the women with no endometrial disease. There was no difference in the extent of conversion of plasma androstenedione to estrone among the women of each group who could be paired by age and excessive body weight. The extent of conversion of plasma androstenedione to estrone as a function of body weight is presented in Fig. 1. In the postmenopausal women weighing 240 to 430 pounds, the efficiency of conversion of plasma androstenedione to estrone was two to four times that found in postmenopausal women of normal weight and was three to 10 times that observed in nonobese premenopausal women.[20] Thus, the increased efficiency of conversion of plasma androstenedione to estrone in these obese postmenopausal women is not solely due to excess body weight; age is also a contributing factor.[12] Nonetheless, from these findings we conclude that increased aromatization of plasma androstenedione is not disproportionately increased in women with endometrial cancer; rather, increased conversion of

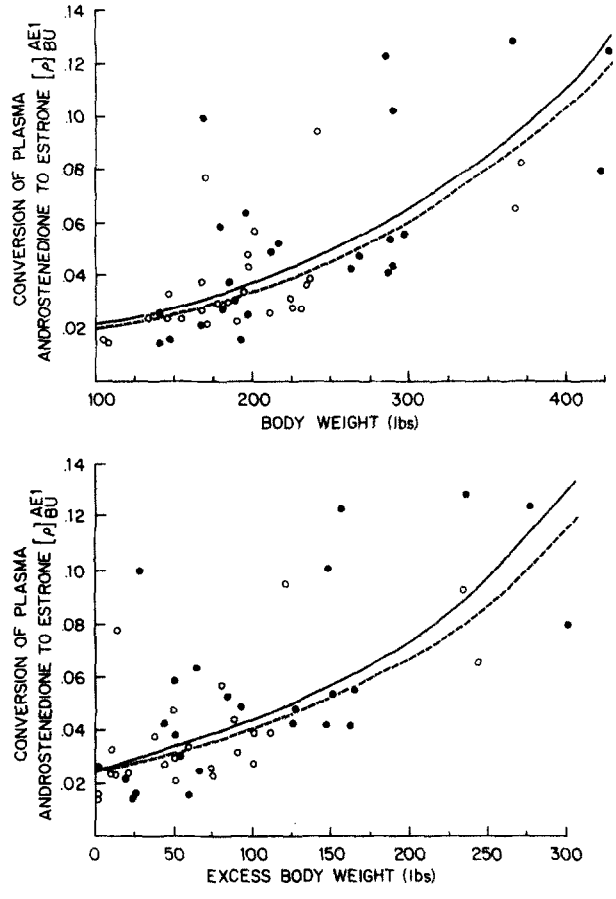

Fig. 1. The extent of conversion of plasma androstenedione to estrone as a function of total body weight (upper panel) or excess body weight (lower panel) in postmenopausal women with endometrial cancer (●——●) and with normal endometria (o---o).In the upper panel, the regression line for the group with endometrial cancer was constructed from the exponential equation $y = 0.0086\ e^{0.0092\ x}$. The regression line for the group with normal endometria is described by the equation $y = 0.0003\ e^{0.0092\ x}$. The correlation coefficients of the lines were 0.6856 and 0.6958, respectively; at 23 degrees of freedom, each was highly significant ($p < 0.001$). In the lower panel, the regression line for the endometrial cancer group was constructed by the equation $y = 0.034\ e^{0.0092\ x}$; for the group with normal endometria, the line is described by $y = 0.025\ e^{0.0092\ x}$. The correlation coefficients of these lines were 0.6848 and 0.6526, respectively, and each was highly significant ($p < 0.001$).

plasma androstenedione to estrone in women with endometrial cancer is related to aging and obesity. However, both of these factors are commonly found in women with endometrial cancer.

Comment

There is substantial evidence that estrogen(s) plays a crucial, if not causative, role in the development of endometrial carcinoma; it is also likely that estrogen is involved in the development or perpetuation and spread of breast cancer. Presently, the nature of this

Table III. ^{3}H to ^{14}C ratio of urinary estrogens following the intravenous infusion of (^{3}H)-estrone and (^{14}C)-androstenedione*

