Obesity produces a variety of alterations in the reproductive system and, similarly, manipulations of the hypothalamic–pituitary–gonadal axis produce changes in food intake, body weight and fat distribution. In men, the primary effects of obesity are a weight related reduction in testosterone and, with massive overweight, a reduction in free testosterone. In females, the weight-related development of menarche leads to earlier menarche in obese girls than in normal weight girls. One explanation for the relationship of fatness to menarche may be the ob protein (leptin) which is defective in the obese (ob/ob) mouse. Leptin is secreted by adipose tissue in proportion to the quantity of fat and may serve as a signal to the hypothalamus that fat stores are adequate to nourish a conceptus to term. In women, parity affects obesity and obesity in turn affects the regularity of the menstrual cycle. In many experimental animals with obesity, particularly the genetic forms of obesity, there is complete infertility in the females and marked impairment of reproductive function in the males. In animals with hypothalamic lesions, there is a gender effect on the magnitude of weight gain associated with the sexually dimorphic regions in the medial preoptic area. Castration with removal of oestrogen is followed by obesity in female animals and this can be prevented, as can most forms of obesity, by adrenalectomy. The inhibitory effects of oestrogen on food intake may result from suppression of neuropeptide-Y or galanin peptidergic systems in the arcuate nucleus or medial preoptic area.

Key words: body fat/galanin/neuropeptide Y/neurotransmitters/steroids

Introduction
Both over-nutrition and under-nutrition are associated with alterations in the reproductive system. In women who are long-distance runners, ballet dancers, or those who undergo significant weight loss from anorexia nervosa, the menstrual cycle becomes irregular or ceases. At the other extreme, excess body weight and obesity are associated with alterations in the reproductive system in women and frequently accompany obesity in experimental animals. This paper will focus primarily on the relationship between obesity and reproduction and will be divided into two parts, the first part dealing with alterations in human beings, and the second part with data from experimental animals which may provide enhanced understanding of the altered state in human beings.

Obesity and the reproductive system in human beings

Males
Table I presents a brief summary of the alterations observed in males in relation to obesity. Although testicular size remains normal, the plasma concentration of testosterone decreases as obesity increases (Kley et al., 1980). This decrease in total testosterone results from a reduction in the level of sex hormone binding globulin (SHBG). The reduction in SHBG, on the other hand, appears to reflect the increased level of insulin and insulin
Table I. Testis and obesity

<table>
<thead>
<tr>
<th>Testis size</th>
<th>N</th>
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</thead>
<tbody>
<tr>
<td>Serum testosterone (total)</td>
<td>↓</td>
</tr>
<tr>
<td>(free)</td>
<td>N</td>
</tr>
<tr>
<td>SHBG</td>
<td>↓</td>
</tr>
<tr>
<td>Production testosterone</td>
<td>N</td>
</tr>
<tr>
<td>FSH–LH (basal)</td>
<td>N</td>
</tr>
<tr>
<td>Response to LHRH</td>
<td>N</td>
</tr>
<tr>
<td>Clomiphene</td>
<td>N</td>
</tr>
<tr>
<td>HCG stimulation</td>
<td>N</td>
</tr>
<tr>
<td>Oestrone and oestriadiol production</td>
<td>↑</td>
</tr>
</tbody>
</table>

SHBG = sex hormone binding globulin; FSH = follicle stimulating hormone; LH = luteinizing hormone; LHRH = luteinizing hormone-releasing hormone; HCG = human chorionic gonadotrophin.

The recent isolated ob-protein (leptin) may provide this signal. This protein is only produced in adipocytes. The larger the fat mass the more leptin that is produced. When this protein is defective in the obese (ob/ob) mouse, the reproductive system remains pre-pubertal. Leptin provides an ideal signal to tell the brain that the body has sufficient stores of nutrients to nourish the fetus to term.

Women with hirsutism and anovulatory cycles are on average 14 kg heavier than women with no menstrual abnormalities. As the degree of excess weight increased the number of women with anovulatory cycles also increased. Of women who were <20% overweight only 2.6% had anovulatory cycles compared with 8.4% of women who were >74% overweight. The greater the duration of obesity the greater the amount of facial hair which is present. Obesity occurring in the teenage years is associated with an increased number of married women who never became pregnant and with a higher likelihood of surgery for polycystic ovaries.
These findings indicate that excess body weight can influence the age at onset of menstruation as well as the subsequent regularity of this process. Though the mechanisms for the disorders are unknown the attendant hormonal abnormalities in obese women are reversible with weight loss.

The function of the reproductive system in women is complicated by the metabolism of steroids in other organs with resulting production of biologically active steroidal products. Δ4-Androstenedione which is produced by the adrenal gland can be converted to oestrone by the stromal cells of adipose tissue. Muscle may also convert oestrone to oestradiol. Because the ovarian production of oestradiol in premenopausal women is high, the enhanced conversion of Δ4-androstenedione to oestrone in obese women does not increase circulating concentrations of oestrogen. However, in the post-menopausal woman, the concentrations of oestrogen appear to increase. When castrated obese and non-obese women were given implants of oestradiol, the obese women had higher levels of Δ4-androstenedione and free testosterone. Studies of oestradiol metabolism show that obese women had decreased hydroxylation at the C2 position and increased oxidation at the 17-α position. Hydroxylation of the 16-α position, however, was not significantly influenced by obesity.

