Caloric Restriction as a Mechanism Mediating Resistance to Environmental Disease

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It has been observed that susceptibility to many degenerative diseases increases concurrently with industrialization and rising living standards. Although epidemiologic studies suggest that specific environmental and dietary factors may be important, caloric intake alone (as reflected in body size) may account for much of the differential risk observed among diverse human populations. It has been suggested from animal studies that caloric intake may be the primary effector for many hormonal, metabolic, physiologic, and behavioral responses that coordinate reproductive strategy to apparent availability of food. When caloric intake is excessive, particularly at critical developmental stages, physiologic priorities are set for body growth and fecundity rather than for endurance and longevity. The converse occurs during periods of famine, thus increasing the probability that sufficient individuals survive to restore the population when conditions improve. Calorically restricted rodents have significantly longer reproductive and total life spans than their ad libitum-fed controls and exhibit a spectrum of biochemical and physiologic alterations that characterize their adaptation to reduced caloric intake. These include reduced stature, hypercorticism in the absence of elevated adrenocorticotropic hormone levels, increased metabolic efficiency, decreased mitogenic response coupled with increased rates of apoptosis, reduced inflammatory response, induction of stress proteins and DNA repair enzymes, altered drug-metabolizing enzyme expression, and modified cell-mediated immune function. The overall profile of these changes is one of improved defense against environmental stress. This has been suggested as the mechanistic basis for the protective effects of low body weight on radiation- and chemically induced cancers in experimental animals. It may also explain the significantly higher thresholds of acute toxicity observed when calorically restricted rodents are exposed to certain test compounds. — Environ Health Perspect 106(Suppl 1):313–324 (1998).

http://ehpnet1.niehs.nih.gov/docs/1998/Suppl-1/313-324/frame/abstract.html

Key words: caloric restriction, dietary restriction, aging, calories, cancer, diet, carcinogenesis, glucocorticoids, life span, longevity, body mass index, adaptation, evolution

Introduction

Cancer and life span are complex end points, appearing as a consequence of a chain of molecular events (1–3). Actions or agents that accelerate this progression of events are candidate risk factors for chronic disease, though precise mechanism(s) remain poorly understood. Both epidemiologic studies (4,5) and laboratory based animal research (6) now support an association between high caloric intake and the diseases of aging. This paper describes new insights into the underlying mechanisms by which caloric intake may influence degenerative disease progression and reviews the evidence for calorie-dependent disease susceptibility in humans.

The dose–response relationship between caloric intake and life span is not simple. In rodent models, for example, animals are at an increased risk of dying from protein–calorie malnutrition if dietary intake is extremely low. Interestingly, among survivors, caloric restriction is associated with a significant reduction in cancer incidence compared to that in ad libitum-fed controls. With moderate caloric restriction an optimal range may be found that generally supports reproduction, disease resistance, and longevity. The highest levels of caloric intake enhance growth and reproductive capacity but also significantly increase risk of morbidity, primarily because of development of specific cancers (7). These effects are reflected in the relationship between body weight and mortality, which is essentially J-shaped in rodent models (8,9) and the human population (10–13).

Under the usual experimental paradigms, calorically restricted animals receive a balanced reduction of the protein, carbohydrate, and fat content of the diet without a defined range of micronutrient content. Within a defined range of caloric restriction (typically 30–50% of ad libitum consumption), they show a decrease in the incidence and proliferative rate of spontaneous and chemically induced neoplasia. They also demonstrate a significant increase in maximum achievable life span compared to ad libitum-fed controls (6,14). Many biochemical and physiologic changes observed in calorically restricted animals are common among different species, yet the mechanisms responsible for these effects are not well understood. It is clear that calorically restricted animals exhibit changes in stress resistance, mitogenic, and immune responses that differ from those of animals fed ad libitum (15). The mechanisms controlling the adaptive response to reduced caloric intake may involve the complex dynamic interplay between the hormones that control energy balance, appetite, cell proliferation and apoptosis, stress response, metabolic rate, inflammation, and repair systems (7,16).

