Obesity is a physiological state associated with alterations in hormone production and metabolism. These hormonal changes may bear on the increased risk for selected neoplastic disorders.

Obesity is associated with increased estrone production in young and older women as well as in men. The source of this increased estrogen appears to be extragonadal metabolism of the prehormone androstenedione, which increases 3- to 4-fold in proportion to the obesity. In severe obesity, androstenedione production itself may be increased, providing extra prehormone for conversion to estrogens. In addition, obesity appears to shift peripheral metabolism of estradiol, resulting in decreased excretion of catechol estrogens which in turn may influence target organ stimulation.

Testosterone production is unchanged in obesity; however, there are decreased levels of sex hormone-binding β-globulin leading to increased clearance rates and spuriously low levels of circulating testosterone in both obese men and obese women. Alterations in sex hormone-binding β-globulin may further lead to changes in ‘free’ estradiol, which may play a role in target organ stimulation.

Other changes noted in obesity include: (a) increased excretion of corticoid metabolites; (b) increased secretion of insulin but decreased insulin effectiveness; (c) blunted growth hormone responses to various challenges; and (d) possibly blunted prolactin responsiveness. There are no reasons at present to suspect that these changes influence cancer risk.

With weight loss, sex hormone-binding β-globulin changes are restored toward normal as are the elevated plasma estrogens and decreased testosterone levels. Because weight loss and dieting per se are associated with many physiological changes, hormonal measurements during these times are difficult to interpret. Few studies to date have been performed in formerly obese patients stabilized at their new weight.

At the Senate Select Committee on Nutrition and Human Needs, the current American diet was characterized as being high in fats, sugars, and total calories (68). Obesity is common in our society; in the United States, it is estimated to exist in 30 to 60% of the adult population (7, 8, 36). Several types of neoplastic disorders, such as carcinomas of the breast, endometrium, and colon, appear to occur more commonly in populations consuming this type of overabundant, obesity-generating diet (6, 46, 79, 82). It thus becomes relevant to question whether a particular diet, obesity, or both factors may be involved as tumor promoters.

At the present time, there are but fragmentary data indicating that a specific eucaloric dietary pattern alters hormone production and metabolism in a given individual (33, 74). There is, however, a growing body of data indicating that obesity per se is associated with alterations in hormone production and metabolism. Some of these changes may provide a link between nutrition and cancer. In the subsequent review, we will consider the hormonal changes associated with obesity and relate their potential significance to the cancer problem.

Estrogen Production and Metabolism

Postmenopausal Women. Studies by Siiteri and MacDonald (71), Longcope (47), and others (30, 63) helped to establish that urinary estrone production rates are elevated in obese postmenopausal women (Table 1). MacDonald et al. (51, 52) showed that, if estrogen production were of sufficient magnitude, endometrial hyperplasia and uterine bleeding could result. Since the postmenopausal ovary no longer secretes estrogens (35, 77), extraneous sources of production were investigated to explain the hyperestrogenemia observed in these women. Several groups have demonstrated increased peripheral metabolism of the prehormone androstenedione to estrone in obese women (30, 47, 50, 63, 71). This pathway of metabolism which normally accounts for all estrogens produced in postmenopausal women becomes even more important in the obese woman (Chart 1). MacDonald et al. (50) have shown a close relationship between excessive body weight and metabolic transformation of androstenedione to estrone. In the postmenopausal woman, androstenedione continues to be secreted by the ovaries, although the adrenal gland is likely to be the major source in this age group. As noted in Table 1, increased peripheral transformation of normal amounts of androstenedione could account for all the estrone produced in obese women; however, recent studies in men suggest that marked obesity is also associated with increased androstenedione production,3 providing an additional source of prehormones for conversion to estrone.

The above data linking obesity with excessive estrogen production have led to much speculation on the relationship of obesity to increased frequency of selective neoplasms. Endometrial cancer has been shown to be 2 to 3 times more common in obese women (53), and a similar increased risk for breast cancer has been noted in obese women (19, 57). Since both neoplasms arise in tissues which normally respond to estrogenic stimulation, a sequence of events shown in Chart 2 can be constructed leading from obesity to excess estrogens to target organ neoplasia. At present, these considerations cannot be applied to link obesity with carcinoma of the colon. The possibility that carcinoma of the endometrium per se in a given patient alters peripheral steroid metabolism was raised by Haukeknecht and Gusberg (30) and Calaog et al. (14), who

1 Presented at the Workshop on Fat and Cancer, December 10 to 12, 1979, Bethesda, Md.
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...demonstrated increased conversion of androstenedione to estrone in such women. These conclusions could not be substantiated by MacDonald et al. (50), who found no differences in androstenedione conversion to estrone between women with endometrial cancer versus normal women when the transfer constants were related to the degree of obesity. Similarly, we found no evidence for increased conversion of androstenedione to estrone in postmenopausal women with established breast cancer (37). It thus appears that obesity and not the presence of cancer influences transformation of androstenedione to estrone.