Pregnancy influences obesity and vice versa. Obese women tend to have heavier infants and larger placentas. Both placental weight and maternal weight are predictors of childhood weight at entry to school. Conversely, the number of pregnancies influences the degree of obesity. Women who have children have a step-wise increase in weight and likewise show an increased prevalence of obesity.

Just as the onset of menarche is earlier in obese women, so data suggests that the onset of ovarian failure and increased production of FSH at menopause occurs four years earlier in obese women than in women of normal weight. In women there is a positive association between the degree of visceral fat accumulation and free testosterone levels. The increased testosterone produced from peripheral tissues may account for enhancing visceral fat accumulation in post-menopausal women.

The polycystic ovary syndrome (PCOS)

Obesity, hirsutism, anovulation, multiple cysts in the ovaries and insulin resistance characterize a syndrome known as the polycystic ovarian syndrome (PCOS), a disorder of unknown aetiology (Kiddy et al., 1990; McClusky et al., 1992; Pasquali and Casimirri, 1993; Insler et al., 1993; Holte et al., 1994; Singh et al., 1994). The high frequency of increased fat tissue in such women again suggests the coupling of reproduction to nutritional factors. This syndrome is characterized by increased levels of circulating LH which is secreted in exaggerated pulses. The increased LH is thought to be responsible for the increased ovarian production of steroids and impaired follicular development. When LH secretion is inhibited with long-acting GnRH agonists, androgen secretion is reduced showing the importance of LH stimulation of the ovary in the hyperandrogenization associated with this state. In contrast to the increased levels of LH, FSH concentrations are generally reduced (Dunaif et al., 1989; Nestler et al., 1991; Rittmaster, 1993; Buyalos et al., 1995; Dos Reis et al., 1995). Women with PCOS and anovulation have high levels of insulin resistance and altered IGF-I binding protein levels. It may enhance risk for myocardial infarction (Dahlgren et al., 1992; Anderson et al., 1995) and can be treated with antiandrogens (Diamanti-Kanarakis et al., 1995).

Experimental obesity and the reproductive system

Hypothalamic obesity

In early studies following the demonstration by Hetherington and Ranson (1940) that electric lesions in the ventromedial hypothalamus (VMH) could induce hyperphagia and obesity, Brobeck et al. (1942) demonstrated that these lesions not only induced hyperphagia and increased body weight but also decreased physical activity and produced irregular oestrous cycles. Subsequent studies demonstrated that VMH lesions were produced more routinely in female rats which have increased numbers of sexually dimorphic neurons in the ventromedial and preoptic areas. As hypothalamic lesions became more discrete, two separable syndromes emerged, neither of which impaired
the reproductive axis (Bray et al., 1989). The first syndrome associated with discrete lesions in the ventromedial nucleus was associated with decreased activity of the sympathetic nervous system, increased activity of the parasympathetic nervous system and little or no increase in food intake. A second syndrome associated with discrete lesions in the paraventricular nucleus was associated with hyperphagia but with limited alterations in the function of the autonomic nervous system. These two discrete areas suggest that obesity can be the result of hyperphagia alone following damage to the paraventricular nucleus or occur in relation to disturbances in the balance between sympathetic and parasympathetic nervous systems observed after lesions in the ventral medial nucleus, (VMN) or reciprocal changes in these systems observed after lesions in the lateral hypothalamus.

**Genetic obesity**

Table III is a list of the single gene models of obesity and the status of their reproductive system. In the obese (ob/ob) and diabetes (db/db) mouse, the females are infertile and the males show marked impairment in their reproductive function. The fatty Zucker rat (fa/fa), which has a syntonic genetic locus on rat chromosome 5 to the diabetes (db/db) mouse locus on chromosome 4, also shows marked impairment of the fertility of the female and some impairment of mating in the male. Other models, including the fat mouse, tubby mouse and the yellow mouse show only modest impairments in fertility relative to the recessively inherited forms described above. Removal of adrenal steroids by adrenalectomy or treatment with RU486 will reduce weight gain and correct most of the abnormalities in the recessively inherited forms of obesity. The two systems for which adrenalectomy produces no improvement are the reproductive system and the temperature regulatory system (Shimizu et al., 1993). In this paper, we suggest that these defects might modulate the action of a number of members in the steroid super family including glucocorticoid, oestradiol, aldosterone, thyroxine, vitamin D and retinoids.

