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Vegan proteins may reduce risk of cancer, obesity, and cardiovascular disease by promoting increased glucagon activity

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Summary Amino acids modulate the secretion of both insulin and glucagon; the composition of dietary protein therefore has the potential to influence the balance of glucagon and insulin activity. Soy protein, as well as many other vegan proteins, are higher in non-essential amino acids than most animal-derived food proteins, and as a result should preferentially favor glucagon production. Acting on hepatocytes, glucagon promotes (and insulin inhibits) cAMP-dependent mechanisms that down-regulate lipogenic enzymes and cholesterol synthesis, while up-regulating hepatic LDL receptors and production of the IGF-I antagonist IGFBP-1. The insulin-sensitizing properties of many vegan diets – high in fiber, low in saturated fat – should amplify these effects by down-regulating insulin secretion. Additionally, the relatively low essential amino acid content of some vegan diets may decrease hepatic IGF-I synthesis. Thus, diets featuring vegan proteins can be expected to lower elevated serum lipid levels, promote weight loss, and decrease circulating IGF-I activity. The latter effect should impede cancer induction (as is seen in animal studies with soy protein), lessen neutrophil-mediated inflammatory damage, and slow growth and maturation in children. In fact, vegans tend to have low serum lipids, lean physiques, shorter stature, later puberty, and decreased risk for certain prominent 'Western' cancers; a vegan diet has documented clinical efficacy in rheumatoid arthritis. Low-fat vegan diets may be especially protective in regard to cancers linked to insulin resistance – namely, breast and colon cancer – as well as prostate cancer; conversely, the high IGF-I activity associated with heavy ingestion of animal products may be largely responsible for the epidemic of 'Western' cancers in wealthy societies. Increased phytochemical intake is also likely to contribute to the reduction of cancer risk in vegans. Regression of coronary stenoses has been documented during low-fat vegan diets coupled with exercise training; such regimens also tend to markedly improve diabetic control and lower elevated blood pressure. Risk of many other degenerative disorders may be decreased in vegans, although reduced growth factor activity may be responsible for an increased risk of hemorrhagic stroke. By altering the glucagon/insulin balance, it is conceivable that supplemental intakes of key non-essential amino acids could enable omnivores to enjoy some of the health advantages of a vegan diet. An unnecessarily high intake of essential amino acids – either in the absolute sense or relative to total dietary protein – may prove to be as grave a risk factor for 'Western' degenerative diseases as is excessive fat intake.

DIETARY PROTEIN MODULATES GLUCAGON/INSULIN ACTIVITY

Dietary protein triggers release of both insulin and glucagon. However, the pancreatic islets obviously do not detect 'protein' per se, but rather the postprandial increase in circulating amino acids (1–4). The mechanisms whereby pancreatic α and β cells respond to amino acids are clearly distinct, since their responses to individual amino acids differ greatly. As a rough rule of thumb, essential amino acids are relatively more effective for releasing insulin, whereas non-essential amino acids – particularly arginine and pyruvate precursors – preferentially release glucagon. This makes sense homeostatically. When essential amino acids are amply available, it is appropriate to stimulate protein synthesis and storage

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with an insulin burst. When the non-essential amino acids used avidly for gluconeogenesis, as well as arginine (a catalyst of the urea cycle), are present in excess, it is reasonable for increased glucagon activity to stimulate gluconeogenesis. The failure of branched-chain amino acids to trigger glucagon release is understandable in light of the fact that these amino acids are catabolized primarily in skeletal muscle, which is not responsive to glucagon.

In general, vegan proteins tend to contain a higher fraction of non-essential amino acids than the main animal-derived dietary proteins do (5). (A notable exception is gelatin.) For this reason, it is reasonable to expect that, if total protein intake is kept invariant, a vegan diet will promote greater net glucagon activity than an omnivorous diet. This in fact has been observed, both postprandially and during fasting metabolism. For example, Descovich and co-workers, working with hypercholesterolemic volunteers, fed them a low-fat omnivorous diet for one month, followed by one month of a diet that was substantially comparable nutritionally except for the substitution of textured soy protein for virtually all of the animal protein (6). During the vegan diet, morning fasting glucagon levels rose by an average of 19%, while insulin levels declined by 17% , resulting in an increase of over 40% in the glucagon/insulin ratio. (A 21% increase in plasma growth hormone was also noted – possibly as a consequence of reduced IGF-I activity, as explained below). A similar observation has been made in rats fed diets based on a variety of animal or vegan proteins (7). These shifts in glucagon/insulin ratio may be attributed to alterations of the fasting serum amino acid profiles; thus, when cardiovascular patients were placed on a vegan diet for four weeks, fasting serum levels of the pyruvigenic amino acids (glycine, alanine, serine, cysteine, threonine) increased by an average of 10%, and arginine increased by 16%, while significant decreases were noted in valine, leucine, tyrosine, and histidine (8). Presumably, the fasting amino acid profile is as crucial a determinant of basal glucagon secretion as fasting glucose is for insulin secretion. Conversely, even though basal plasma levels of essential amino acids may not in themselves have a potent impact on insulin secretion, they can be expected to modulate beta cell response to fasting or post-prandial glucose. Thus, when dietary protein is relatively high in non-essential amino acids, down-regulation of insulin and up-regulation of glucagon is a logical consequence.

As compared to soy protein, casein is a relatively poor source of non-essential amino acids; it is notably low in arginine and glycine, which are excellent secretogogues for glucagon. Sanchez and colleagues demonstrated that addition of arginine and glycine to a casein-based liquid meal resulted in a substantial increase of the postprandial glucagon/insulin ratio (9). (The fact that milk proteins are relatively poor glucagon releasers is probably not accidental – milk protein is 'intended' for the anabolic needs of the growing infant, not as substrate for gluconeogenesis).

HEALTH BENEFITS OF INCREASED GLUCAGON ACTIVITY

The liver appears to be the sole significant target for glucagon activity. The action of glucagon on hepatocytes is mediated by a stimulation of adenyl cyclase that raises cAMP levels (10). Insulin acts to antagonize hepatic glucagon activity, by activating cAMP phosphodiesterases and by additional mechanisms (11,12). Thus, the ratio of circulating glucagon to insulin is a crucial determinant of net glucagon activity in hepatocytes.

cAMP and protein kinase A regulate the synthesis of a wide range of hepatic proteins. In particular, cAMP down-regulates the synthesis of a number of enzymes required for de novo lipogenesis and cholesterol synthesis (including citrate lyase, acetyl coA carboxylase, fatty acid synthetase, and HMG-CoA reductase), while up-regulating key gluconeogenic enzymes as well as the LDL receptor and IGFBP-1 (13–23). cAMP also post-translationally modulates the phosphorylation of key hepatic enzymes to stimulate gluconeogenesis and fatty acid oxidation (24–28).

The actions of cAMP in hepatocytes are readily rationalized when we realize that glucagon, as well as epinephrine (which likewise increases hepatocyte cAMP), are signals evoked by hypoglycemia. These hormones suppress less urgent anabolic activities of hepatocytes (such as fat or cholesterol synthesis) so that most available free energy can be diverted to fuel gluconeogenesis. Hepatic fatty acid oxidation accelerates to meet the increased energy needs for gluconeogenesis and to generate ketone bodies as ancillary fuel for the central nervous system. The induction of IGFBP-1 – a short half-life protein that sequesters unbound IGF-I, blocking its activity – is likewise physiologically adaptive. During hypoglycemia, the tonic insulin-like activity of the circulating pool of IGF-I could worsen matters by pushing serum glucose lower (29–31). The cAMP-mediated acceleration of IGFBP-1 synthesis minimizes this problem by rapidly down-regulating IGF-I activity. Suppression of serum 'somatomedin' activity following glucagon administration has in fact been documented in human volunteers (31).