Glucocorticoids and insulin appear to play reciprocal roles as the major mediators of energy balance and glucose homeostasis in mammals (17–19). Serum corticosterone levels rise in response to hypoglycemia and increase blood glucose levels by inhibiting glucose transport into peripheral tissues.
while increasing gluconeogenesis and glucose output by the liver. In the hypoglycemic state corticosterone also stimulates appetite by inducing neuropeptide Y production in the arcuate nucleus of the hypothalamus (20) and stimulates lipolysis in adipose tissue while reducing energy expenditure in other peripheral tissues by decreasing thermogenesis and inhibiting the effects of mitogenic and excitatory hormones (16,18). Conversely, in the hyperglycemic state insulin levels rise and decrease blood glucose levels by stimulating glucose uptake and glycogen synthesis in liver and muscle and by increasing glucose uptake and lipogenesis in adipose tissue (17,18).

Insulin also stimulates leptin production in adipose tissue, which in turn decreases appetite and increases metabolism and energy expenditure in peripheral tissues (21–24). Thus, under normal physiologic conditions a balanced opposing relationship exists between insulin and corticosterone that maintains blood glucose levels within the normal physiologic range (17).

Nutrient stress such as fasting, starvation, or insulin-induced hypoglycemia results in elevated glucocorticoid levels, but unlike classic stress, hypothalamic release of corticotropin-releasing factor (CRF) does not appear to play a major role in initiating the glucocorticoid response (25–27). Rather, arginine vasopressin (AVP) plays the major role in the hypothalamus and the adrenal response to adrenocorticotrophic hormone (ACTH) appears amplified by pancreatic polypeptide, which is secreted by the pancreas during periods of hypoglycemic stress (28,29). In addition, adrenal corticosterone secretion may be increased further by neural stimulation via the adrenal medulla (30,31). This results in elevated corticosterone concentrations in the absence of elevated ACTH (and by inference CRF) in both starved (25) and calorically restricted (27,32) rats. Under normal physiologic conditions, once the hypoglycemic crisis has been rectified, insulin levels will rise and, as suggested by in vitro experiments (33), may downregulate adrenal corticosterone secretion in favor of dehydroepiandrosterone (DHEA) secretion. Like insulin, DHEA is generally anabolic in function and reportedly antagonizes many of the effects of glucocorticoids (34–37).

However, during pathologic conditions such as Cushing’s syndrome or prolonged excessive glucocorticoid therapy, natural feedback regulation is bypassed and a pathologic hyperglycemia develops, which is characterized by concurrent elevated insulin and glucocorticoid levels. Such conditions of hypercorticism concurrent with hyperinsulinemia, if prolonged, would be expected to result in pathologic conditions such as atherosclerosis and mature-onset diabetes (38). Classic stress appears to be controlled primarily by the hypothalamo–pituitary–adrenal axis (HPA). CRF and AVP secretion from the hypothalamus increase in response to interleukins or neuropeptides and stimulate ACTH secretion by the pituitary (39). Thus, plasma concentrations of both CRF and ACTH are increased in addition to serum corticosterone levels. CRF decreases hyperphagia (40) and is pyrogenic and an inflammatory mediator (41).

**Antineoplastic Effects of Glucocorticoids**

The net effects of hypercorticism resulting from nutrient stress are, therefore, reductions of glucose uptake and energy metabolism in peripheral tissues. This in itself may provide a beneficial effect on aging and carcinogenesis by reducing rates of intracellular glycoxidation and oxidative damage from respiratory chain enzymes (42,43). However, the primary mechanism by which glucocorticoids impact aging and degenerative disease may be through their antimitotic and antiinflammatory functions.

