5 0 8 0 1 6 0 0

Request # 50801600

ODYSSEY

JAN 29, 2020

Web (PDF) to: illemail@unthsc.edu

University Of North Texas Health Science Center
Gibson D. Lewis Health Science Library
ATTN: Interlibrary Loan
3500 Camp Bowie Boulevard
Fort Worth, TX 76107-2699

FILLED
JAN 29 20
TXUTTA

DOCLINE: Copy EFTS Participant

Title:	Acta medica Scandinavica. Supplementum
Title Abbrev:	Acta Med Scand Suppl
Citation	1988;723():153-60
Article:	Hormonal abnormalities in obesity.
Authors:	Zumoff B
NLM Unique ID:	0370331
PubMed UI:	3293358
ISSN:	0365-463X (Print)
Fill from:	**Any Format**
NLM Call Number:	W1 AC8552 (Gen); Film S02853
Publisher:	, Stockholm [etc.], distrib
Copyright:	Copyright Compliance Guidelines
Authorization:	mls0621
Need By:	N/A
Maximum Cost:	**$10.00**
Patron Name:	TN: 61458
Library Groups:	HEALTHLI, SCAMEL
Phone:	+1 817-735-2464
Fax:	+1 817-735-0281
Email:	illemail@unthsc.edu
Odyssey:	206.107.44.44/ILL
Alt Deliv.	Article Exchange, Email (PDF), Odyssey
Latest Route:	**Library**: Texas Tech University Health Sciences Center (TXUTTA) **Action**: New Docline Request **Via**: Cell 1

THIS MATERIAL IS PROVIDED IN ACCORDANCE WITH COPYRIGHT LAW (US CODE TITLE 17)

This material may be protected by copyright law (TITLE 17, U.S. CODE)

Bill to: TXUTCO

University Of North Texas Health Science Center
Gibson D. Lewis Health Science Library
ATTN: Interlibrary Loan
3500 Camp Bowie Boulevard
Fort Worth, TX 76107-2699

Acta Med Scand, Suppl. 723: 153–60

Hormonal Abnormalities in Obesity

BARNETT ZUMOFF

From the Division of Endocrinology and Metabolism, Department of Medicine, Beth Israel Medical Center, New York, NY, and the Mt. Sinai School of Medicine of the City University of New York, USA

ABSTRACT. We have found a number of interesting hormonal abnormalities in obese men and women: 1) Obese women have normal levels of estrone, total estradiol, and total testosterone, but as a consequence of their subnormal levels of SHBG, their levels of free estradiol and free testosterone are significantly elevated. 2) Massive weight loss in obese women (to still elevated weight) results in normalization of the previously elevated free estradiol and free testosterone. 3) Obese women have normal plasma DHEA levels, but a significant, age-invariant decrease of the plasma DHEA/T ratio, which could be due to increased tissue activity of 3β-hydroxysteroid dehydrogenase. 4) Massive weight loss produces an age-dependent effect on DHEA levels in obese women: the levels increase to supranormal values in women around age 20, with diminishing increases at higher premenopausal ages and no increase at all at perimenopausal age. 5) Obese men have elevated levels of estrone and both free and total estradiol, and subnormal levels of free and total testosterone and of FSH; all these abnormalities are proportional to the degree of obesity. They also have *relatively* subnormal LH levels, i.e. normal in the face of hypotestosteronemia. The combination of these findings represents a state of mild hypogonadotropic hypogonadism (HHG), which we believe to be induced by the hyperestrogenemia. 6) Normalization of the estrogen levels of obese men, by suppression of adrenocortical secretion of aromatase substrates or by inhibition of aromatase, tends to normalize the HHG. 7) Massive weight loss in obese men normalizes their HHG *without* any decrease in plasma estrogen levels. This suggests that weight loss in obese men results in diminished sensitivity of the GnRH-gonadotropin secretory mechanism to suppression by a given concentration of estrogen. *Key words: obesity, hormones, testosterone, estradiol, FSH, hypogonadotropic hypogonadism, dehydroepiandrosterone.*

The purpose of this review is to brush in the details of a picture of our current understanding of some of the hormonal abnormalities that occur in otherwise healthy obese men and women. Some of the information presented has been obtained by other investigators, but most of it has been obtained in my own laboratory.