The effects of a chronic net increase in hepatic glucagon activity are readily predicted:

- a reduction in de novo lipogenesis, decreasing fat storage in animals;
- a reduction in cholesterol synthesis and in circulating LDL cholesterol;

- an increase in hepatic lipid oxidation (in part owing to lower malonyl-coA levels) that, in conjunction with the decrease in lipogenesis, causes a reduction in triglyceride synthesis and in serum triglycerides;
- a decrease in effective IGF-I activity that can be expected to retard cancer development and in some instances slow cancer growth. (IGF-I, a crucial 'progression' growth factor, enhances the mitotic rate of stem cells, pre-neoplastic lesions, and some cancers, while inhibiting apoptosis (32–36).)

These effects are precisely what are observed when animals or humans are switched from omnivorous or casein-based diets to comparable diets in which soy protein is substituted for animal proteins. Soy-based diets decrease weight gain in obesity-prone rats (37), lower elevated serum LDL cholesterol in cholesterol-fed rodents and in hypercholesterolemic humans (6,7,38,39), lower elevated serum triglycerides (39), and often inhibit cancer induction and/or slow cancer growth in various animal cancer models (40,41).

HYPOLIPIDEMIC EFFECTS OF VEGAN DIETS

The hypolipidemic effects noted when soy or other vegan proteins are substituted for casein in rodent diets, have prompted a number of controlled clinical investigations in which soy protein has been substituted for dietary animal proteins while all other nutritional variables (including dietary fat profile) are kept as constant as feasible. A recent meta-analysis of these studies concluded that, on average, soy-based diets were associated with reductions of 9.3%, 12.9%, and 10.5% in total cholesterol, LDL cholesterol, and triglycerides, respectively; a modest increase in HDL cholesterol (2.4%) was not statistically significant (39). In practice, since vegan diets are usually very low in saturated fats, devoid of cholesterol, high in fiber, and often promote weight loss, the impact of vegan diets on serum lipids is even greater, as borne out in long-term studies evaluating the effects of ad libitum vegan diets, or cross-sectional studies comparing vegans to omnivores (42–46).

The ability of increased glucagon activity to stimulate hepatic fatty acid oxidation (owing to transcriptional and post-translational effects that diminish malonyl-CoA synthesis while decreasing the sensitivity of carnitine palmitoyl transferase to inhibition by this metabolite), while up-regulating the LDL receptor and down-regulating HMG-CoA reductase, provides a satisfying explanation for the clinical hypolipidemic activity of vegan proteins.

WEIGHT REDUCTION WITH VEGAN DIETS

The effects of a long-term vegan diet on body-weight tend to be substantial. Most clinical studies examining the impact of soy protein on serum lipids have been short-term and have insured comparable caloric intakes during the soy and control periods, such that little weight change is seen or expected. However, in the long-term, open clinical studies in which ad libitum vegan diets were used to treat hypertension, asthma, and rheumatoid arthritis, weight loss after four months averaged 10 kg (42,43,47). Since the fat content of self-chosen vegan diets tends to exceed 30% (46), fat restriction is not likely to be an adequate explanation for the magnitude of weight loss observed when a vegan diet is adopted. Although suppression of de novo lipogenesis probably contributes importantly to the decrease of weight gain seen in soy protein-fed genetically obese rodents (37), this is not likely to be an important factor in humans. On the other hand, since hepatic fatty acid oxidation promotes appetite control and lowers the respiratory quotient (48), a relative disinhibition of hepatic fatty acid oxidation in vegans may play a role in the body weight reduction observed during ad libitum vegan diets. Increased thermogenic activity may also be involved; glucagon has thermogenic effects that is part may reflect the uncoupled nature of hepatic ketogenesis (49–51). Additionally, Iritani et al. recently reported that conversion of thyroxine to triiodothyronine is catalyzed more efficiently by liver microsomes derived from soy protein-fed rats (as compared to casein-fed controls); this was paralleled by significantly higher plasma T_3 levels in the soy group (37). Conveivably, this up-regulation of 5′-deiodinase activity may reflect increased growth hormone produciton (52) – a consequence of soy feeding observed clinically (6).

Vegan diets may also impact adipocyte function. Kern et al. report that human adipocytes express IGF-I receptors, and that indeed the physiological activator of human adipocyte lipoprotein lipase activity is IGF-I rather than insulin (53). This intriguing finding merits replication. The implication is that IGF-I has an important anabolic impact on adipocytes – very reasonable in light of IGF-I's function as a signal of abundance – and that conversely, measures (such as vegan diets) which down-regulate IGF-I activity should promote leanness. Analogously, some of the weight loss on vegan regimens presumably is attributable to loss of lean mass consequent to a decreased anabolic impact of IGF-I on skeletal muscle.

Carter et al. have stated, 'The mean weight of vegans is 20 lbs less than that of ovolactovegetarians and non-vegetarians, despite similar caloric intakes and physical activity, which suggests that calories of vegan diets may be used inefficiently' (54). The findings of the China Health Project are consistent with this view (55). Using data standardized for a reference adult male whose job entails 'very light physical activity', the researchers

conclude that 'energy intake, when adjusted for body weight, is more than 30% higher in China than in the United States.' Nonetheless, the average BMIs of adult males in rural China and in the USA are 20.5 and 25.8, respectively. On average, rural Chinese obtain only about 10% of their dietary protein from animal sources; fat intake averages 15% of calories. A portion of the 30% caloric excess can be attributed to the use of bicycles for transportation; also, this excess would have been somewhat less impressive if it had been feasible to calculate caloric intake per unit lean mass. These modest corrections would not negate the conclusion that a low-fat vegan diet is associated with increased thermogenesis and a decreased propensity to store calories in adipose tissue.

A corollary of these considerations is that vegan proteins should promote the efficacy of obesity therapies whose intent is to maximize hepatic fatty acid oxidation (56,57).

VEGAN DIETS VS CANCER

In a nutshell, the thesis presented here is that animal protein – precisely because it is 'high-quality' protein, rich in essential amino acids – will up-regulate IGF-I activity and thereby act as a cancer promoter; 'low-quality' vegan proteins can be expected to have the opposite effect. As stated previously, IGF-I acts as a 'progression factor' for most normal and pre-neoplastic tissues; although often not sufficient to induce mitosis by itself, IGF-I usually works in tandem with 'competence' growth factors to promote cell turnover (33). Induction of the IGF-I receptor is often one of the essential roles of competence growth factors. Recent studies also show that IGF-I can inhibit apoptosis in many normal and neoplastic cell lines (35,36,58). It is now believed that apoptosis of genetically-damaged cells is crucial to cancer prevention; cancer promotional agents invariably demonstrate anti-apoptotic activity (59–64). Increased IGF-I activity can be expected to increase the rate at which fixed mutations are accumulated in stem cells by promoting stem cell turnover; by suppressing apoptosis, it can be expected to increase the chance that initiated cells will engender clinical cancer. In addition, the mitotic and apoptotic rates of many cancers are sensitive to IGF-I activity (34). Dietary modulation of IGF-I activity can therefore be expected to have profound consequences for cancer risk and progression.