**Antimitotic effects**

Growth hormone and glucocorticoids are mutually antagonistic in their effects on body growth (44) and wound healing (45), and some of the antimitogenic effects of glucocorticoids are mediated through changes in the hypothalamic–pituitary–liver growth hormone/insulinlike growth factor 1 (IGF-1) axis. Glucocorticoids disrupt the pulsatile secretory profiles of growth hormone (46,47) in rats and decrease hepatic IGF-1 expression (48). They also antagonize the proliferative effects of epidermal growth factor (EGF) and platelet-derived growth factor (PDGF) in various cell culture systems (49,50) and antagonize the stimulatory effects of luteinizing hormone (LH) on the adenyl cyclase/cAMP system in Leydig cells and possibly other endocrine tissues (51,52). Although high glucocorticoid levels can cause atrophy of skeletal muscle, they stimulate hypertrophy in cardiac muscle (53). This effect is associated with alterations in expression of myosin isoforms and results in the high efficiency V3 isoform being favored over the low efficiency V1 isoform (53,54). Thus, the antimitogenic effects of glucocorticoids appear to be selective.

Apoptosis recently has been proposed to play an important role in inhibiting tumor development by eliminating damaged and genetically transformed cells from tumor-susceptible tissues (55–60). Apoptosis is characterized as differing from tissue necrosis in that only selected cells are eliminated and the resulting cell debris is immediately phagocytized by adjacent cells so that an inflammatory response is not initiated (61,62). Glucocorticoids induce apoptosis in lymphatic tissues (56) and fibroblasts (63) and possibly in mammary epithelium (61,64). Glucocorticoids may also selectively mediate the effects of transforming growth factor beta (TGF-β) in stimulating apoptosis in preneoplastic hepatocytes (42,50).

**Antiinflammatory effects**

When used therapeutically, glucocorticoids are extremely potent antiinflammatory agents that interact with practically every stage of the inflammatory response (65). Although it was once proposed that physiologic levels of endogenous glucocorticoids stimulated the inflammatory response as part of the general adaptation to stress (66), it now appears that their physiologic role during stress is to protect the organism from an overstimulated inflammatory response (65,67). Glucocorticoids achieve this by inhibiting the production of, or antagonizing the actions of, inflammatory mediators such as prostaglandins, leukotrienes, interleukins, and atrial natriuretic factor (7,16,65). It is now generally accepted that many of the antiinflammatory and antimitogenic effects of glucocorticoids are mediated by the glucocorticoid-inducible protein lipocortin 1 (65,68). Lipocortin 1 (also known as annexin 1) is a glycosylated 37-kDa Ca2+-dependent phospholipid-binding protein that inhibits phospholipase A2, a key enzyme in the synthesis of inflammatory prostaglandins and leukotrienes from arachidonic acid (65). In addition to directly inhibiting phospholipase A2 activity, lipocortin 1 recently has been shown to inhibit the EGF-mediated phosphorylation of the cytosolic form of this enzyme (phospholipase C [PLC]) (69,70). PLC is activated by phosphorylation as part of a G-protein-dependent, EGF-mediated mitogenic response (69). Lipocortin 1 also mediates glucocorticoid feedback effects on the HPA axis by inhibiting both basal and interleukin-induced release of CRF and AVP by the hypothalamus (39,68,71).
Glucocorticoids also downregulate mRNA expression of several key inflammatory enzymes. These include 12-lipoxigenase (72) and the inducible but not constitutive forms of prostaglandin synthase, cyclooxygenase isoform 2 (COX-2) (73–76), nitric oxide synthase (NOS) (76–78), and intestinal phospholipase A2 (79). These enzymes generally are induced by endotoxins, tumor necrosis factor, interleukins, phorbol esters, or growth factors. Although it is not known whether glucocorticoids directly or indirectly repress transcription of these enzymes, lipocortin 1 appears to mediate glucocorticoid-mediated downregulation of NOS1 (80) but not COX-2 (81).