Finally, if endometrial carcinoma occurs more frequently in obese women through the mechanism of increased estrogen production, MacMahon (53) reminds us that endometrial cancer occurs most frequently at menopausal age, a time when endogenous estrogen production is falling. Similarly, de Waard (19) has shown that obesity is associated with a higher incidence of postmenopausal breast cancer, again at a time of decreased estrogen production. Since estrogenic stimulation is thought to induce hyperplastic (and possibly neoplastic) changes over a prolonged period of time, interest has focused on whether obese women produce excessive estrogens during their younger, reproductive years which then are manifested as neoplasms at target organ sites in later life.

**Women in Reproductive Years.** The determination of estrogen production rates and prehormone conversion to estrogens in younger women is considerably more difficult to determine, because the menstrual cycle is associated with rapid changes in ovarian estrogen secretion. Estrone production rates in normal young women range from a low point of 60 to 100 μg/day to elevations of 2- to 4-fold at peak times prior to ovulation and midluteal phases (4). Edman et al. (21) have shown that a minimum of 4 days is necessary to ensure complete tracer production rates and prehormone conversion to estrogens as neoplasms at target organ sites in later life.

**Table 1.** Estrone production in postmenopausal women (47, 71)

<table>
<thead>
<tr>
<th>Estrone production (μg/day)</th>
<th>Conversion androstenedione to estrone (%)</th>
<th>Estrone from androstenedione (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>20-40</td>
<td>2-3</td>
</tr>
<tr>
<td>Obese</td>
<td>50-120</td>
<td>4-8</td>
</tr>
</tbody>
</table>

**Table 2.** Estrone production rates in obese women (4, 5)

<table>
<thead>
<tr>
<th>Wt (lb)</th>
<th>Estrone Production (μg/day)</th>
<th>Conversion of androstenedione to estrone (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>101-150</td>
<td>113</td>
<td>1.3</td>
</tr>
<tr>
<td>151-200</td>
<td>191</td>
<td>1.6</td>
</tr>
<tr>
<td>201-250</td>
<td>221</td>
<td>2.49</td>
</tr>
<tr>
<td>Over 250</td>
<td>228</td>
<td>4.23</td>
</tr>
</tbody>
</table>

**Chart 1.** Peripheral metabolism of androstenedione in normal and obese subjects. Peripheral aromatization of this C19 prehormone to estrone is significantly elevated in obese subjects, accounting for most or all of the elevated estrogens noted in obese subjects.

**Chart 2.** Schematic diagram showing potential relationships between obesity, increased estrogen production, and target organ stimulation leading to neoplasia. See text for details. Δ4, androstenedione; E1, estrone.

**Production rates.** The data presented in Table 2 thus represent a compilation of estrone production rates and androstenedione conversion to estrone obtained from the combined laboratories of Edman, Longcope, and Kirschner. In each case, estrone production was determined on Days 5 to 8 of the menstrual cycle. These data indicate that estrone production rates in young women increase progressively with body weight. Similarly, peripheral conversion of androstenedione to estrone shows increasing values as a function of obesity. These data strongly suggest that obese women in their reproductive years produce increased (basal) amounts of estrone. Superimposed on this high level are the cyclical estrogens, chiefly estradiol, produced from the ovary during the course of the menstrual cycle. To date, there is no evidence that the developing ovarian follicle of the obese woman hypersecretes estrogens, although Zumoff has found markedly elevated plasma estradiol versus estrone levels in young obese women. The current data indicate that normally menstruating obese women probably produce more estrogens chronically than do their lean counterparts.