STUDY POPULATION

In selecting the normal and obese subjects to be studied, we tried to eliminate as many potentially confounding factors as possible. In women, we excluded subjects with historical, physical, or laboratory evidence of the polycystic ovary syndrome and subjects who had been pregnant or had taken oral contraceptives within one year prior to any study. In both men and women, we excluded significant psychiatric illness, major chronic illness of all kinds and recent acute illness, significant medications within 6 months, and abnormalities of thyroid, kidney, liver, or hematological function. All the women studied were between ages 18 and 47, and were having regular menstrual cycles at a normal interval; all the studies were done in the early follicular phase (days 2–7), when blood hormone levels, especially estrogens, are at their most nearly stable level in the cycle.

METHODS

All hormone levels presented are 24-hour mean plasma levels, obtained by sampling blood (through an indwelling venous catheter) every 20 min, pooling aliquots of the 72 samples, and assaying the pool (1). This procedure eliminates fluctuations due to the inherent pulsatility of the secretion of nearly all hormones and greatly decreases the inter-individual variation of measurements within groups.

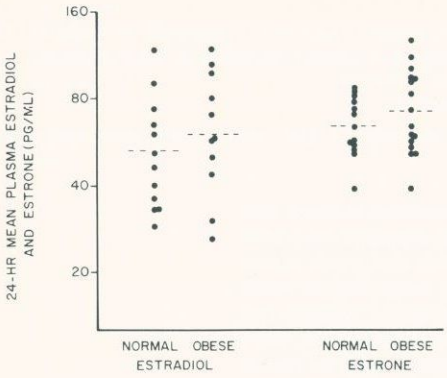


Fig. 1. 24-Hour mean plasma estradiol and estrone in normal and obese women in the follicular stage of the menstrual cycle. There were no significant differences between the normal and obese women with respect to either hormone.

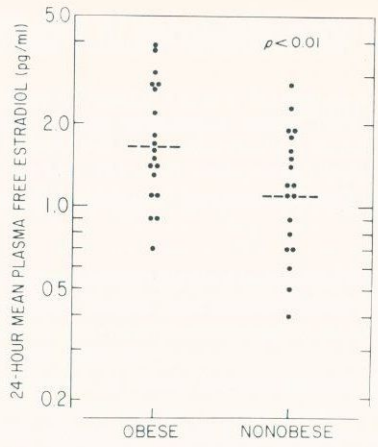


Fig. 2. 24-Hour mean plasma free estradiol in obese and non-obese women. Mean ± SD was, respectively, 1.5±0.7 pg/ml (5.6±2.6 pmol/l) and 1.0±0.26 (3.6±1.0) ($p<0.01$).

Obesity was quantified by reference to the US Air Force table of ideal weights (2). We have found that deviation from the ideal weight so calculated is very highly correlated with total body fat content, as determined by tritium-water dilution, in both men and women. We did not routinely characterize the obesity of our subjects as "gynoid" or "android", though we recognize the great importance of the distinction, clinically and epidemiologically (3, 4). There is some question whether the implications of the "gynoid–android" dichotomy continue to be valid at extreme degrees of obesity, such as that of many of our subjects.

RESULTS

Obese women

Interesting findings have been obtained with respect to estradiol, estrone, sex-hormone-binding globulin (SHBG), testosterone, and dehydroepiandrosterone (DHEA).