As noted above, reduction of IGF-I activity during a vegan diet can be expected owing to up-regulation of IGFBP-1. However, the possibility that such diets may also modestly decrease hepatocyte synthesis of IGF-I should be considered. In clinical or animal studies, low-protein diets of adequate caloric content decrease the serum level and hepatic synthesis of IGF-I (65-67); this effect appears to be attributable to a dietary deficit of certain essential amino acids (68–72). Low intake of these essential amino acids markedly destabilizes the 7.5kb form of the IGF-I mRNA, and may also impede translation of IGF-I mRNAs (72–74). Severe protein restriction may not be required to evoke this effect. Miura et al. fed rats 12% protein diets featuring either casein, gluten, or soy protein; serum IGF-I was significantly lower in rats receiving gluten or soy, and a parallel reduction was noted in hepatocyte IGF-I mRNAs (75). Addition of methionine to the soy diet minimized the decline in IGF-I. More recently, Koutessis and colleagues fed isocaloric diets of adequate protein content (~1g/kg/day), featuring either animal or vegetable protein, to type 1 diabetic patients in a crossover design; serum IGF-I was about 18% lower during the vegan regimen (76). These findings suggest that, even when protein intake is not notably deficient, quality of dietary protein can modulate IGF-I synthesis; the low–normal intake of certain essential amino acids provided by many healthful vegan diets may not be sufficient to maximize IGF-I produciton.

Moreover, down-regulation of IGF-I activity in vegans is often not solely attributable to the protein content of vegan diets. To the extent that vegan diets, as compared to omnivorous diets, tend to be relatively low in fat (especially saturated fat), and high in fiber, these factors should promote increased insulin sensitivity – both acutely, and by aiding prevention of obesity (77,78). This improved insulin sensitivity will down-regulate insulin secretion, thus contributing to the protective increase in glucagon/insulin ratio and the resulting up-regulation of IGFBP-1. Evidently, several independent mechanisms can interact to reduce IGF-I activity in vegans. (Perversely, the saturated fats featured in many animal products are the most efficient at inducing insulin resistance, whereas ingestion of monounsaturates – found in such favorite vegan foods as avocadoes, olives, and olive oil – appear to have little impact on insulin sensitivity in humans (79,80); perhaps this is a major reason why monosaturates emerge blameless in much recent epidemiology.)

A reduction in IGF-I activity may explain several intriguing effects of soy-based or vegan diets. Hawrylewicz et al. reported a reduction of ornithine decarboxylase activity in the mammary epithelium of rats fed soy protein (41); IGF-I's ability to induce ornithine decarboxylase activity is crucial to its role as a progression factor for cell mitosis (81). Increases in sex hormone binding globulin (SHBG) are reported in soy-fed animals as well as in vegan men (82); IGF-I is a potent inhibitor of hepatic SHBG production (83). An increase in serum growth hormone during soy feeding was noted during the Descovitch study cited earlier; this is readily explained by a reduction in IGF-I's feedback inhibition of pituitary growth hormone secretion (84). Third World

peoples who traditionally consume predominantly vegan diets throughout life, typically achieve a shorter stature than do more affluent omnivores; this may reflect a relative deficit of IGF-I activity. However, in some instances this deficit of IGF-I activity may be reinforced by periods of involuntary caloric restriction. Caloric restriction potently suppresses hepatic IGF-I synthesis while up-regulating IGFBP-I (72) – an effect which is no doubt crucial to the prevention of cancer and renal disease observed in calorically-restricted rodents (32).

There have been a handful of anecdotal reports of 'spontaneous' cancer regression in patients who have adopted a vegan 'macrobiotic diet' (85,86). Conceivably, these cases reflect cancers in which the apoptotic rate is exquisitely sensitive to modest reductions in IGF-I activity. It is evident that such overt responses are rare; the more realistic possibility is that vegan or macrobiotic regimens may slow the progression of certain cancers. This possibility could only adequately be evaluated in controlled studies that thus far are non-existent; proponents of 'orthodox' oncology have proven more adept at ridiculing and decrying the therapies of 'alternative' practitioners than at testing them. However, a small retrospective analysis of the case histories of patients with pancreatic and metastatic prostate cancer who chose to adopt a very-low-fat, high-fiber diet, suggests that, as compared to concurrent patients who did not modify their diets, these patients may have experienced longer survival and improved quality of life (86).

While the effects of soy protein on cancer induction have typically been attributed to phytoestrogens, protease inhibitors, or other 'contaminants' (40,87,88), it should be noted that soy protein diets often impede the induction of cancers not known to be hormone dependent, that relatively pure soy protein isolates with lower phytochemical levels are often effective for cancer prevention (41), and that the levels of bioavailable (free + sulfated) genistein measured in the plasma of Japanese men (whose traditional consumption of soy protein is high) are three orders of magnitude lower than the concentration required for effective tyrosine kinase inhibition (89). Thus, while a role for phytochemicals in the cancer preventive activity of soy protein should not be ruled out, such phytochemicals appear unlikely to be solely responsible for the observed protection. The impact of other vegan proteins (e.g. wheat protein isolates) on cancer induction in rodents requires evaluation.

In regard to the phytoestrogen question, it is surprising that, with the exception of several recent studies with falxseed lignans, and the known ability of conmestrol-rich clover to inhibit fertility in sheep, few if any studies demonstrate that the addition of ordinary dietary levels of phytoestrogens to basal diets low in phytochemicals can exert meaningful physiological effects. Most in vivo studies use soy protein concentrates, or administer phytoestrogens parenterally in doses of questionable nutritional relevance. A couple of recent animal studies demonstrate that ethanol-extracted soy protein has a less favorable impact on serum lipids or vascular function than does non-extracted soy protein (90,91); this suggests that phytochemicals in soy may potentiate some of its benefits, but does not prove that these agents would provide protection when added to a casein-based diet, nor determine the nature of the protective chemicals. As far as in vitro studies go, while they may provide insight into the pharmaceutical potential of phytoestrogens, the concentrations used in most of these studies are not relevant to the low nanomolar concentrations of available phytoestrogens measured in the serum of humans consuming soy. Does the phytoestrogen emperor have any clothes?

A recent analysis of the urinary excretion of isoflavonoids in various population groups found 6.8 μmol in the 24-hour urine of young macrobiotics (the group with by far the highest excretion); this amounts to less than 2 mg (87). Estradiol, in a micronized form said to be efficiently absorbed, is administered postmenopausally in doses of 1–2 mg daily – yet the affinity of isoflavonoids for the estrogen receptor is reported to be several orders of magnitude lower than that for estradiol (40). These considerations render it extremely doubtful that nutritional intakes of phytoestrogens could meaningfully modulate estrogen activity – though they don't eliminate the possibility that these compounds could have other interesting effects. In any case, we should not allow a fascination with phytoestrogens to distract us from giving careful attention to the possibility that the *structure* of soy protein – and of vegan protein generally – is a crucial factor in the demonstrable protective effects of soy-based and vegan diets.

Hawrylewicz is one of the few cancer researchers to focus attention on the amino acid content of soy protein; he reports that enrichment of a soy-based diet with methionine partially offsets the antipromotional impact of this diet on NMU-induced breast cancer in rats (41). This finding brings to mind the previously-cited report that methionine supplementation increases serum IGF-I levels in soy-fed rats (75), and puts in a new light previous suggestions that soy protein concentrates intended for human use should be 'enriched' with methionine.

HYPERINSULINEMIA AS A RISK FACTOR FOR BREAST, ENDOMETRIAL, AND COLON CANCERS

Recently, several authors have presented cogent evidence that hyperinsulinemic insulin resistance is an important risk factor for postmenopausal breast cancer, and that

hyperinsulinemia induces the increased testosterone production, the reduction in serum SHBG, and the increased free estradiol levels that characterize subjects at high risk for this disorder (92–95). It may be reasonable to extend and clarify this hypothesis by proposing that the fundamental risk factor is a high activity of insulin relative to glucagon in hepatocytes, resulting in a suppression of IGFBP-1 production. As suggested previously (93–95), the consequent increase in effective IGF-I activity can be expected to potentiate the LH-induced production of androgens by ovarian stroma (96–98), while decreasing hepatic production of SHBG (82,88). Peripheral aromatization of these androgens will give rise to estrogens, an increased proportion of which will remain unbound owing to the decrease of circulating SHBG and the increased competition by testosterone for binding to this SHBG. The increased effective activities of both estrogen and IGF-I will then synergize to stimulate mitosis and inhibit apoptosis in pre-neoplastic breast tissue; this synergism results, at least in part, from estrogen-mediated induction of IGF-I receptors (99,100).