Obesity has been associated with other endocrine phenomena which may bear on the hormonal milieu. For example, menarche has been reported to occur earlier in obese girls, possibly triggered by a critical body mass (25, 26). Similarly, menopause is thought to occur later in the obese woman (70). Thus, the obese woman has a prolonged 'menstrual life,' with longer years of exposure to higher estrogen levels. Furthermore, obesity has been associated with an increased incidence of abnormal menstrual cycles, functional uterine bleeding, and anovulation (43, 64). The relationship of abnormal menstrual cycles in women to the increased incidence of breast cancer has been speculated upon by Sherman and Korenman. (69).
Men. Studies in our laboratory demonstrated increased production of both estrone and estradiol in obese men (66), as noted in Chart 3. Schneider et al. (66) further showed increased peripheral metabolism of androstenedione to estrone as well as increased conversion of testosterone to estradiol in obese men. Elevated plasma estrone and estradiol levels have been described in obese men by Stanik et al. (75), Schneider et al. (66), Kley et al. (40), and Zumoff. It is of interest that the increased estrogens produced by obese men appear to have little or no biological effect, evidenced by: (a) lack of gynecomastia or other signs of hyperestrogenism; (b) normal (unsuppressed) plasma concentrations of follicle-stimulating and luteinizing hormones; and (c) decreased rather than increased levels of the sex hormone-binding globulin (see below). The relationship of hyperestrogenemia to neoplastic disorders affecting men is unknown.

Effects of Obesity on Peripheral Estrogen Metabolism. Earlier studies of Lemon et al. (44, 45) showed differences in estril excretion in women with breast cancer and women with varying risks for human breast cancer. Dickinson (20) showed that estril ratios were different in subpopulations of Hawaiian women at varying risks for breast cancer. Estriol quotients comparing estril with other estrogen metabolites were lowest in women at greatest risk for breast cancer and vice versa. An interesting hypothesis was devised suggesting that estril represented an "impeded" or protective estrogen which blocked excessive stimulatory effects of more potent estrogens, such as estrone and estradiol, on the target organ (breast cell) (15, 54). Subsequent studies of Longcope et al. showed, however, that plasma estril levels and estril production rates were no different in women with breast cancer versus normal women (24, 60) and in women with high urinary estril ratios versus those with low estril ratios (48). Thus, it seems likely that differences in excretory patterns of estrogen metabolites seen by Lemon, Dickinson, and others may well be related to diet, obesity, or other influences. These influences probably shift distal estrogen metabolism rather than influence circulating or tissue levels of estril.

Of considerable interest have been the observations of Fishman et al. (23) that peripheral metabolism of estradiol to form catechol estrogens (2-hydroxy metabolites) is decreased in obese women. (Chart 4). The 2-hydroxy metabolites are interesting in view of the data showing that these substances bind to estrogen cytosol receptors (55) but have no inherent uterotrophic action (32). Although much early emphasis had been placed on estril as being an impeding estrogen, it may well be that catechol estrogens are the "truly impeding estrogens." In this regard, Fishman et al. (23) have demonstrated that obesity is associated with increased peripheral metabolism of estradiol to the 16-hydroxy metabolite (estriol) and decreased transformation to the 2-hydroxy metabolite (Chart 4). Additional developments in this area are anxiously awaited.

Androgen Production and Metabolism

Testosterone. Testosterone production rates were found to be normal in obese men (66) as well as in normally menstruating obese women. However, many laboratories, including our own, reported decreased circulating testosterone levels in obese men (1, 29, 39, 40, 66), and we now have data indicating decreased testosterone levels in obese women. It became apparent that obesity was associated with increased metabolic clearance rates of testosterone caused at least in part by alterations in the sex hormone-binding plasma protein (66). Several groups using different techniques to assess sex hormone-binding protein binding have confirmed the association of obesity with decreased concentrations of this β-globulin (1, 29, 40, 66). As a result, testosterone which is produced in normal amounts is cleared at an excessive rate in the obese person. Although decreased sex hormone-binding β-globulin levels seen in obese men and women may account entirely for the phenomenon of increased clearance rates, the possibility of increased tissue extraction (presumably at adipose tissue sites) cannot be excluded and will be considered below. In any event, determination of the "free testosterone," calculated as a product of the testosterone and the dialyzable testosterone fraction, shows normal rates in both obese men and obese women.

The significance of decreased sex hormone-binding globulin levels in obesity and the resultant alterations in testosterone metabolism remain obscure at the present time. In this regard, a recent study by Kley et al. (39) suggests that "free estradiol" is elevated in obese men. Since estradiol is also bound with
high affinity to the sex hormone-binding globulin, decreased levels of this binding protein along with increased extragonadal production of estradiol from testosterone resulted in the finding of elevated free estradiol levels. Thus, alterations in sex hormone-binding globulins may become more relevant with regard to circulating biologically active estrogens than to androgens.