Lipocortin 1 recently has been proposed to be a mediator of glucocorticoid-induced apoptosis. It is induced in apoptotic cells where it has been proposed to inhibit recognition of the dying cells by macrophages (61). Lipocortin 1 has been shown to protect cultured rat thymocytes from H2O2-elicited necrosis. Glucocorticoid treatment, which induced lipocortin 1, stimulated apoptosis, whereas treatment with an antilipocortin 1 antibody enhanced necrosis (84).

Despite their global antiinflammatory effects, glucocorticoids have been shown to potentiate certain aspects of the host defense system. For example, they reportedly induce expression of both heat shock protein 70 (HSP70) (85) and the DNA repair enzyme O6-methylguanine–DNA methyltransferase (86) in certain tissues. They also potentiate the effects of interleukin-6 and hepatocyte-stimulating factor in inducing hepatic acute phase proteins such as Mn-superoxide dismutase and α2-macroglobulin (87–91). Although both glucocorticoids and lymphocyte stimulatory agents that are mediated via intracellular Ca2+ or protein kinase C (e.g., calcium ionophors/phorbol esters, antibodies to the T-cell antigen receptor) initiate apoptosis in maturing lymphocytes, they are mutually antagonistic to the extent that glucocorticoids protect lymphocytes from activation-induced apoptosis (92,93). Thus, the effects of glucocorticoids on the inflammatory and immune systems are modulatory rather than simply suppressive.

Inflammation, necrosis, oxidative damage, and regenerative hyperplasia all play significant roles in chemically induced tumor promotion, and glucocorticoids have been shown to inhibit hyperplasia and neoplasia in a number of systems. For example, glucocorticoids are used therapeutically as antineoplastic agents in treating several types of leukemia and lymphoma (36,94) and suppress growth of certain lung or mammary adenocarcinomas (64,95–97).

Dexamethasone inhibits both peroxisome-proliferator-induced and lead-nitrate-induced proliferative hyperplasia in rat liver (98,99). Glucocorticoids also induce connexin expression and stimulate gap junction formation in cultured hepatocytes and embryonic cells (100–102). Inflammatory agents such as phorbol esters promote, and glucocorticoids inhibit, papilloma formation in mouse skin (103).

### Toxic Effects of Glucocorticoids

Chronic and excessive elevation of glucocorticoid levels increases the risk of developing hypertension, hyperkalemia, diabetes, atherosclerosis, osteoporosis, glaucoma, and impairment of the immune and reproductive systems (104,105). The organ most susceptible to glucocorticoid toxicity appears to be the hippocampus. High doses of corticosterone administered to adrenalectomized rats resulted in neuronal atrophy in the hippocampus but not in other areas of the brain (38,106,107). Because the hippocampus, in conjunction with the hypothalamus, controls feedback regulation of the HPA, it was suggested by Sapolsky and co-workers (107) that glucocorticoid-evoked hippocampal damage impairs the feedback regulation of adrenal glucocorticoid output, which could result in further increases in glucocorticoid levels and additional hippocampal damage. This concept has become known as the glucocorticoid cascade hypothesis. Over a lifetime such an effect may result in premature aging of the brain. Evidence supporting this hypothesis includes in vitro studies that have demonstrated that glucocorticoids impair the ability of cultured hippocampal cells to withstand neurotoxic stresses (107). The proposed mechanisms responsible for these effects include inhibition of glucose transport and disruption of Ca2+ homeostasis (107–109). In humans, patients with Cushing’s syndrome can exhibit memory impairment that correlated with serum cortisol levels (110), and dexamethasone treatment has also been shown to impair declarative memory performance (111). However, although hypercorticism often is manifested in Alzheimer’s patients (108), long-term treatment with glucocorticoids is associated with delay in the onset of Alzheimer’s disease (112). Lipocortin 1 is expressed throughout the brain including the hippocampus and has been shown to protect against neuronal damage resulting from either ischemia or N-methyl-D-aspartate agonists (113,114).