Recently, the genes and gene products for three of these mice have been identified. The agouti protein in the yellow mouse is over-expressed in a variety of tissues and appears to be a competitive inhibitor for the melanocyte stimulating hormone (MSH) receptor (Lu et al., 1994). Such an inhibition would impair the darkening of the coat colour...
by blocking the response to MSH and would lead to hyperphagia by blocking the inhibitory effects of feeding observed with α-MSH. The second gene to be cloned was the ob gene on chromosome 6 (Zhang et al., 1994). In the obese (ob/ob) mouse, this 167 amino acid protein is truncated with a stop codon at bases 105 in the protein sequence leading to a truncated ineffective protein. The message for this gene is expressed only in white adipose tissue. This suggests that this secreted peptide may be the regulator between adipose tissue and the brain, muscle, and liver, which has been long sought. This peptide could provide the signal for the onset of menarche since the quantity of ob protein appears to be related to the quantity of body fat (Considine et al., 1995). The third mouse, FAT, has a defective carboxypeptidase which is involved in cleavage of a number of peptides.

**Oestrogen and obesity**

In experimental female animals, castration produces obesity (Wade and Schneider, 1992). This effect can be prevented by treatment with oestradiol. Rhythm in the reproductive cycle is also associated with alterations in food intake, with oestrogen producing a decrease in food intake in rodent models. Like the genetic forms of obesity, adrenalectomy prevents the effects of castration on the development of obesity (Bray et al., 1989).

**Neuropeptides, reproduction and food intake**

The isolation of neuropeptide Y (NPY) in 1982 (Tatemoto et al., 1982) and galanin in 1983 (Tatemoto et al., 1983) opened a new vista on the relation of food intake and reproduction. NPY was rapidly recognized to increase food intake dramatically when injected into the ventricular system of the brain or into many hypothalamic nuclei. Food intake was particularly increased during the nocturnal phase. If NPY was chronically infused, obesity could be produced (Cazeflis et al., 1993). Antibodies to NPY (Shibasaki et al., 1993) or antisense oligonucleotides to NPY injected into the paraventricular nucleus (PVN) (Akabayashi et al., 1994) both decreased food intake. Injections of NPY produced a drastic suppression of ejaculatory and mounting behaviour in experimental animals. Castration in males was shown to decrease the mRNA concentration for NPY in the arcuate nucleus and testosterone restored this value to normal (Sahu et al., 1992; Urban et al., 1993). Progesterone was shown to produce a parallel modulation in the concentration of GnRH and NPY. Sar et al. (1990) and Brann et al. (1991) showed that oestradiol and NPY were co-localized in a subset of cells in the arcuate nucleus. The clear reciprocal relationships between feeding and the reproductive system were demonstrated in the work of Cazeflis et al. (1993) who infused NPY at several dose levels into the ventricular system of rats. There was a dose-dependent increase in food intake, water intake and body weight in these animals. Similarly there was a dose-dependent decrease in pituitary and ovarian weight and a significant inverse correlation between ovarian and pituitary weight and food intake suggesting that NPY had activated one system and inhibited another.

Galanin likewise has important effects on feeding and on the reproductive system. Injection of galanin into the ventricular system or into the paraventricular nucleus significantly increases food intake and inhibits the sympathetic nervous system. Unlike NPY, however, chronic infusion of galanin does not produce a chronic weight gain or obesity (Smith et al., 1994). Galanin will increase the intake of fat or carbohydrate depending upon the primary preference of the animal. Use of antisense oligonucleotides to galanin mRNA produced a dramatic decline in fat ingestion and body weight in rats suggesting that this peptide may be important in the control of feeding. Galanin-like immunoreactivity is increased in the median eminence and anterior pituitary during the first oestrous and dioestrous phases of the reproductive cycle. Injection of pregnant mare’s serum gonadotrophin (PMSG) increased mRNA for galanin by approximately two-fold in the paraventricular and preoptic regions of the hypothalamus (Gabriel et al., 1992). In the medial preoptic area (MPOA), 13% of the cells which concentrate oestradiol were positive for immunoreactive galanin. There was likewise an increase of 3–5 fold in the oestradiol concentrating cells in the sexually dimorphic medial preoptic areas of female versus male rats.
These data on galanin and NPY show that each has an important role in the reproductive process modulating the LH surge and GnRH production by hypothalamic neurons. Can either of these peptides directly account for the castration induced hyperphagia and obesity? The gonadal hormones appear to increase galanin and NPY and yet decrease food intake. One possibility is suggested by the interaction between progestogens and the reproductive system. The progestogen megestrol acetate (Megace) is known to increase food intake and body fatness and has been used in treatment of patients with breast cancer. In experimental animals, Megace increased food intake and increases the concentration of NPY in the arcuate nucleus, lateral hypothalamus, MPOA, VMN and + DMN (McCarthy et al., 1994). One might argue that the feeding system has a reciprocal relationship to arcuate NPY neurons modulating feeding which involve the progestational receptors serving a positive effect and the oestradiol receptors serving as an inhibitory system to the progestational agent. Such a two pronged system could account for the effects observed in the hyperphagia and obesity associated with castration and the suppression of food intake associated with oestrogen and its stimulation by progestational agents.

References