**Androstenedione.** This C_{19} steroid has no androgenic activity of its own but, as discussed earlier, is a key prehormone in the extragonadal production of estrogens noted in obesity. Recent data from our laboratory indicate that androstenedione production rates are elevated in markedly obese men as noted in Chart 5. Our data on androstenedione production in obese women are too limited to draw a similar conclusion at this point. It is of interest that clearance rates of androstenedione are considerably elevated from 2500 to 8000 liters/day in markedly obese men. Since androstenedione is not appreciably bound to the sex hormone-binding globulin, these data suggest increased tissue extraction and/or other factors as playing a role in excessive clearance of androgenic steroids. Furthermore, if androstenedione production rates are increased in obesity, then more prehormones are available for extragonadal metabolism to estrone. Thus, excessive production of this steroid in obesity may bear greatly on hyperestrogenism noted in obese individuals.

**DHEA.** This C_{19} androgen has been of interest in defining the hormonal milieu of women with breast cancer. Poortman et al. (61) reported decreased DHEA production in women with breast cancer. DHEA is transformed in its peripheral metabolism to Δ^{5}-androstenediol, and this metabolite was observed to competitively bind with estrogen cytosol receptor in target tissues (61, 76). These data raise the possibility that the DHEA metabolite could, under physiological conditions, be active as an impeding estrogen, modulating the stimulatory effect of more potent estrogens. In this regard, an earlier report by Lopez and Kiehl (49) indicated decreased excretion of DHEA in the urine of very obese subjects. Confirmatory data are needed here.

**Other Androgens.** Bulbrook et al. (9, 11, 12) observed a correlation between excretion of urinary 17-ketosteroid metabolites and response of patients with metastatic breast cancer to endocrine manipulation. From these data, a discriminant function was constructed relating the excretion of the 17-ketosteroids to that of 17-hydroxysteroids. A positive discriminant in urine of a given patient with breast cancer suggested the presence of a hormone-responsive tumor; similarly, a negative value suggested hormone unresponsiveness of the patient. Subsequent studies from this group showed that lower levels of urinary etiocholanolone were present in the urine of asymptomatic women who subsequently developed breast cancer (10). Decreased 17-ketosteroid excretion was thus associated with a higher incidence of breast cancer in women and a poor response of patients with breast cancer to endocrine therapy. These workers subsequently demonstrated decreased excretion of 17-ketosteroid metabolites in Japanese (low-risk) versus British (high-risk) women, a trend opposite to that expected (13). Furthermore, Zumoff et al. (81) found that chronic illness, undernutrition, or even dieting could decrease the conversion of circulating androgens to their usual urinary 17-ketosteroid metabolites, thereby decreasing the quantity of 17-ketosteroids excreted. Again, the role of under- or overnutrition comes to the foreground in our understanding of hormonal changes noted in patients with hormone-responsive cancers.

**Cortisol Metabolism in Obesity**

In earlier studies, Schteingart et al. (67) suggested increased adrenal cortical activity in obese subjects, as reflected by increased urinary 17-hydroxysteroids and increased cortisol secretion rates. By contrast, plasma cortisol and urinary free cortisol concentrations are not elevated in obese subjects. Furthermore, the normal diurnal pattern of cortisol secretion is generally maintained (7), and obese subjects usually exhibit suppressibility with exogenous glucocorticoids (67). Migeon et al. (56) demonstrated that obese subjects exhibit enhanced turnover rates of cortisol, possibly accounting for lower-than-expected plasma cortisol concentrations. The explanation for apparent increased cortisol secretion rates and excretion rates in obese subjects is not apparent. Adrenocorticotropic hormone levels are normal in obese men.

Normalization of adrenocortical functions by relating the excretion and secretion rates on a weight basis has been attempted (16, 41, 56). The significance of these minor abnormalities of cortisol production and hydroxysteroid excretion in obese subjects in relation to oncogenic potential is not understood at present.

