Nor should it be assumed that scientific results and hypotheses, elaborated from within the various subdisciplines in cancer research, are hatched in a vacuum. Epidemiologists sometimes borrow fearlessly from scientists at the bench in framing new hypotheses. Likewise, bench scientists are better informed when they realize the trends that epidemiologists can tease out of massive data from population studies.

Ultimately, public health policy planners don't give a hoot for the mechanisms underlying a disease. Their goal simply is to reduce disease incidence. Thus, NRC's policy recommendations inevitably didn't and couldn't take into account much that is currently exciting in fundamental research on cancer.

Regardless of such drawbacks, however, somebody must deal with public health policies, especially those relating to diseases such as cancer. NRC diet recommendations cannot "be regarded as offering a cancer-free life," Grobstein points out. "But the weight of evidence in favor of preventative measures is growing. . . . Cancer is not as inevitable as death and taxes." □

Eating disorders linked to hormone imbalances

To endocrinologists, the axiom isn't: "You are what you eat," but rather: "You are how much you eat." At least that is the impression one gets from research findings on the hormonal effects of disordered nutrition described at the 65th annual meeting of the Endocrine Society held recently in San Francisco.

That research focused on the endocrine systems of people who severely overeat or undereat. It turns out, perhaps not surprisingly, that both obesity and anorexia nervosa—the clinical name for what amounts to self-imposed starvation—are associated with significant changes in the body's hormone balances.

Barnett Zumoff, a physician at Beth Israel Hospital in New York City, described research on the system of reproductive hormones in obese women and men. Such studies, Zumoff says, "have revealed multiple abnormalities in the levels of pituitary, ovarian, and testicular hormones." The abnormalities, he says, "are strikingly different in men and women; endocrinologically, obesity is virtually two different diseases in the two sexes."

According to Zumoff, research on the endocrine effects of obesity began because of clinical observations that suggest that obese men and women suffer impaired reproductive function. However, he says, such conclusions are somewhat shaky: For men, the reference is a 1926 paper that virtually no subsequent data support; and for women, an unrelated disease—polycystic ovary syndrome—which does affect reproductive function, likely accounts for the clinical observations.

Nevertheless, research has revealed hormonal irregularities in the obese. It has been known for some time that women retain intravenously administered estradiol (one of the family of estrogen molecules) in proportion to the degree of their obesity, Zumoff says. Recent research in Zumoff's laboratory has shown, however, that men do not exhibit this effect, a sex difference that Zumoff calls surprising. Zumoff suggests that women may have considerably more estrogen receptors in their adipose tissue than men, which, if true, could act to amplify the effects of estrogens in women.

In obese women the ratio of follicle-stimulating hormone (FSH) to luteinizing hormone (LH), both of which are produced in the pituitary gland, is elevated. This is caused, primarily, by a decrease in LH levels, Zumoff says. What makes this interesting, he says, is that studies in monkeys on the effects of the frequency of pulses of externally supplied gonadotropic releasing hormone (GnRH), which is produced naturally in the hypothalamus, had similar effects. In monkeys, the hypothalamus normally releases pulses of GnRH about once per hour. When the rate of pulse is decreased to once every 1.5 to 3 hours, the FSH/LH ratio increases because of a resultant decrease in pituitary release of LH. Zumoff suggests that obese women may have a similar slowing of the rate of hypothalamic GnRH pulsing. He points out that premenopausal breast cancer patients demonstrate a similar hormone imbalance and that obesity is a risk factor for breast cancer. He suggests that slow GnRH pulsing might be the link between the two observations.

Many researchers have demonstrated that the male hormone, testosterone, is suppressed in the blood of obese men, Zumoff says. He studied testosterone levels in men who were from 10% below to 336% above normal weight and found that this suppression is proportional to the degree of obesity. Zumoff's research also suggests that the decrease in total testosterone concentration is accompanied by a decrease in the concentration of free testosterone, which is the fraction that is physiologically important. However, the low testosterone levels do not seem to have clinical consequences. Zumoff and his coworkers investigated three measures of sexual function in obese subjects: spermatogenesis by determination of sperm counts and sperm motility; libido, by structured psychiatric interviews; and potency. All were normal in obese men.

According to Zumoff, the probable cause of the low testosterone levels in obese men is increased conversion of androgens to estrogens in the adrenal gland. The increased estrogen levels act by a negative feedback mechanism on the pituitary to suppress the secretion of FSH, and this in turn suppresses testicular production of testosterone. This scenario is supported by the experimental observation that the drug dexamethasone, which suppresses adrenal gland activity, reverses the testosterone abnormality, Zumoff says.

Anorexia nervosa was the subject of two, separate papers at the meeting. Both Michelle P. Warren, a physician at Roosevelt Hospital in New York City, and Jack L. Katz, a psychiatrist at Montefiore Medical Center and Albert Einstein College of Medicine, also in New York City, pointed out the unique aspects of the condition: It occurs almost exclusively in women, it develops in the mid-adolescent years, and it invariably involves amenorrhea, or the absence of menstruation. (Katz noted that the few cases of anorexia nervosa in males generally occurred in early adolescent boys who also displayed other significant psychological disorders.)

The hormonal disorders in anorexia nervosa, Warren and Katz point out, apparently have the hypothalamus as their source. According to Katz, a study of more than 30 women emaciated from anorexia nervosa showed that all displayed immature patterns of LH secretion from the pituitary even though all were biologically adult. Pituitary release of LH and FSH is controlled by hypothalamic release of GnRH. In other studies, Warren says, when a severely ill anorectic is given GnRH, her pituitary response is that of a prepubescent female. If a woman with anorexia nervosa is given pulses of GnRH intravenously, the adult pat-

tern of FSH and LH response eventually resumes, as does ovulation and menstruation. The amenorrhea, therefore, apparently results from the prepubescent hormonal pattern. Unfortunately, such GnRH administration does not change eating behavior and is, therefore, not a treatment for the disorder.

The question, Katz points out, is whether the hypothalamic disorder causes anorexia nervosa or is a symptom of the seriously disturbed pattern of eating and the emaciation that results from it. That answer isn't clear, but the evidence seems to indicate that it is a symptom rather than a cause, at least initially.

Because the hypothalamus is important in regulating food intake, Katz suggests, once its function is disrupted, for whatever reason, it may continue to disrupt eating behavior. "The situation would thus very much resemble an addiction," he says, "where, regardless of whatever psychodynamic forces put the addiction into motion, eventually the physiological consequences take on a life of their own and the syndrome becomes virtually independent of the causes."

Warren and Katz suggest that anorexia nervosa may be the extreme in a continuum of endocrine abnormalities in women. For example, bulimia, in which young women ingest large numbers of calories and then induce vomiting, may not involve weight loss, but it does involve many of the hormonal abnormalities found in anorexia nervosa. Studies of women who are long-distance runners show that amenorrhea is relatively common among them. They also display some of the same hormone abnormalities, but their abnormalities are completely reversible.

Warren points out that the hormonal irregularities involved with poor nutrition and/or heavy exercise may have evolved as a form of natural birth control. A study of birth rates among women of the Bushmen tribe reveals that by far the maximum birth peak occurs nine months after weight is at a maximum which, in turn, is controlled almost completely by fluctuations in food supply in the Kalahari Desert where they live. "Thus, a seasonal suppression of ovulation appears to occur in these women," she says, "at a time when they are most active and weigh less. In contrast to starvation, [this condition] is readily reversible and may act as a mechanism of natural fertility control."

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