Exposing adult rats to stress, hypercorticism, or glucocorticoid therapy reduces reproductive hormone levels in both sexes (7). In males, for example, glucocorticoids appear to inhibit LH-mediated testosterone synthesis by cultured rat Leydig cells (115) and dexamethasone treatment decreases (whereas adrenalectomy increases) serum testosterone levels in vivo (116,117). In females, glucocorticoids decrease follicle-stimulating hormone (FSH)-stimulated aromatase activity and estrogen production by ovarian granulosa cells (118), suppress ovulation, and inhibit ovarian progesterone metabolism (119). They also inhibit the pre-ovulatory pituitary LH surge in female rats (120) and estradiol- and gonadotropin-releasing hormone-induced LH production in cultured rat pituitary cells (121). In male rats glucocorticoids inhibit pituitary secretion of prolactin (122) but not mean LH levels (123). However, CRF and stress inhibit pituitary LH secretion in both sexes (124,125).

### Glucocorticoid-mediated Effects of Caloric Restriction

Caloric restriction not only evokes antiinflammatory and antineoplastic effects consistent with chronic hypercorticism but also protects aging rodents against insulin-resistant diabetes (126–129), impaired tissue growth and regeneration (130,131), certain neurologic impairments (132,133), and reproductive senescence (134,135) (Table 1). Although these latter effects appear initially to be inconsistent with hypercorticism, on further analysis they appear to be the natural consequence of the nutrient stress produced by caloric restriction under the conditions used for most experimental paradigms (7).

Several factors differentiate the nutrient stress produced by caloric restriction from other stress situations or glucocorticoid therapy (7). First, unlike treatment with pharmacologic doses of synthetic glucocorticoids, hypercorticism resulting from nutrient stress involves the natural glucocorticoids corticosterone or cortisol. The effects of these natural glucocorticoids are mediated by serum transcortin and 11β-hydroxysteroid dehydrogenase, which may...
protect tissues from extreme hypercorticism (7). Furthermore, unlike synthetic steroids such as dexamethasone, corticosterone and cortisol bind to both Type I and Type II glucocorticoid receptors, so the Type I receptor response is not inhibited concurrently with an excessive Type II receptor response (136).

Second, the hypercorticism exhibited by calorically restricted rodents differs from the continuously elevated serum corticosterone levels exhibited by starved or chronically stressed rodents in that corticosterone levels are increased above those of their ad libitum-fed counterparts only during a limited circadian period prior to and coincident with feeding activity (137). This type of intermittent hypercorticism appears less damaging to mitogenic processes than continuously elevated glucocorticoid levels (7).

Third, because the hypercorticism is a response to calorically restricted and potential hypoglycemia and occurs in conjunction with normal feedback regulatory systems, it is not associated with chronic hyperglycemia or hyperinsulinemia (16,127,138). Thus, insulin resistance and protein glycation, which are the usual pathologic consequences of glucocorticoid-induced hyperglycemia, should not occur. Instead, rates of intracellular glycation and oxidation of protein would be expected to decrease in peripheral tissues because of reduced glucose incorporation. Reduced collagen glycoxidation has been observed in skin from calorically restricted rats (139), and accumulative oxidative damage to both protein and DNA is reduced by calorific restriction in a number of tissues (43,140-142).

Fourth, under the usual conditions for calorically restriction experiments, significant hypercorticism only occurs during the early stages of restricted feeding (143,144). In most strains of rodent used in calorically restriction experiments, body weight gain is reduced in the restricted animals to an extent where the body weight difference between the restricted and ad libitum-fed animals equals or exceeds the calorific deficit (Figure 1). Thus, during the latter half of a calorically restricted rat's life span, its calorific consumption per gram body weight is equal to or greater than that of its ad libitum-fed counterpart. Under these conditions, significant hypercorticism would not be required to protect the animal from potential hypoglycemia. As a consequence, during senescence, when rodents are most susceptible to tissue degeneration because of reduced capacity for cellular proliferation and reduced output of mitogenic hormones (131,146), serum corticosterone levels normally are no longer significantly increased in chronically calorically restricted animals (7,143,144).