Subject	Excessive body weight (pounds)	Estrone	Estradiol	Estriol	Days of urine collection
Postmenopausal women without endometrial disease					
A	0	25	—	22	3
B	0	26	25	28	3
C	10	16	16	17	3
D	10	12	13	13	3
E	10	16	15	14	3
F	21	17	24	23	3
G	40	14	14	17	3
H	35	11	12	12	3
I	50	19	21	23	3
J	16	5	5	5	3
K	50	13	12	13	3
L	75	17	17	20	3
M	60	12	—	13	3
N	85	9	9	9	3
O	52	8	7	8	3
P	80	7	6	7	3
Q	72	15	16	20	3
R	90	12	12	13	3
S	95	14	13	18	3
T	100	14	15	14	3
U	100	11	11	12	3
V	112	10	10	11	3
W	120	4	4	4	3
X	245	6	6	6	5
Y	233	4	4	4	3
Postmenopausal women with endometrial cancer					
1	0	16	15	26	5
2	23	26	21	23	3
3	23	25	25	24	3
4	19	18	18	17	3
5	29	4	4	4	3
6	50	7	6	7	3
7	43	14	14	15	3
8	50	11	13	10	6
9	56	13	12	14	3
10	60	25	27	28	4
11	63	6	6	8	3
12	65	16	—	17	3
13	91	8	9	8	3
14	81	8	8	14	5
15	125	9	9	11	3
16	129	8	7	11	3
17	161	3	3	3	5
18	144	9	9	13	3
19	150	7	8	8	3
20	161	10	10	11	3
21	147	4	4	5	3
22	166	7	6	7	3
23	238	3	3	4	3
24	305	5	4	5	6
25	280	3	4	5	3

*^{3}H:^{14}C ratios have been corrected to a common ^{3}H:^{14}C tracer dose ratio of 0.4.

role of estrogen in carcinogenesis is unclear. Moreover, the role of nutrition and obesity in the development of endometrial and breast cancer is equally obscure, but there is reason to believe that these factors may modify the activity of the extraglandular, extrahepatic aromatase system to cause increased synthesis of estrone from plasma androstenedione. Importantly, extraglandular, extrahepatic estrone formation is the nearly exclusive mechanism of estrogen formation in postmenopausal women.

Obesity is common among women with endometrial carcinoma; indeed, Corscaden[21] described the constitutional features most frequently encountered in women with endometrial carcinoma: ". . . overweight, of a broad, husky habitus. . . ." Numerous investigators have observed that endometrial carcinoma and obesity are commonly associated, but few have presented specific assessments of the true incidence of obesity in patients who develop endometrial carcinoma. The reported incidence of obesity ranges from 22 per cent of 610 patients with endometrial cancer in one series[22] to 80 per cent of 254 patients in another series.[23] The difference appears to be related to the criteria used to define obesity. Nonetheless, in an in-depth epidemiologic study of 1,000 women with endometrial carcinoma, Wynder and associates[24] stated, "It is apparent from this study that the primary clinical problem of the endometrial cancer patient is obesity."

The present study was undertaken to determine if a relationship exists between the transfer constant of conversion of plasma androstenedione to estrone and body weight or excessive body weight in postmenopausal women and to ascertain if the extent of extraglandular aromatization of plasma androstenedione is increased disproportionately in women with endometrial cancer.

Among the women of the present study, the mean age of the 25 postmenopausal women with Stage I endometrial adenocarcinoma was 61 years (range 47 to 78). Weights ranged from 135 to 430 pounds (mean 234 pounds); all women except one were 14 per cent or more overweight. Twenty of the subjects with endometrial cancer exceeded the ideal body weight for height by 30 per cent and almost half of these women exceeded the ideal weight by 100 to 265 per cent. The women with endometrial cancer had a mean excess body weight of 106 pounds, 36 pounds greater than that of the women in this study with no endometrial disease.

The mean transfer constant of conversion of plasma androstenedione to estrone in the 25 women with endometrial carcinoma was 0.051 (range 0.015 to 0.129, Table II). The mean of these values is greater than that seen in the postmenopausal women with no endometrial disease, 0.039 (range 0.015 to 0.095), and is two times greater than the mean which we found previously for postmenopausal women of normal weight, 0.027 (range 0.016 to 0.036).[6] However, in the women with no endometrial disease, the mean body weight of

194 pounds was 40 pounds less than that of the women with endometrial cancer; the mean excess body weight of these women was 70 pounds.

The extent of conversion of plasma androstenedione to estrone as a function of body weight in both groups of postmenopausal women is illustrated in Fig. 1. A highly significant correlation is found between the $[\rho]^{AE1}_{BU}$ and body weight in these women. However, the regression lines for the relationship of the $[\rho]^{AE1}_{BU}$ as a function of body weight are nearly identical for both groups of women. From these findings, we conclude that the increased conversion of plasma androstenedione to estrone observed in women with endometrial carcinoma is related to obesity and aging and is not unique to women with endometrial cancer. From an analysis of the correlation of plasma estradiol and estrone levels and body weight in postmenopausal women, Judd and associates[25] reached a similar conclusion.