Numerous investigators have reported increased aromatization of adrenal androgens (e.g. Δ^4-androstenedione) to estrogens in obese women (5, 6), and several have suggested or implied that obese women have elevated plasma estrogen levels (7–9), but none has presented convincing evidence of the latter. We found quite normal 24-hour mean plasma levels of both estrone and total estradiol in such women (Fig. 1), regardless of the degree of obesity. On the other hand, since their SHBG levels were subnormal, their levels of *free* estradiol were significantly elevated (Fig. 2). These elevated free estradiol levels are of great interest epidemiologically, in the light of recent reports of elevated free estradiol levels in women with breast cancer (10, 11); perhaps the elevated free estradiol levels of obese women contribute to their well-known increased risk for breast cancer (12).

Turning to the effect of obesity on plasma testosterone levels in women, we were somewhat surprised to observe a phenomenon that seems not to have been reported previously: total testosterone levels showed an inverse linear correlation with age in the non-obese premenopausal women (Fig. 3); the levels declined by about 50% between age 20 and age 50. The values in the obese women showed a parallel curve, very slightly higher than that of the non-obese women, but not significantly so. Because of the subnormal SHBG values of the obese women, however, their *free* testosterone levels were signifi-

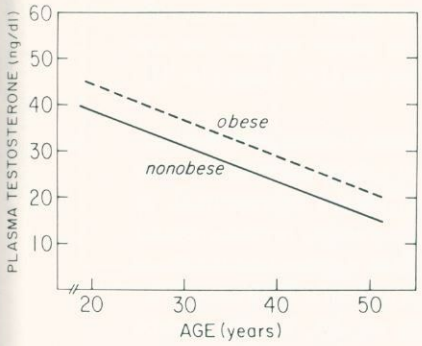


Fig. 3. Influence of age on plasma testosterone in obese and non-obese women. Both groups show about a 50% decrease from age 20 to age 50.

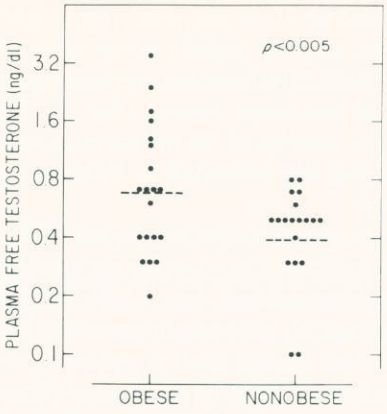
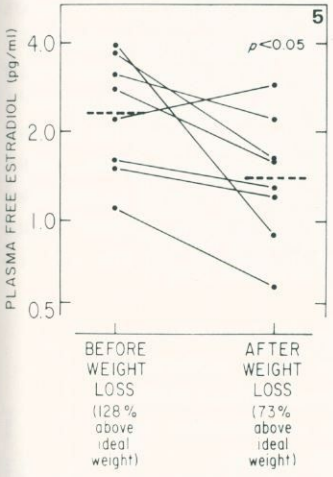


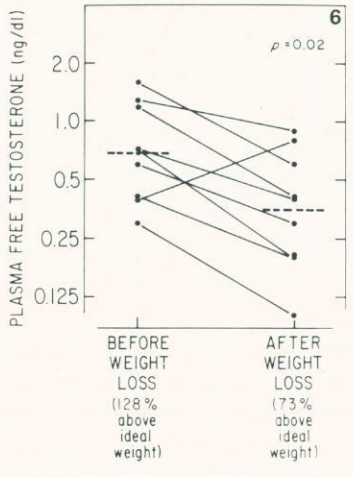
Fig. 4. 24-Hour mean plasma free testosterone in obese and non-obese women. Mean ± SD was, respectively, 0.76±0.47 ng/dl (0.026±0.016 nmol/l) and 0.43±0.11 (0.015±0.009) ($p<0.005$).

cantly higher than those of the non-obese women (Fig. 4). Since elevated plasma testosterone levels have been reported in women with breast cancer (13, 14) and in women with precancerous lobular hyperplasia of the breast (13), this finding too may have some relation to the increased breast cancer risk in obese women.