The effects of calorific restriction on biomarkers of mitogenesis are generally consistent with the occurrence of hypercorticism during the early but not the late stages of calorific restriction. For example, calorific restriction from 16 weeks of age abolishes growth hormone pulsatility in 6-month-old male Brown Norway rats, but pulsatility is restored in older animals (148). In male rats pulsatile growth hormone controls hepatic expression of both IGF-1 and sex-specific drug metabolizing enzymes such as cytochrome P450 2C11 (CYP2C11) (149,150). As expected from its effects on pulsatile growth hormone, calorific restriction decreases hepatic expression of both IGF-1 and CYP2C11 in young male rats (151,152). However, as the rats age hepatic IGF-1 and CYP2C11 expression decreases in the ad libitum-fed rats but is maintained by calorific restriction so that in old rats hepatic IGF-1 and CYP2C11 expression is greater in the calorically restricted animals (151,152). This age-dependent biphasic effect of calorific restriction is illustrated in Figure 2 and is a common feature of several of the reported
The effects of caloric restriction in rodents. These include cell proliferation rates in kidney, pancreas, and possibly liver from B6D2F1 mice (131), serum DHEA levels in Fischer 344 rats (153), and reproductive function in both rats and mice.

Effects on female reproductive function include delayed puberty (154,155), inhibition of LH pulsatility concurrent with hypercorticism (156), inhibition of ovulation (157), decreased litter size (158,159), increased lactational diestrus (160), and reduced milk production (161) during the initial period of caloric restriction and delayed reproductive senescence during the latter stage (135,158). In males the initial effects of caloric restriction include decreased LH pulsatility (162), reduced ratios of serum testosterone to estradiol (163), decreased sperm motility in rats (164,165), decreased prostrate weight, testicular sperm density, and fertility in mice (159). Long-term caloric restriction reduces testicular hyperplasia and delays Leydig cell adenoma formation in old male rats (163,166), whereas chronic feeding of a high-calorie diet reduced reproductive performance in old male CF-1 mice (167).

The antinflammatory effects of caloric restriction are also generally consistent with effects resulting from hypercorticism. For example, caloric restriction reportedly induces lipocortin 1 immunoreactive proteins in rat liver (16), inhibits carrageenan-induced inflammation in mice (168), decreases 12-lipoxygenase activity in rat liver and testes (7), delays the onset of autoimmunity in autoimmune-prone mice (169), and inhibits promotion of mouse skin papillomas by phorbol esters (170,171). In the latter case adrenalectomy reversed the effect of caloric restriction. Interestingly, caloric restriction both potentiates regenerative hepatocyte proliferation in partially hepatectomized rats (172) and reduces cell proliferation while stimulating apoptosis in preneoplastic liver (173,174). Such an effect is consistent with the reported dual synergistic and antagonistic effects of glucocorticoids on TGF-β in neoplastic and nonneoplastic hepatocytes (7,50).

Although older caloric-restricted mice exhibited improved cognitive function, motor performance, and reduced oxidative damage in the brain (132,133), caloric restriction did not inhibit hippocampal aging in rats, although it did not appear to be overly detrimental to the hippocampus (109,175). However, dieting and dietary restriction reportedly impair cognitive function in humans (176). Despite potential endangerment to the hippocampus, moderate hypercorticism during nutrient stress would be expected to be beneficial because the alternative, hypoglycemia in conjunction with increased inflammatory activity, would pose a greater threat to the entire central nervous system.

Taken together, these effects suggest that caloric restriction in rodents produces a series of pleiotropic biochemical and physiologic effects consistent with a hypercorticism condition that is more severe in the early stages of caloric restriction than in the later stages and that occurs without concurrent hyperglycemia. The overall effect of this condition is to conserve energy by minimizing metabolism, proliferation, and nonessential functions in peripheral tissues. This in turn appears to minimize damage to the affected tissues so that progression of degenerative or neoplastic lesions is delayed.