This formulation recognizes a countervailing protective role for glucagon – and, by implication, for vegan proteins that preferentially promote glucagon release. It also stresses the importance of insulin *activity* on hepatocytes. The equivocal impact of diabetes on breast cancer risk (95) is rationalized by the realization that net insulin activity on hepatocytes is *decreased* in diabetics – even in type 2 diabetics who are hyperinsulinemic. Hepatocytes are typically insulin resistant in type 2 diabetics; in type 1 diabetics and in type 2 diabetic with profound beta cell failure, portal insulin concentrations are sub-normal. That some studies nevertheless do see an increased breast cancer risk associated with type 2 diabetes (101,102) may reflect the fact that this type of diabetes is usually preceded by a long period of compensated hyperinsulinemic insulin resistance.

These considerations enable the prediction that a low-fat vegan diet will be profoundly protective with respect to risk for postmenopausal breast cancer. The protein content of this diet will preferentially support glucagon activity and possibly decrease IGF-I synthesis. Other aspects of the diet – a low intake of fat, increased fiber, decreased propensity to induce obesity – will promote good peripheral insulin sensitivity and thus down-regulate insulin secretion. Such diets are likely to be relatively high in phytochemicals that may have anti-initiating activity, and the possibility that phytoestrogens contribute some protection does merit further evaluation (103).

Endometrial cancer is also associated with obesity (and, by implication, insulin resistance), and the role of increased unopposed estrogen activity in its etiology is well known. A favorable impact of a low-fat vegan diet on endometrial cancer risk is therefore readily predicted. As in the breast, estrogen induces IGF-I receptor expression in the uterus (104).

Risk of colon cancer has likewise been linked to hyperinsulinemia in recent research (105). That induction of this cancer may be particularly sensitive to IGF-I activity is suggested by the high-incidences of colon polyps and colon cancer associated with acromegaly (106,107). The normal colonic mucosa, as well as many colon adenocarcinomas, are IGF-I sensitive (108–112).

The puzzling fact that postmenopausal estrogen replacement does not increase breast cancer risk as greatly or consistently as might be expected, may reflect the fact that orally-administered estrogens (but not transdermal or endogenous estrogens) suppress hepatic production of IGF-I (113). This suggests that long-term estrogen replacement therapy may reduce the risk of colon cancer and perhaps of other cancers that are not estrogen-dependent. In fact, decreased colon cancer risk associated with estrogen replacement has recently been demonstrated (114–118), this effect is quite substantial – 30–50% reduction in risk is seen in current or long-term users. A concurrent vegan diet and insulin-sensitizing lifestyle should amplify this benefit, and also reduce the breast cancer risk associated with estrogen replacement. Indeed, the down-regulation of IGF-I activity achievable by oral estrogen in conjunction with a vegan diet might be sufficiently large to be useful in cancer therapy – either as a palliative regimen or as an adjuvant to apoptosis-inducing measures. Tamoxifen, which is reported to decrease IGF-I and/or up-regulate IGFBP-1 (119,120), might be a useful alternative to estrogen in men or in women who have estrogen-sensitive tumors. It will be interesting to determine whether soy phytoestrogens can influence hepatic IGF-I production. In light of the media frenzy regarding hormone replacement therapy's impact on breast cancer risk, wouldn't it be ironic if such therapy proves to have a neutral or even favorable impact on *overall* cancer mortality?

In fact, Ettinger and colleagues have recently published a case-control analysis of all-cause and specific-cause mortality in women who began estrogen replacement within three years of menopause and continued it for at least five years (121). As compared to age-matched postmenopausal non-users, their overall relative risk of cancer death was 0.85 – not significantly different from unity. The increased risk of breast cancer mortality in users was most notably balanced by substantially reduced risk of death from lung cancer (RR 0.22). (As noted below, lung cancer is one of those cancers whose incidence may be markedly influenced by IGF-I activity.) The most striking finding was a relative risk of all-cause mortality of 0.54 (CI 0.38–0.76) – a finding reasonably consistent with

other investigations that have examined this parameter. (122–124). Recent findings from the gigantic Nurses Health Study, however, suggest that net protection may decline somewhat for women using estrogen for over 10 years, owing to a cumulative impact on breast cancer mortality (RR 0.80) (124). (Nurses presumably would derive less benefit from lung cancer prevention than the general population, as comparatively few of them smoke.) These considerations suggest that 5–10 years of hormone replacement therapy are indicated for women not known to have high breast cancer risk, with longer usage contemplated for women at high risk for estrogen-preventable disorders such as cardiovascular disease, lung cancer, and colon cancer. Epidemiology focusing specifically on long-term estrogen use in smokers could be valuable. Perhaps estrogen analogues can be found that down-regulate IGF-I and protect bone health without stimulating estrogen-sensitive tissue – these would be worthwhile for elderly women. (Does raloxifene influence IGF-I levels?)

IGF-I ACTIVITY AND PROSTATE CANCER RISK

Inasmuch as incidence of microscopic carcinoma-in-situ of the prostate does not vary greatly between countries, the extraordinary international variations in the occurrence of clinical prostate cancer appears to be primarily attributable to promotional rather than initiating factors (125). IGF-I is a potent growth factor for normal prostatic epithelium, as well as for prostate adenocarcinoma cell lines (58,126–132). That IGF-I activity is crucial for prostate cancer growth is suggested by studies showing that IGFBP-1 and other IGF-1 antagonists suppress the proliferation of cultured prostate cancer cells, that transfection of such cells with antisense DNA to the IGF-I receptor inhibits their growth and invasiveness in vivo, and that an antagonist of GHRH (which decreases IGF-I levels) suppresses the growth of human prostate cancer cell lines in nude mice (131–135). Prostate-specific antigen (PSA), a marker for prostate cancer prognosis, is a serine protease that cleaves and inactivates IGFBP-3; it may therefore serve to induce a local increase in IGF-I activity (136). There is recent evidence that IGF-I may activate the androgen receptor in human prostate cancer cell lines, in the *absence* of androgens (137,138).

Increased IGF-I activity can also up-regulate testosterone availability. In addition to suppressing hepatic SHBG production, IGF-I may promote GnRH secretion, potentiate the LH response to GnRH in pituitary gonadotrophs, and likewise potentiate the steroidogenic response of Leydig cells to LH (139–144). Reduced levels of free testosterone reported in vegetarians may reflect these effects (145,146). It can be concluded that high IGF-I activity should have a potent growth promotional/anti-apoptotic impact on prostate epithelium, owing both to a direct impact of IGF-I, as well as an increase in testosterone availability.

These considerations rationalize a recent Greek case-control study in which increased serum IGF-I was associated with increased prostate cancer risk (147). Increased height – a correlate of IGF-I activity during development – has also been linked to prostate cancer risk (148,149). However, attempts to correlate obesity with prostate cancer risk have yielded inconsistent results; this may reflect the fact that, in obese men as in postmenopausal women, synthesis of estrogen is increased (150–153).