The effects of massive, sustained weight loss (mean 35 kg) on the abnormal SHBG, free estradiol, and free testosterone of obese women were pronounced: their levels of SHBG, free estradiol, and free testosterone were completely normalized (Figs. 5 and 6).

With respect to DHEA levels, non-obese women showed a linear decline with age, a





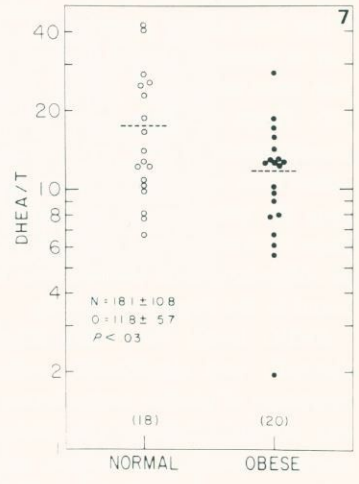


Fig. 5. Effect of weight loss on plasma free estradiol in obese women. All the women showed a decrease; the mean ± SD decreased from 1.5±0.71 pg/ml (5.6±2.6 pmol/l) to 1.4±0.39 (5.3±1.4) ($p<0.05$).

Fig. 6. Effect of weight loss on plasma free testosterone in obese women. All the women showed a decrease; the mean ± SD decreased from 0.76±0.47 ng/dl (0.026±0.016 nmol/l) to 0.49±0.26 (0.018±0.010) ($p<0.025$).

Fig. 7. Plasma dehydroepiandrosterone/testosterone ratio in normal and obese women. Mean ± SD was, respectively, 18±11 and 12±5.7 ($p<0.025$).

phenomenon that has been previously reported (1). The obese women we studied showed a parallel curve, at levels slightly below those of non-obese women, but not significantly so. The ratio DHEA/testosterone was age-invariant and was significantly lower in obese women than in non-obese women (Fig. 7). This could be interpreted as evidence for increased tissue activity of 3β-hydroxysteroid dehydrogenase in obese women; we are currently studying this possibility by Fishman's radiometric technique (15), using (3α-^{3}H)-DHEA Tracers.

The effect of massive weight loss on the DHEA levels of the obese women was startling: the age-vs-concentration curve "pivoted upward", as it were, on a fixed point at its lower end, i.e. at perimenopausal age. Levels became much higher, indeed supranormal, in women around age 20, but were progressively less affected with increasing premenopausal age and showed no change at all at perimenopausal age. A possible explanation for these results can be hypothesized on the basis of recent studies from Kitabchi's laboratory (16): those workers found normal DHEA levels in obese women, as we did, but the normal levels were a resultant of marked, proportionately equal increases in both the production rate (PR) and metabolic clearance rate (MCR) of DHEA; if massive weight loss depressed MCR faster or to a greater degree than it depressed PR, the result would be elevation of plasma DHEA levels.

Why this should happen in younger women but not in older women is not clear, but it is possible that the elevations of the two rates are greater in young obese women than in older obese women in the first place. It is of interest that a similar situation with respect to testosterone in obese women, i.e. normal plasma levels with markedly elevated PR and MCR, has been reported from Kirschner's laboratory (17).

The possible biological implications of the changes in DHEA with weight loss are not clear, but the fact that DHEA levels are subnormal in human coronary artery disease (18) and premenopausal breast cancer (19), and that DHEA is a powerful anti-obesity agent in rodents (20), suggests that there may indeed be important biological implications.

Obese men

It has been widely reported (21, 22), that obese men have elevated plasma estrogen levels, and we obtained similar findings several years ago (23). It has also been reported that those men have subnormal plasma total testosterone levels (21, 24–26), and we too found this (27). There has been some controversy about whether obese men also have subnormal plasma levels of *free* testosterone (21, 24–26), although the controversy has been more verbal than evidentiary: close reading of the literature, including papers by authors who deny the existence of subnormal free testosterone levels in obese men (21, 26), clearly show such subnormal levels in most studies (21, 24–26). Our studies clearly redemonstrated subnormal total testosterone levels in obese men, with the degree of decrease proportional to the degree of obesity.