**Insulin Secretion and Action**

Obesity is associated with insulin hypersecretion. Perley and Kipnis (59) found fasting levels of plasma insulin to be elevated 3-fold in obese subjects. Furthermore, insulin responses to glucose, proteins, or other insulin secretagogues administered p.o. or i.v. were approximately double those observed in lean controls. With progressive obesity, there is an increased inci-
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Evidence of impaired glucose tolerance despite elevated basal insulin levels and excessive insulin responses, implying an impaired peripheral action of insulin or 'peripheral insulin resistance.' The mechanism and sites of insulin resistance in obesity have been areas of great interest. Roth et al. (3, 73) demonstrated a decreased number of available insulin-binding sites in tissues obtained from experimentally obese animals and from circulating lymphocytes of obese patients. Other groups have found impaired insulin action at the level of adipose tissue (35, 58), liver (22), and other sites (62). Studies from other laboratories, however (2, 58), suggest impaired insulin action at cellular sites distal to the binding of insulin. Most groups agree that marked improvement of insulin effectiveness is observed in obese patients shortly after institution of weight loss and/or starvation programs (3). Most cases of maturity onset diabetes mellitus are remarkably ameliorated by weight loss and/or starvation (27, 38).

Although the phenomena of hyperinsulinism, blunted insulin action, and increased incidence of impaired glucose tolerance observed in obese subjects provide an explanation for the genesis of maturity onset diabetes mellitus, there is as yet no ready association between hyperinsulinism and neoplastic induction. It should be remembered, however, that under normal circumstances insulin is a potent anabolic hormone, and its potential role in tumor stimulation should not be overlooked.

Human Growth Hormone Metabolism

Several lines of data indicate that obesity is associated with blunted growth hormone responses to a variety of challenges. Although basal levels of growth hormone are normal in obese subjects, both Roth et al. (65) and Yalow et al. (80) observed that late growth hormone responses which occur 4 to 6 hr after a glucose load were decreased in obese subjects. Furthermore, the growth hormone responses to hypoglycemia, 2-deoxyglucose, and arginine (5, 80) all are impaired in obese compared with normal subjects. The significance of blunted growth hormone responses noted in obesity with hormone-related neoplasms is presently obscure.

Prolactin

Evidence for disordered prolactin secretion in obesity is sketchy at present. Wilcox (78) demonstrated normal basal prolactin levels and normal response to TRH-provocative tests in obese women. By contrast, Copinschi et al. (17) observed decreased nocturnal release of prolactin as well as growth hormone in obese subjects. Recently, Kopelman et al. (42) reported normal basal prolactin levels in obese subjects but decreased prolactin responses to both standard 200-µg doses of TRH and insulin in massively obese women. By contrast, prolactin responses in these same patients to a combined test of pituitary function using insulin, gonadotrophin-releasing hormone, and TRH were normal. These conflicting sets of data raise the question of the adequacy of the stimulus used to provoke prolactin secretion. Perhaps a standard 200-µg dose of TRH may be inadequate as a test of prolactin secretion in normal or slightly obese women; however, a dose per weight schedule may be needed in markedly obese women. In any event, these data suggesting decreased prolactin secretion in obese women along with the studies of Hill and Wynder (33) showing that prolactin secretion is lowered in women after high-carbohydrate, high-fiber diets provide grounds for further investigation on the roles of nutrition and obesity in the secretory responses of this hormone.

Effect of Weight Reduction

If obesity is a physiological state characterized by alterations in hormone production and metabolism as well as by increased predilection for certain cancers, what are the prospects of reversing these abnormalities? In this regard, Sitteri et al. (72) reported no change in urinary estrone production rates or in androstenedione conversion to estrone in 6 obese subjects studied before and after significant weight loss. The validity of these studies, however, has been questioned by the authors, who point out that "after" studies may have been performed during an unphysiological state. More recent data by Stanik et al. (75) demonstrated that 10 weeks of weight loss in men corrected the increased plasma estrone and estradiol and the decreased levels of plasma testosterone toward normal. Ongoing studies in our laboratory have shown that starvation and weight loss are associated with restoration of the sex hormone-binding β-globulin toward normal in both obese men and obese women. It is important to emphasize that dieting may be associated with significant changes in hormone metabolism per se. It thus seems quite risky to extrapolate hormonal values obtained during the process of weight loss as being indicative of changes that might be expected after the period of weight loss is ended and the subject is stabilized at a new, lower weight level. At the present time, only a few studies are available that examine hormone parameters in the stabilized, formerly obese subjects. Until such data are more abundant, we can only speculate that some or most of the hormonal abnormalities reported in obese subjects are reversed with weight loss.

References


Obesity, Hormones, and Cancer

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