Two other high-incidence cancers in Western society are those of the ovary and pancreas. Both theca and granulosa cells of the normal ovary are IGF-I responsive (96–98,154). Virtually all ovarian cancers and cancer cell lines examined express IGF-I receptors, and respond to IGF-I as a growth factor (155,156). Estradiol potentiates the response to IGF-I in some ovarian cancer cell lines by up-regulating the IGF-I receptor (157). Case-control studies often but not invariably point to obesity as a risk factor (158–161). With regard to the pancreas, IGF-I appears to be a progression factor for cells of the exocrine pancreas, and many recent reports indicate that pancreatic adenocarcinomas express IGF-I receptors and are IGF-I responsive (162–165). In some pancreatic cancer cell lines, IGF-I functions as an autocrine growth factor, such that antibodies to the IGF-I receptor, or antisense DNA to this receptor, inhibit cell growth in vitro. An LHRH agonist, which down-regulates IGF-I receptor expression in carcinogen-induced autogenous pancreatic cancers in hamsters, markedly retards the growth of these cancers (166). Some epidemiology links pancreatic cancer risk to high BMI as well as to diabetes; the latter correlation, however, declines with time, suggesting that the associated diabetes is sometimes caused by the nascent pancreatic cancer (167–171). Overall, these findings appear consistent with the possibility that IGF-I activity modulates the promotion and progression of both ovarian and pancreatic cancer.

IGF-I ACTIVITY MAY REGULATE ONSET OF PUBERTY

It is well known that puberty occurs, on average, at an earlier age in Western society than in Third World predominantly vegan cultures, and that age at puberty has declined over the last 100 years in Western nations (172). Conversely, age of menopause has tended to increase. Thus, women in Western society experience a greater number of ovulatory cycles during their reproductive years – an effect often compounded by a decrease in time spent in pregnancy and lactation. Since ovulatory cycles promote mitosis in the breast, ovary, and endometrium, the increased number of ovulatory cycles

in Western women is believed to be an important factor in their increased risk for cancer of these tissues – a view supported by case-control epidemiology (173,174). (The epidemiology of endometrial cancer, however, is complicated by the fact that anovulatory cycles associated with obesity can increase risk owing to progesterone deficiency.)

In light of data cited earlier regarding the ability of IGF-I to potentiate GnRH and LH release, it is reasonable to suspect that increased IGF-I activity plays a role in the early onset of sexual maturity in Western women. Indeed, IGF-I activity increases early in puberty, owing to an increase in IGF-I synthesis and a reduction in insulin sensitivity consequent to increased growth hormone production (175–177). A recent study shows that intraventricular IGF-I administration promotes LH release and accelerates the onset of puberty in immature female rats (178). Furthermore, administration of IGF-I to adolescent female rhesus monkeys has been shown to accelerate the decline in sensitivity to estrogen feedback that triggers increased LH production (179). Thus, IGF-I activity may participate in a positive feedback loop that initiates sexual maturity. It can be anticipated that the greater IGF-I activity associated with habitual ingestion of a fatty omnivorous diet will amplify this positive feedback loop and thus promote early puberty and the early achievement of regular ovulatory cycles. A regulatory impact of IGF-I on the onset of puberty makes sense homeostatically – why should sexual maturity be initiated if the availability of food energy is insufficient to support pregnancy?

The impact of the age at menarche on breast cancer risk is far larger than it should be if the only relevant issue were total number of ovulatory cycles; Henderson and colleagues cite a 20% reduction in breast cancer risk for each year that menarche is delayed (174). Conceivably, late menarche may serve as a marker for decreased IGF-I activity – a factor which, if it persists through subsequent years, may confer substantial protection from breast cancer and indeed other cancers. Two case-control studies note a decreased risk of colon cancer associated with late menarche (180,181); however several other studies fail to observe this.

Does IGF-I activity likewise regulate age at menopause? This possibility requires evaluation. Prolongation of fertility when food energy is abundant would be appropriate.

EPIDEMIOLOGY OF 'WESTERN' CANCERS – THE ROLE OF DIET

Many of the major cancer killers can be characterized as 'Western' cancers based on the fact that their age-adjusted incidences are astoundingly higher in modern urbanized nations than in Asian and other cultures whose traditional diets are low in fats and animal products. These include cancers of the breast (particularly postmenopausal), endometrium, colon, prostate, pancreas, and ovary. Although lung cancer is prominent wherever cigarette smoking is common, its incidence in Asian countries is anomalously low relative to the high proportion of heavy smokers. Comparative international epidemiology shows strong correlations between incidence of or mortality from these cancers and average estimated daily intakes of total fat or saturated fat; many though certainly not all within-country case-control or prospective cohort studies similarly indict total fat and saturated fat as a risk factor – although fat does not emerge as a risk in most case-control studies of breast cancer (182–186). These findings have encouraged many experts to speculate that restriction of dietary fat would greatly reduce cancer incidence.

However, a peculiarity of much of the relevant epidemiology is that intakes of unsaturated fats usually (though not invariably) fail to correlate with cancer risk. This is particularly puzzling in light of the fact that, in rodent models of cancer induction, linoleic acid is typically more effective than saturated fats as a cancer promoter. A possible resolution of this difficulty is that high intakes of total and saturated fat may be serving as a marker for heavy ingestion of animal products. While saturated fat ingestion per se may have a genuine effect on cancer induction (by promoting insulin resistance, obesity, activation of protein kinase C, etc.), the concomitant ingestion of animal protein may likewise exert a significant cancer promotional effect. Ingestion of animal products also implies a compensatory reduction in the intake of plant-derived foods that offer protective phytochemicals, fiber, and vegan proteins. Conversely, ingestion of unsaturated fats may not be truly innocuous, but may appear so because it correlates with a higher intake of plant-derived foods.

Current epidemiology appears to be reasonably consistent with the thesis that animal product ingestion is primarily responsible for the high incidence of Western cancers in urbanized societies (185–207). (The references cited are representative rather than exhaustive). Two exceptions should be noted, however. In Western cohort or case-control studies, dairy products sometimes appear to be protective with respect to several cancers, quite possibly because these foods are often major dietary sources of calcium and vitamin D. Similarly, fish ingestion is sometimes reported as protective; marine fish can be rich in vitamin D, as well as in long-chain omega-3 polyunsaturated fats that inhibit cancer promotion and growth in numerous animal cancer models. (However, fish protein per se does not appear to have any advantages over other animal proteins in regard to modulation

of cholesterol metabolism in animals.) The failure of some case-control or cohort studies to indict dietary fat or animal products might be traced to such factors as limited variability of dietary patterns in the populations assessed (few such studies include a significant proportion of lifelong vegans), the imprecision inherent in assessing lifelong dietary intake by examining a single timepoint, and the possibility that nutrition prior to adulthood (rarely analyzed in these studies) may have a crucial impact on cancer risk.

THE CHINESE EXPERIENCE

The massive China Health Project has provided evidence strongly consistent with the thesis that animal product ingestion has important cancer promotional activity – not only with respect to typical 'Western' cancers, but also several cancers encountered predominantly in the Third World.

The dietary intakes of rural Chinese populations are still predominantly vegan, but consumption of animal products (modest by Western standards) is significant in some regions. Owing to the fact that rural Chinese tend to live in the same region and consume a characteristic diet all of their lives, rural China is an exceptionally appropriate venue for ecologic epidemiology. Scientists from Cornell, Oxford, and Beijing have determined that the incidences of numerous types of cancer (including the 'Western' cancers discussed above), as well as of coronary heart disease, correlate positively and significantly with animal product intakes throughout rural China. The authors conclude that 'even small intakes of foods of animal origin are associated, in turn, with significant increases in chronic degenerative disease mortality rates (55)'.

When diets are predominantly vegan, even a modest increase in the ingestion of animal products can have a notable impact on serum cholesterol levels (in large part owing to the cholesterol content of these foods). Thus, serum cholesterol in rural China can serve as a marker for animal product intake. The China Health Project found that 'plasma cholesterol was associated directly with all-cancer mortality rates measured in this study. Most notably, these associations were statistically significant for eight different cancers…: Thus, in China, only small intakes in meat and very modest elevations of dietary fat are associated with increases in plasma cholesterol, which is associated in turn with the emergence of diseases that typically occur in Western countries'.