SHBG levels were also subnormal, but despite this free testosterone levels were distinctly and significantly subnormal (Fig. 8). It is of interest that these moderate decreases of plasma testosterone were not accompanied by clinical hypogonadism: libido was normal; potency was normal, as determined by history and by measurement of nocturnal penile tumescence; and sperm counts and semen volume were normal.

It seems reasonable to attribute the hypotestosteronemia to the effects of the elevated estrogen levels, a relationship that is well known to clinical endocrinologists. The conventional wisdom is that hyperestrogenemia lowers plasma testosterone levels by suppressing the secretion of pituitary gonadotropins; for that reason, we sought evidence of diminished FSH and LH levels in the obese men. Previous literature has been equivocal on this question; several workers have reported subnormal FSH levels and normal or subnormal

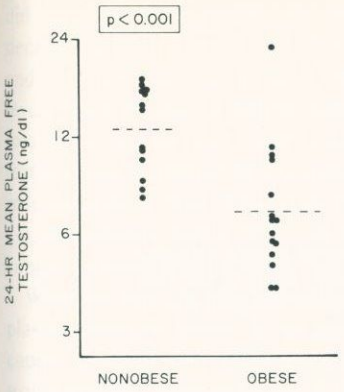


Fig. 8. 24-Hour mean plasma free testosterone in age-matched non-obese and obese men. Mean ± SD was, respectively, 18±5.5 ng/dl (6.1±1.9 nmol/l) and 9.5±5.0 (3.3±1.7) ($p<0.001$).

LH levels in obese men (25, 28), but the data have been inconsistent and unconvincing. Our studies showed clear-cut diminution of FSH levels in obese men (Fig. 9) and normal LH levels. It must be emphasized, however, that normal LH levels are inappropriate, i.e. too low, in the presence of hypotestosteronemia; a recent study by Glass (29) indicates that the LH levels in our subjects should have been elevated to about 195% of normal to be appropriate for their observed degree of hypotestosteronemia.

Putting our data together, what we found in the obese men was a state of mild hypogonadotropic hypogonadism (HHG), presumably induced by hyperestrogenemia. To prove this hypothesis, we set out to lower the plasma estrogen levels of the obese men, in the expectation that this would normalize the HHG in these men.

There are potentially three ways to lower the elevated plasma estrogen levels of obese men: by diminishing the production of the adrenal androgens that are aromatized to estrogens; by decreasing the activity of tissue aromatase; or by decreasing the body weight towards normal, on the assumption that the excess weight is the ultimate cause of the excess estrogen formation. We investigated all three of these approaches.

In the first approach, we gave nine obese men 4.5 mg of dexamethasone daily for 7 days, measuring hormone levels before and at the end of the treatment period; plasma levels of Δ^4-androstenedione and DHEA are decreased about 60% by such treatment (30). Plasma levels of estrone and estradiol were lowered to normal and FSH levels were increased to normal, but testosterone levels remained unchanged. We believe this is because of the complicating direct inhibitory effect of corticoids on testicular secretion of testosterone: normal subjects show a significant *decrease* of plasma testosterone after corticosteroids (31, 32), and the absence of such a decrease in the dexamethasone-treated obese men

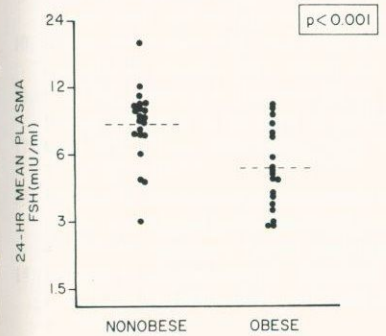


Fig. 9. 24-Hour mean plasma FSH in age-matched non-obese and obese men. Mean ± SD was, respectively, 9.7±5.1 IU/l and 6.5±4.7 ($p<0.001$).