The recent finding that the body weight of rodents used in cancer bioassays directly correlates with terminal incidence of background tumors (8,177) is also consistent with effects on growth and cell proliferation, which play a major role in mediating the antineoplastic effects of caloric restriction. These body weight–tumor correlations were demonstrated from analysis of the control animals from cancer bioassays conducted by the U.S. National Toxicoity Program. In B6C3F1 mice terminal lung tumor incidence exhibited a positive correlation with body weight at 9 months on test, whereas terminal liver tumor incidence correlated optimally with body weight at 12 months on test (8,178). In Fischer 344 rats terminal pituitary tumor incidence exhibited a positive correlation with body weight at 13 months on test, whereas terminal leukemia incidence exhibited a positive correlation with body weight at 14 weeks (179). Interestingly, caloric restriction initiated at 6 weeks of age inhibited leukemia to a much greater extent than restriction initiated at 14 weeks, whereas pituitary adenoma formation was...
affected equally by both caloric restriction paradigms (179). This suggests that critical periods exist when rodents are most susceptible to subsequent development of specific cancer end points. This effect can also be demonstrated for background liver tumors in B6C3F1 mice (7).

It would appear, therefore, that the rate of growth during the early adult period of an organism's life determines its subsequent susceptibility to neoplastic or degenerative diseases, and rates of growth in part depend on glucocorticoid status and caloric intake. As stated above, glucocorticoids are a major component of the stress and inflammatory responses, where their primary functions appear to be: a) to globally reduce energy consumption so that energy is channeled to the site of trauma or inflammation, and b) to prevent excessive tissue damage due to overexpression of the inflammatory response. During severe nutrient stress hypercorticism allows an organism to conserve energy so that it may survive, but in the process growth and reproductive, immune, and cognitive functions may be compromised. However, caloric excess may be equally detrimental and result in overstimulated growth, uncontrolled cell proliferation, autoimmunity, inflammatory diseases, and neoplasia. Between these two extremes lies a physiologic window in which health and longevity are maximized (Figure 3). Hypercorticism as a hormonal response to nutrient stress appears common to most mammalian species and probably evolved as a mechanism to ensure survival of the species through periods of famine (180–183). In times of abundant food supply, rapid growth and fecundity are favored over endurance and longevity. Conversely, when food becomes scarce reproductive performance and growth are sacrificed in favor of extended total and reproductive life spans, thus increasing the probability that sufficient individuals will survive to restore the population when conditions improve.

Over the past 30 years the animal husbandry conditions used by commercial breeders and rodent-testing houses have been significantly modified to favor growth and fecundity (184,185). This has resulted in rodent strains that characteristically suffer from caloric excess and exhibit reduced life expectancy and many of the symptoms listed on the left side of Figure 3. When used in toxicity studies these animals are highly sensitive not only to chemically induced carcinogenesis but also to the acute effects of toxic chemicals (186). When used in moderation with these animals, dietary restriction decreases the incidence of both spontaneous and chemically induced carcinogenesis and also reportedly decreases the acute toxicity of several chemicals (186,187). Such effects are consistent with the antiinflammatory and antineoplastic effects of hypercorticism because a heightened inflammatory response amplifies the toxicity of carcinogens such as carbon tetrachloride (188–191). Although moderate dietary restriction is recommended for increasing life span and standardizing background tumor incidence between studies (192), excessive dietary restriction, whether a result of reduced food allocation or anorectic effects of the test chemical, should be avoided in cancer bioassays, as such conditions would render the bioassay insensitive for the detection of chemically induced tumors and reduce life expectancy because of the pathologic conditions listed on the right-hand side of Figure 3.

**Influence of Caloric Intake on Human Morbidity and Mortality**

Although the effects of caloric restriction on circadian profiles of serum cortisol have not been studied in detail, fasting has been shown to increase serum cortisol levels in humans while concurrently decreasing serum insulin, IGF-1, triiodothyronine, and testosterone levels (193–196). This suggests that nutrient stress evokes similar effects in humans as in rodents.