Hausknecht and Gusberg[26] reported that the average transfer constant of conversion of plasma androstenedione to estrone was 0.031 in 21 women with endometrial carcinoma, 49 to 70 years of age (mean 59 years). They did not present the body weights of these subjects but did comment that the subject with the highest $[\rho]^{AE1}_{BU}$, 0.06, was "extremely obese." These investigators also reported that the average transfer constant of the conversion of plasma androstenedione to estrone was 0.017 in 12 normal postmenopausal women whose average age was 58 years (range 50 to 68) but, again, body weights were not presented.

Poortman and associates[27] found that the average $[\rho]^{AE1}_{BU}$ in eight normal postmenopausal women, 49 to 64 years of age (mean 57 years), was 0.025 (range 0.013 to 0.038). None of these women weighed more than 152 pounds. These same investigators found a mean $[\rho]^{AE1}_{BU}$ of 0.029 (range 0.027 to 0.037) in seven women with carcinoma of the breast who were 58 to 76 years of age (mean 68 years), but, again, none of the women weighed more than 158 pounds. If the transfer constant of conversion of plasma androstenedione to estrone is compared in the postmenopausal subjects of the present study, whose body weights are similar to those of the women studied by Poortman and associates,[27] i.e., 104 to 160 pounds, the mean $[\rho]^{AE1}_{BU}$ values are similar in both studies, 0.023 (range 0.015 to 0.038) in our study and 0.025 (range 0.013 to 0.038) in the study of Poortman and associates.

Rizkallah and associates[17] measured the $[\rho]^{AE1}_{BU}$ in 10 women with endometrial carcinoma, seven of whom "were clearly obese." These investigators found that "$[\rho]^{AE1}_{BU}$ was strongly correlated with weight, percent of ideal weight and the weight of excess fat in obese women."

From a number of investigations, considerable evidence has accrued which is strongly supportive of the view that most extraglandular estrogen formation occurs in adipocytes. First, aromatase activity has been demonstrated in adipose tissue in vitro.[28–30] Second, the extent of conversion of plasma androstenedione to estrone in vivo is highly significantly correlated with excessive body weight in postmenopausal women as well as in young ovulatory and anovulatory women.[20] Indeed, the extent of conversion of plasma androstenedione to estrone may be increased tenfold in morbidly obese postmenopausal women. Third, when (^{14}C)-androstenedione is infused intravenously, the (^{14}C)-estrone formed in extraglandular sites enters the blood in obese subjects much more slowly than in nonobese subjects.[19, 31] Only six hours of tracer infusion are required to reach steady-state conditions in thin women (<120 pounds) whereas 48 hours of tracer infusion are required in morbidly obese women (>300 pounds). These findings can be explained most easily if the adipocyte is both the principal site of extraglandular aromatase activity and the site of sequestration of the estrogen product. The slow release of extraglandularly formed (^{14}C)-estrone is also reflected by the slower urinary excretion of (^{14}C)-labeled estrogen metabolites than of (^{3}H)-labeled estrogen metabolites in obese compared to nonobese subjects after the intravenous infusion of(^{14}C)-androstenedione and (^{3}H)-estrone.[19]

The observation that estrone is the nearly exclusive product of extraglandular aromatization of plasma androstenedione,[2, 19] whereas estradiol is the nearly exclusive product of aromatization of plasma testosterone,[32] provides further support for the proposition that adipose tissue is the principal site of extraglandular aromatization. Nimrod and Ryan[30] found that there was little metabolism of estrone formed from androstenedione in adipose tissue in vitro. From these findings it can be surmised that there is little further metabolism of the extraglandularly formed estrogens in the tissue site(s) of aromatization. Based on these observations we conclude that most extraglandular aromatization takes place in adipocytes.

The constitutional features of postmenopausal women that are associated with increased extraglandular estrone formation are also those which dispose women to an increased risk of developing endometrial cancer. Increased extraglandular estrone synthesis can occur if the extent of aromatization of plasma androstenedione increases. Several conditions, in addition to obesity, are known in which increased extraglandular aromatization is found, for instance, aging[12] and hepatic disease.[13–16] Each of these conditions also predisposes women to an increased risk of endometrial cancer.[22, 23, 33, 34] Increased rates of extraglandular es-

trone synthesis also occur if the plasma levels of androstenedione are increased. Several conditions are known in which the plasma level of androstenedione is high, e.g., polycystic ovarian disease,[7] hyperthecosis,[35] and endocrine[7] and nonendocrine[9, 10] tumors of the ovary. With each of these conditions, the risk of development of endometrial carcinoma is also increased. From these considerations, we conclude that the constitutional features of women that are associated with increased extraglandular estrone formation are similar to those observed in women who are at increased risk of developing endometrial cancer. This correlation constitutes another substantive piece of evidence that endogenous estrogen plays a crucial role in the development of endometrial cancer.[36] It is not known whether this role of estrogen is mediated by the action of estrone directly, by the action of estradiol formed from estrone, or by some remote metabolic event.

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