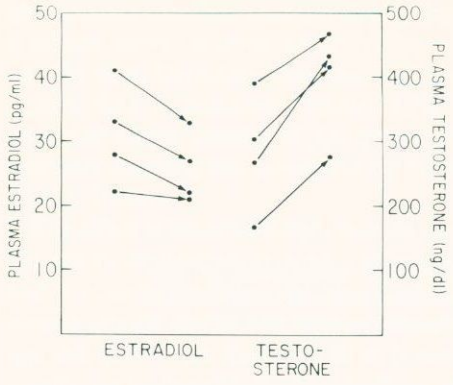


Fig. 10. Effect of testolactone on plasma estradiol and testosterone in obese men. Each of the four men showed a decrease in plasma estradiol and an increase in plasma testosterone.

represents a *relative increase* in testosterone levels. Thus, our study data provide suggestive, but not conclusive, evidence in support of our hypothesis of hyperestrogenemia-induced HHG in obese men.

In the second approach, we gave four obese men 1 g daily of testolactone for 3 weeks, measuring hormone levels before and at the end of the treatment period. With the collaboration of Dr Richard Hershcopf, of Dr Jack Fishman's laboratory at Rockefeller University, we confirmed in vivo (in two subjects) the aromatase-inhibiting effect of testolactone by the radiometric technique, using a tracer of (19-^{3}H)-androstenedione as an aromatase substrate; the drug decreased aromatase activity by about 50%. The testolactone produced a clear-cut decrease in plasma estradiol and a definite increase in plasma testosterone (Fig. 10); FSH values are not yet available. These data too support our hypothesis about the genesis of HHG in obese men.

The third approach, weight loss, produced complex and puzzling results. Stanik et al. (33), in Korenman's laboratory, had reported that weight loss to normal in moderately obese men normalized the elevated estrogen levels and the low testosterone levels; they

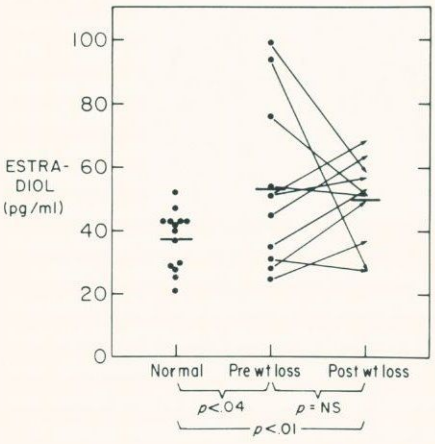


Fig. 11. 24-Hour mean plasma estradiol in normal men and in obese men before and after weight loss. Changes with weight loss varied considerably in magnitude and direction, but there was no significant change in the mean value, which remained supranormal.

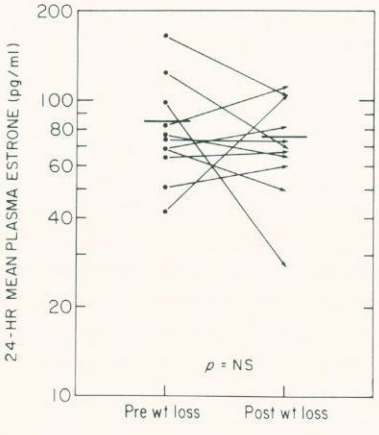


Fig. 12. 24-Hour mean plasma estrone in normal men and in obese men before and after weight loss. Changes with weight loss varied considerably in magnitude and direction, but there was no significant change in the mean value, which remained supranormal.

did not measure gonadotropin levels. We studied 11 men, who lost an average of 53 kg, decreasing from a mean of 167% above ideal weight to a mean of 93% above ideal weight and then maintaining the new, reduced-but-still-obese weight for 6–24 months; hormone levels were measured before weight loss and after stabilizing at the new weight. Plasma total testosterone rose towards normal, proportionately to the amount of weight lost. Free testosterone remained at a constant proportion of total testosterone and therefore likewise rose towards normal; FSH rose essentially to normal. Unexpectedly, estradiol levels (Fig. 11) and estrone levels (Fig. 12) showed no change, on the average; indeed, more of the subjects showed an increase than a decrease.