Although the relationship between body weight and morbidity is readily apparent in laboratory animals raised from similar genetic stock under controlled laboratory environments (177,178,197), establishing similar trends in the human population is considerably more difficult. It is now well established that genetic factors play a significant role in determining risk for both cancer and coronary heart disease (198,199) and behavioral factors such as cigarette smoking and heavy consumption of alcohol also influence susceptibility to these diseases (199–201). Nevertheless, when these factors are taken into consideration, dietary caloric consumption may be one of the most important risk factors for a spectrum of human degenerative diseases (4,202), and human epidemiology studies have established that increased body weight—or body mass index (BMI)—is positively correlated to a number of morbidity/mortality indices. These include overall mortality in both men and women (13,203); cardiovascular disease (10,13,204); breast, renal, and endometrial cancer in women (205–207); and colon cancer in men (208). As in animal studies (8) the relationship between BMI, weight, and morbidity/mortality risk is not always linear in human studies;
J-curve profiles are frequently produced instead. Whereas some of the risk for low-body-weight individuals can be attributed to smoking (12), the studies quoted above used Western populations, which include relatively few individuals on low-calorie diets. Including populations from developing countries would be expected to produce mortality curves resembling that shown in Figure 3. Indeed it frequently has been noted that as caloric consumption relative to caloric demand increased in developed countries, disease susceptibilities changed from those characteristic of caloric deficit to those characteristic of caloric excess (209).

**Relevance of Caloric Restriction Studies to Antiaging and Anticancer Therapies**

Of the several interventions proposed as life extenders, none have been as successful in experimental animal studies as caloric restriction. If the mechanisms described above prove correct, this is to be expected. For example, although high pharmacologic doses of antioxidants can be expected to reduce or eliminate oxidative damage to intracellular macromolecules from free radicals such as superoxide, free radicals themselves play a beneficial role in cell regulation, apoptosis, and in fighting pathogenic bacteria (210,211). Excessive overconsumption of purified antioxidants by healthy individuals could therefore be detrimental to health and has in some cases been shown to be ineffective as cancer preventive agents (212). Mitogenic hormones such as somatotropin or the natural anabolic steroid DHEA may be useful to maintain tissue mass in elderly patients exhibiting a genuine deficit in these hormones, but their abuse in younger individuals could result in an excessive mitogenic response and possible insensitivity in later life. Likewise, although natural glucocorticoids appear to play a significant role in mediating the effects of caloric restriction, chronic consumption in the absence of caloric deficit may result in hyperglycemia and diabetes. Moreover, even caloric restriction may not be beneficial under all circumstances. Although a decreased inflammatory response appears to be beneficial during the early stages of the carcinogenesis process (103,213), immunodeficiency once carcinogenic tumors have developed will facilitate metastatic growth (209). As explained above, in most animal experiments the caloric deficit and resultant hypercorticism has subsided before most tumors reach the metastatic stage. However, if caloric restriction is initiated in cancer patients once the carcinogenic tumors have been established, the benefits of its antimitotic effects may be outweighed by the risk of its immunosuppressive effects. In such cases, immunotoxic stress by using bacterial toxins or purified cytokines (214–217) may prove a more effective therapy because this type of stress would be expected to inhibit mitogenesis while stimulating the inflammatory response.

**Conclusions**

Caloric intake and body weight can markedly influence mortality and morbidity rates in laboratory animals. As the mechanistic basis for the effect of caloric intake on disease processes becomes increasingly understood, it is becoming apparent that caloric intake may exert a similar impact on human mortality and disease. However, it is also becoming apparent that caloric restriction or related interventions should not be applied indiscriminately to all individuals. Rather, the relative risks and benefits of all such interventions must be assessed on a case-by-case basis, taking into consideration the age, nutritional, and pathologic status of the individual subject.

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