(In some Western epidemiology, low serum cholesterol has been reported to be *predictive* of subsequent cancer incidence (208). It should be noted that, in omnivorous societies where almost all individuals indulge heavily in animal products, serum cholesterol is useless as a marker for animal product ingestion. It is now suspected that the apparent cancer risk associated with low cholesterol in some studies is indicative of a catabolic effect of occult cancer (209).

The concluding paragraph of a summary of the findings of the China Health Project merits quotation in full:

> 'The findings from this survey in China might be considered rather provocative because they suggest that substantial decreases in intakes of dietary fat and animal protein and substantial increases in dietary fiber and other complex carbohydrates should result in continuing reductions in plasma cholesterol and the associated chronic degenerative diseases. Moreover, there seems to be no evidence thus far from these data to indicate that if risks for these diseases were reduced there would be compensatory increases in other adverse health effects, as long as food choice is varied, of good quality, and adequate in amount. Therefore, simultaneous and substantial modification of all dietary factors that beneficially modify various neoplastic and cardiovascular diseases may be necessary to obtain significant reductions in these diseases. These modifications can be obtained most readily and comprehensively by consumption of a diet rich in foods of plant origin, and, to ensure a comprehensive effect for all relevant diseases, a generous variety of products ought to be used (55).

Of particular interest is the fact that the incidences of hepatic and gastric cancer likewise correlate with animal product ingestion and serum cholesterol in rural Chinese. This may seem paradoxical because, in international epidemiological comparisons, these cancers are most common in Third World societies in which traditional diets are high in carbohydrate and low in fat. However, these high-carbohydrate low-fat diets may simply be a marker for poverty, which in turn is associated with the chief initiating factors for these cancers – hepatitis and salt-preserved foods. The findings of the China Health Project suggest that dietary animal products, acting as promotional factors, interact with these initiating agents to enhance the incidence of gastric and hepatic cancers. These cancers are comparatively rare in Western society only because the initiating factors are less common – owing to better hygiene and the availability of refrigeration. Leukemia and childhood brain cancers are also cited as rare among rural Chinese vegans. The fact that animal product ingestion has such broad promotional activity, suggests that it is influencing a very fundamental aspect of cancer induction; since IGF-I activity promotes mitosis and inhibits apoptosis in a great many tissues, an up-regulation of IGF-I activity is a very credible explanation for the promotional impact of such foods.

Conversely, a recent nationwide Italian ecologic study concludes that vegan protein consumption correlates negatively with total cancer mortality; each 1g increase in daily vegan protein intake was associated with a 2.5% reduction in age-associated cancer mortality (210). Other epidemiological data bases should be re-examined in light of the hypothesis that vegan protein consumption is protective. Likewise, the variable 'percent of calories from plant foods' should be used in epidemiological analysis.

An overview suggests the following hypothesis: that IGF-I activity is an important promotional factor in many malignancies – most notably those characteristic of Western society; that this effect of IGF-I is often mediated not only by a direct impact on pre-neoplastic tissues, but also indirectly through modulation of sex hormone availability, onset of puberty and menopause, neutrophil activity (see below), and possibly other factors; that the characteristic structure of vegan proteins, as well as other aspects of low-fat, fiber-rich vegan diets, can significantly down-regulate IGF-I activity; and that this phenomenon thus plays a crucial role in the relatively low incidence of 'Western' cancers in predominantly vegan rural societies.

IGF-I activity can be viewed as a centrally integrated signal of abundance, monitoring caloric adequacy as well as availability of carbohydrate and essential amino acids. As a signal of abundance, IGF-I promotes cell multiplication and fertility; this effect is crucial for growth, protective anabolism, and procreation. Unfortunately, the relatively high IGF-I activity induced by Western diets contributes to an increased risk for various hyperplastic pathologies, including many cancers as well as atherogenesis. The lesser IGF-I activity associated with calorically adequate vegan diets is sufficient to maintain health, while markedly reducing risk for these pathologies.

ANTI-INFLAMMATORY IMPACT OF VEGAN DIETS

A vegan diet, proceeded by a one-week juice fast, is a traditional treatment for rheumatoid arthritis and other inflammatory disorders at Nordic health spas. A controlled study has confirmed the efficacy of this regimen in providing moderate but significant symptomatic relief in rheumatoid arthritis, accompanied by improvements in objective parameters of inflammation such as sedimentation rate and C-reactive protein (47). Particularly notable is a decline in the white blood cell count, observed not only in this study, but in three other medium- to long-term clinical studies assessing vegan diets (42,43,211). In one of these, in which a two-week modified fast was succeeded by a three-week vegan regimen, relief of dermatological inflammation tended to correlate with declines in serum lactoferrin, a marker for neutrophil degranulation (211). These findings may be rationalized by recent evidence that IGF-I is a crucial stimulant of granulopoiesis, and also 'primes' mature neutrophils, rendering them more responsive to stimulants that induce an oxidative burst and degranulation (212–214). A very recent report indicates that IGF-I can likewise increase the expression of adhesion receptors on endothelial cells (215). Thus, down-regulation of IGF-I activity can be expected to have an anti-inflammatory impact, most notably in disorders such as rheumatoid arthritis in which activated neutrophils play a prominent pathogenic role. The value of the preliminary fast in the Nordic treatment regimen is clear: this will produce a sharp reduction in IGF-I activity, not only by a marked up-regulation of IGFBP-1, but also by suppressing hepatic production of IGF-I (216). Fasting produces rapid and often dramatic symptomatic relief in rheumatoid arthritis (217).

An elevated white cell count is an independent cardiovascular risk factor, and activated leukocytes can exacerbate tissue ischemia by wedging in capillaries downstream from stenotic lesions (218–220). Thus, the ability of a vegan diet to decrease the production and activation of neutrophils may contribute to its favorable impact on vascular health, and may help to explain anecdotal reports that vegan diets provide symptomatic relief in angina (221).

There is recent evidence that oxidants produced by activated neutrophils make a significant contribution to the pathogenesis of lung cancer in smokers (222,223). Thus, it is conceivable that down-regulation of neutrophil levels and activity may be a factor in the lower incidence of lung cancer in Asian smokers ingesting predominantly vegan diets. (However, as with all other prominent Western cancers, the available evidence is consistent with IGF-I activity having a direct promotional impact on preneoplastic cells, as well as a growth-promoting effect on cancer: IGF-I receptors are expressed on bronchial epithelial cells of normal lung, and the great majority of human lung cancers examined likewise express functional IGF-I receptors that, when activated, promote mitosis in vitro (224–230); IGF-I is an autocrine growth factor in most small cell lung cancers. In some (231,232), but not all (233) case-control studies, serum IGF-I is increased in lung cancer patients as compared to age-matched controls; in one of these studies, these high levels were noted to persist after surgical removal of the tumor (231).

REGRESSION OF ATHEROMA

Ornish and colleagues have demonstrated that a low-fat, predominantly vegan diet (egg whites and non-fat milk or yogurt were allowed in very restricted amounts), coupled

with aerobic exercise training and stress reduction techniques, typically induces modest regression of coronary stenosis over the course of a year; stenosis progressed in a control group following American Heart Association guidelines (234,235). Angina symptoms also improved dramatically in the experimental group – an effect not wholly attributable to the regression of atheroma, as it was noted within a month of initiating therapy. Not surprisingly, lesion regression was greatest in those subjects judged most compliant. Although serum LDL cholesterol fell by an average of over 37%, most subjects enrolled had 'normal' cholesterol levels at baseline; thus, it would be questionable to attribute the benefits of this regimen solely to serum lipid reduction.