What we saw, in other words, was a normalization of the HHG *without* a decrease in plasma estrogen levels. If, as we have hypothesized and continue to believe, the HHG is caused by hyperestrogenemic suppression of the hypothalamic-pituitary Gn-RH-gonadotropin system, normalization of the HHG without a decrease in the estrogen levels implies a diminution of the sensitivity of the GnRH-gonadotropin system to suppression by a given level of estrogen. Such a possibility could be tested directly by determining the gonadotropin response to infusions of measured amounts of estradiol before and after weight loss; we plan to conduct such experiments.

ACKNOWLEDGEMENTS

Supported in part by Grant AM 30978 from the National Institutes of Health of the US, and by a grant from The Friends of Research, Beth Israel Medical Center.

REFERENCES

1. Zumoff B, Rosenfeld RS, Strain GW et al. Sex differences in the 24-hour mean plasma concentrations of dehydroisoandrosterone (DHA) and dehydroisoandrosterone sulfate (DHAS) and the DHA to DHAS ratio in normal adults. J Clin Endocrinol Metab 1980; 51: 330–3.
2. Strain GW, Zumoff B, Strain JJ et al. Cortisol production in obesity. Metabolism 1980; 29: 980–5.
3. Kissebah AH, Vydelingum N, Murray R et al. Relationship of body fat distribution to metabolic complications of obesity. J Clin Endocrinol Metab 1982; 54: 254–60.
4. Vague J. The degree of masculine differentiation of obesities: a factor determining predisposition to diabetes, atherosclerosis, gout, and uric calculous disease. Am J Clin Nutr 1956; 4: 20–34.
5. Grodin JM, Siiteri PK, MacDonald PC. Source of estrogen production in postmenopausal women. J Clin Endocrinol Metab 1983; 36: 207–14.
6. Edman CD, MacDonald PC. Effect of obesity on conversion of plasma androstenedione to estrone in ovulatory and anovulatory young women. Am J Obstet Gynecol 1978; 130: 456–61.
7. Vermeulen A, Verdonck L. Sex hormone concentrations in postmenopausal women. Relation to obesity, fat mass, age and years postmenopause. Clin Endocrinol 1978; 9: 59–66.
8. Davidson BJ, Gambone JC, LaGasse LD et al. Free estradiol in postmenopausal women with and without endometrial cancer. J Clin Endocrinol Metab 1981; 52: 404–8.
9. Judd HL, Lucas WE, Yen SSC. Serum 17β-estradiol and estrone levels in postmenopausal women with and without endometrial cancer. J Clin Endocrinol Metab 1976; 43: 272–8.
10. Moore JW, Clark GM, Bulbrook RD et al. Serum concentrations of total and non-protein bound estradiol in patients with breast cancer and in normal controls. Int J Cancer 1982; 29: 17–21.
11. Ota DM, James LA, Jackson GL et al. Obesity, non-protein-bound estradiol levels, and distribution of estradiol in the sera of breast cancer patients. Cancer 1985; 57: 558–62.
12. Choi NW, Howe GR, Miller AB. An epidemiological study of breast cancer. Am J Epidemiol 1978; 107: 510–21.
13. Secreto G, Recchione C, Fariselli G et al. High testosterone and low progesterone circulating levels in premenopausal patients with hyperplasia and cancer of the breast. Cancer Res 1984; 44: 841–84.
14. Secreto G, Recchione C, Cavalleri A et al. Circulating levels of testosterone, 17β-oestradiol, luteinising hormone and prolactin in postmenopausal breast cancer patients. Br J Cancer 1983; 47: 269–75.

15. Fishman J, Bradlow HL, Schneider J et al. Radiometric analysis of oxidation in man: Sex differences in estradiol metabolism. Proc Natl Acad Sci USA 1980; 77: 4957–60.
16. Kurtz BR, Givens JR, Komindr S et al. Maintenance of normal circulating levels of Δ^4-androstenedione and dehydroepiandrosterone in simple obesity despite increased metabolic clearance rates: evidence for a servo-control mechanism. J Clin Endocrinol Metab 1987; 64: 1261–7.
17. Samsjlik E, Kirschner MA, Silber D et al. Elevated production and metabolic clearance rates of androgens in morbidly obese women. J Clin Endocrinol Metab 1984; 59: 949–53.
18. Barrett-Connor E, Khaw K-T, Yen SSC. A prospective study of dehydroepiandrosterone sulfate, mortality, and cardiovascular disease. N Engl J Med 1986; 315: 1519–24.
19. Zumoff B, Levin J, Rosenfeld RS et al. Abnormal 24-hr mean plasma concentrations of dehydroisoandrosterone and dehydroisoandrosterone sulfate in women with primary operable breast cancer. Cancer Res 1981; 41: 3360–3.
20. Yen TT, Allan JA, Pearson DV et al. Prevention of obesity in A^{vy}/a mice by dehydroepiandrosterone. Lipids 1977; 12: 409–13.
21. Schneider G, Kirchner MA, Berkowitz R et al. Increased estrogen production in obese men. J Clin Endocrinol Metab 1979; 48: 633–8.
22. Kley HK, Solbach HG, McKinnan JC et al. Testosterone decrease and estrogen increase in male patients with obesity. Acta Endocrinol (Copenh) 1979; 91: 553–63.
23. Zumoff B, Strain GW, Kream J et al. Obese young men have elevated plasma estrogen levels but obese premenopausal women do not. Metabolism 1981; 30: 1011–4.
24. Barbato Al, Landau RL. Testosterone deficiency of morbid obesity. Clin Res 1984; 22: 647 A.
25. Glass AR, Swerdloff RS, Bray GA et al. Low serum testosterone and sex-hormone-binding globulin in massively obese men. J Clin Endocrinol Metab 1977; 45: 1211–9.
26. Amatruda JM, Harman SM, Pourmotabbed G et al. Depressed plasma testosterone and fractional binding of testosterone in obese males. J Clin Endocrinol Metab 1978; 47: 268–71.
27. Strain GW, Zumoff B, Kream J et al. Mild hypogonadotropic hypogonadism in obese men. Metabolism 1982; 31: 871–5.
28. Amatruda JM, Hochstein M, Hsu TH et al. Testosterone deficiency of morbid obesity: Possible role of the hypothalamus. Clin Res 1975; 23: 571 A.
29. Glass AR. Ketoconazole-induced stimulation of gonadotropin output in men: basis for a potential test of gonadotropin reserve. J Clin Endocrinol Metab 1986; 63: 1121–5.
30. Zumoff B. Unpublished data.
31. Doerr P, Pirke KM. Cortisol-induced suppression of plasma testosterone in normal adult males. J Clin Endocrinol Metab 1976; 43: 622–9.
32. McAdams MR, White RH, Chipp BE. Reduction of serum testosterone level during chronic glucocorticoid therapy. Ann Intern Med 1986; 104: 648–52.
33. Stanik S, Dornfeld LP, Maxwell MH et al. The effect of weight loss on reproductive hormones in obese men. J Clin Endocrinol Metab 1981; 53: 828–32.

Correspondence: Barnett Zumoff, MD, Division of Endocrinology and Metabolism, Department of Medicine, Beth Israel Medical Center, First Avenue at 16th Street, New York, NY 10003, USA.