Consideration should be given to the possibility that down-regulation of IGF-I activity made a significant contribution to lesion regression. IGF-I is a crucial progression factor for vascular smooth muscle; although only weakly mitogenic by itself, IGF-I greatly potentiates the mitogenic response to growth factors such as PDGF and EGF (236–238). Indeed, one of the key effects of 'competence' factors such as PDGF is to increase expression of IGF-I receptors. During intimal hyperplasia, autocrine production of IGF-I by intimal smooth muscle increases, as does expression of IGF-I receptors (239–241). Conversely, antagonists of the IGF-I receptor inhibit smooth muscle mitosis, both in vitro and in vivo, while promoting apoptosis (242–245). It seems higly likely that IGF-I down-regulation played a role in the apparent regression of atheroma noted after semi-starvation in wartime survivors and cachectic cancer victims (246). Conversely, the increased cardiovascular risk associated with acromegaly may reflect excessive IGF-I activity.

Regression of atheroma should be achieved more regularly if down-regulation of IGF-I is coupled with comprehensive 'endotheliophilic' measures which promote endothelial production of nitric oxide and heparan sulfate – factors which are anti-mitotic and pro-apoptotic for vascular smooth muscle cells (247–254). Certain effects of a low-fat vegan diet – reduced serum LDL levels, decreased exposure to free fatty acids, increased serum potassium – could be expected to improve endothelial function. Since angiotensin II inhibits apoptosis in vascular smooth muscle cells (254,253), drugs which suppress the production or activity of this agonist may likewise be useful for atheroma regression therapy.

If a low-fat vegan diet/exercise regimen can regress or stabilize coronary stenoses in most people who are predisposed to ischemic heart disease, it is entirely reasonable to predict that such a regimen would be very effective for preventing this disorder in the general population – a view borne out by the near absence of coronary disease in many Third World cultures prior to Western incursions (55,256,257).

ANCILLARY BENEFITS

Although IGF-I plays an anabolic role in bone (258), the net impact of vegan diets on bone density and osteoporosis risk often appears to be positive (259–263), apparently because such diets are lower in sulfhydryl amino acids that are metabolized to sulfate; the latter is markedly calciuric (264–268). This may explain why, despite demonstrated favorable effects of supplemental calcium on calcium balance, the impact of dietary calcium on bone health assessed epidemiologically has sometimes been equivocal; in Western diets, the bulk of dietary calcium comes from dairy products that concurrently supply calciuric milk protein (269–271). Although advocates of veganism often point to the good bone health of Bantus consuming low-calcium diets, genetic factors may play a role in this phenomenon, as the experience of Chinese vegans on low-calcium diets is less favorable (272). Presumably, eating a vegan diet *and* assuring ample intakes of calcium (and other micronutrients required for bone health) is the safest course of action. Fortunately, a diet high in vegetables is usually rich in calcium; vegans who get few of their calories from vegetables would be wise to take supplemental calcium. (In passing, it may be noted that high-sodium diets likewise are calciuric, and appear to accelerate bone loss in postmenopausal women – an effect whose impact on health may be no less significant than sodium's role in hypertension and stroke risk (273–276). Vegans who wish to maintain adequate bone mass throughout a long lifetime would be well advised to moderate salt consumption.)

Since vegan diets tend to be less calciuric, they may be useful for preventing calcium-dependent renal calculi (227); a possible countervailing factor is that some vegan diets are relatively high in oxalic acid (278). (Paradoxically, calcium supplements taken with oxalic acid-rich diets may *reduce* renal stone formation by precipitating the oxalic acid in the gut, preventing its absorption (279).) Gallstones are also less common in vegetarians, presumably because cholesterol turnover is lower (280).

Since animal products are devoid of fiber, a diet which eschews animal products will of necessity be proportionately higher in fiber. Unless excessive amounts of refined carbohydrates and juices are ingested, vegan diets are fiber-rich. Burkitt, Trowell, and colleagues have pointed to the likely role of bulk-forming fiber in the relative freedom of Third World cultures (prior to Westernization) from such disorders as appendicitis, diverticulitis, hiatal hernia, varicose veins, and hemorrhoids (not to mention that bane of modern life most dear to advertising executives – constipation!) (256–257).

Especially when coupled with regular exercise, fiber-

rich, low-fat predominantly vegan diets have a rapid, highly favorable impact on glycemic control in type 2 diabetics; over the course of a three-week program, roughly half of diabetics can discontinue their medications while sustaining lower serum glucose (78,281). Whether vegan protein per se contributes to this phenomenon is not yet clear. In the longer term, diminution of visceral obesity can compound this benefit. Vegan diet-mediated reduction of IGF-I activity, by decreasing glomerular filtration rate, may decrease the risk of renal failure in diabetics (76). Type 2 diabetes is another of the diseases which used to be virtually unknown in the Third World (256,257). (Claims that 'low fat/high carbohydrate' diets are of little merit in the management of diabetes or syndrome X (282) are based on experience with the dietary recommendations of the American Diabetic Association, which mandate only a very modest reduction of saturated fat.)

Vegetarian regimens also tend to modestly decrease blood pressure, even when little effort is made to restrict dietary sodium (42,283–286). This may reflect the relatively high potassium and magnesium content, and the elevated P/S ratio, of vegetarian diets, as well as their favorable impact on insulin sensitivity. Additionally, IGF-I activity can promote renal tubular sodium reabsorption, and increased IGF-I levels have been observed in low-renin hypertensives (285); the high prevalence of hypertension in patients with acromegaly is well known. Could the association of obesity and insulin resistance with hypertension be mediated in part by increased IGF-I activity? In a group of macrobiotic vegan communes in the Boston area, Sacks et al. determined that average blood pressure was 106/60, and showed little rise with age; subjects who were strict in the avoidance of animals products had significantly lower blood pressure than those who were not (286).

Multiple sclerosis afflicts over a quarter million Americans, and is the most common neurodegenerative disorder in young adults. Prompted by the observation that the clinical course of MS seemed to improve in Europeans deprived of animal products during World War II, epidemiological studies established that MS was far less common in predominantly vegan societies, and tended to correlate internationally with saturated fat consumption (287–292). The saturated fat content of the brain of MS victims was reported to be higher than that of controls (293). These considerations led Swank to evaluate restriction of dietary saturated fat as a therapy for MS (289,294,295). Patients were asked to restrict animal fat consumption to no more than 20 g daily, and cocount and palm oils were banned; polyunsaturate vegetable oils were allowed ad libitum, and a daily teaspoon of cod liver oil was encouraged. Swank has published detailed evaluations of 150 patients enrolled during the years 1949– 1954 and followed up through 1989; daily fat intake was monitored with food diaries. As compared to historical controls, the patients on this regimen had less frequent relapses, a slower decline in functional status, and a much lower death rate related to MS. In patients judged to be highly compliant with the fat restriction, the clinical course was decidedly better than in those who were not. Evaluating the neurological grade (NG) of patients on a scale range from 0 (normal) to 5 (confined to bed), the average NG of compliant patients increased only moderately from 2.2 to 2.9 over more than three decades of follow-up. Twenty percent of the patients in the high compliance groups died of causes related to MS, as opposed to 62% in those who were less compliant. Clinical course was also considerably better in patients who initiated therapy within one to two years of initial symptoms. Most remarkably, in the eleven patients who had symptomatic MS for less than two years prior to therapy and who were compliant with this diet, average NG actually improved non-significantly during the long follow-up (NG=1.0 at baseline, 0.9 at follow-up). Although MS fails to progress in about 4% of untreated cases, it was statistically extremely unlikely that this phenomenon could account for Swank's observation.

That a high polyunsaturate/saturate (P/S) ratio of diet or tissue lipids is the key to prevention and therapy of MS is suggested by several other controlled studies showing an improved clinical course in MS patients supplemented with polyunsaturate-rich oils, as summarized in a meta-analysis by Dworkin et al (296). Not unlikely, P/S ratio has an impact on myelin structure such that a high polyunsaturate content somehow tends to prevent the demyelinating process. If this is indeed the case, then a strict vegan diet that also excludes coconut and tropical oils (but perhaps allows saturate-free fish oil concentrates) would be ideal for the prevention and treatment of MS. Such a regimen would have an extremely high P/S ratio; since humans synthesize very little fat de novo, tissue lipids would be expected to reflect this high P/S ratio. Since myelin forms during early development – and there is some evidence that early nutrition is a determinant of MS risk (291) – optimal protection might be achieved if mothers ate vegan diets throughout pregnancy and lactation. A strict vegan diet may be a more practical treatment for MS than Swank's regimen, as it is inherently easier to control the type of food one eats than the quantity.

These considerations bring up the issue of veganism during pregnancy. To assess the safety of such a practice, Carter and colleagues monitored the course of 775 pregnancies in a large vegan community ('the Farm') in Tennessee (54). Pregnant women at the Farm receive good prenatal care, have ample, varied and nutritious food to eat, are encouraged to consume a cup of soy milk

daily, and receive supplements of B_{12} and standard prenatal vitamins with calcium. The researchers found no evidence that veganism, under these conditions, was harmful to the mother or fetus. Most strikingly, only one of the 775 pregnancies met the clinical criteria for pre-eclampsia (PE). If this extremely low risk of PE in well-nourished vegans proves to be a replicable finding, it may be functionally related to the hypotensive effect of veganism in hypertensives, and may again be traceable to the very high P/S ratio of strict vegan diets. While risk of PE is not known to be notably low in low-fat Third World cultures, this may be attributable to poverty, associated with caloric deprivation and malnutrition in some mothers.

The other major metabolic complication of pregnancy is gestational diabetes. This disorder may be a facet of the insulin resistance syndrome, and is associated with high subsequent risk for type 2 diabetes (297). Since vegan women tend to be relatively lean and can be expected to have good insulin sensitivity, it seems likely that their risk for gestational diabetes will be low. Carter et al. do not comment on this complication in their survey of Farm pregnancies. In a small crossover study enrolling women with gestational diabetes, Nolan found that glucose tolerance was improved and urine glucose reduced after four days of a low-fat (10%), fiber-rich diet (298).

HEMORRHAGIC STROKE AS A POTENTIAL RISK

Despite the remarkably versatile protection afforded by a vegan diet, such a diet may not be an unalloyed blessing. Asian and Hawaiian epidemiology indicates that low serum cholesterol and low intakes of animal protein and fat are risk factors for hemorrhagic stroke (299–302). (Age-adjusted incidence appears to be increased, so this is not merely a trivial consequence of preventing other pathologies.) Presumably, increased fragility of small cerebral arteries may mediate this effect (302,303). It is thus interesting to note that IGF-I promotes arterial elastogenesis, as documented by in vitro studies with aortic vascular muscle cells (304,305). If IGF-I likewise promotes elastin formation in small cerebral arteries (and perhaps works in additional ways to keep arteries strong and resilient, as by preventing medial smooth muscle apoptosis) (245), the apparent adverse impact of vegan diets on hemorrhagic stroke risk is readily explained.

Nutritional countermeasures which promote vascular strength may therefore be of particular value to vegans. Dietary silicon may be elastogenic in rabbit arteries (306). Adequate dietary copper is required for elastin cross-linking (307). The bioflavonoid rutin has been reported to strengthen fragile capillaries; in the extensive clinical experience of Dr John Griffith, rutin treatment of hypertensives with fragile capillaries was associated with a substantial decrease in subsequent stroke risk (308). (A double-blind replication of this finding would be of great value.) High intakes of green tea polyphenols (like rutin, these are bioflavonoids) appear to reduce stroke risk in Japan, and increase the survival of spontaneously hypertensive rats (309,310). The impact of glucosamine on vascular strength also merits evaluation, in light of recent anecdotal observations that varicose veins often shrink during glucosamine supplementation. High dietary potsssium also reduces stroke incidence in stroke-prone spontaneously hypertensive rats, independent of any impact on blood pressure (311,312); increased potassiun intakes are also associated with reduced stroke risk epidemiologically (313). Fortunately, diets high in fruits and vegetables will be inherently rich in potassium.

Hypertension greatly increases risk for hemorrhagic stroke, so control of hypertension may be of special importance in aging vegans. In Japan, subjects with relatively low blood pressure (e.g. systolic pressure below 120) have a low risk for hemorrhagic stroke, even when serum cholesterol is also quite low (299). It therefore may be prudent for aging vegans to strive for blood pressure in the low-normal range. For many individuals, this may entail moderation in salt intake, increased potassium ingestion, exercise, as well as the use of various nutritional supplements.

There are other circumstances in which low-normal IGF-I activity may be a disadvantage. IGF-I plays a role in the mitotic activity required for wound healing and response to infection (314–319). Consumption of animal protein and ample calories following trauma or infarction, or during chronic infection, can be recommended to promote the growth factor activity required for prompt wound healing and the vigorous expansion of pathogen-specific lymphocyte clones. Nutritional supplements which aid lymphocyte function, as well as appropriate vaccinations, may be advisable for vegans.

A DIGRESSION ON DIETARY FAT

An important question which remains to be addressed is this: within the context of a strictly vegan diet, how important is it to restrict or moderate the intake of foods and oils high in unsaturated fat (e.g. avocados, olives, certain soy products, nuts and nut butters, seeds, oils, margarines, etc.)? In rural China, total fat consumption represents about 15% of calories (55), but American vegans tend to consume about twice this much fat (46). The dramatically favorable effects of the Pritikin and Ornish regimens on cardiovascular disease and diabetes are achieved with diets that not only exclude all animal fat, but also proscribe fatty vegan foods.

Presumably, a high intake of fat of any type will increase risk for obesity. In rodent studies, high intakes of

all fats other than omega-3s promote insulin resistance (79) (saturates are the most active in this regard) and once a certain adequate intake of linoleic acid is assured, also tend to promote cancer (320). While the impact of linoleic acid consumption on cancer risk assessed epidemiologically appears equivocal (186), and a favorable impact on cardiovascular risk is sometimes suggested (321), the experience of Israel is cautionary. Israel's Jewish population is distinguished by an exceptionally high absolute intake of polyunsaturates and a high dietary P/S ratio, owing to liberal use of polyunsaturate-rich cooking oils and margarines. It is also characterized by a high prevalence (relative to other Western nations) of diseases linked to insulin resistance – obesity, diabetes, hypertension, cardiovascular disease, and various cancers (322). This suggests that chronic ingestion of high amounts of linoleic acid may promote obesity, insulin resistance, and the diseases associated with them. Also of concern is the fact that LDL and tissue membranes enriched in linoleic acid are more susceptible to oxidative damage. The former conventional wisdom of endorsing heavy use of polyunsaturate-rich oils and margarines therefore appears very questionable.

Recent epidemiological and clinical findings regarding monounsaturates are much more favorable. Epidemiological correlations between monounsaturate intake and disease risk can be skewed by the fact that fatty animal products are often a major source of dietary oleic acid. However, since olive oil is 80% oleic acid and is not notably high in other nutrients, epidemiological associations of olive oil ingestion with disease risk can offer valuable insight into the impact of oleic acid per se on health (with the possible caveat that olive oil use may often be a marker for decreased use of more unsaturated oils). Recent case-control studies report an inverse association between olive oil consumption and breast cancer risk, and limited evidence suggests that olive oil might also be protective in regard to endometrial, gastric, and pancreatic cancers (323–330). The reduced cardiovascular risk associated with an olive oil-rich Mediterranean diet is now well known, and case-control studies in Mediterranean populations suggest that olive oil may indeed be protective in this regard (331,332). The epidemiology of Israel is once again instructive: the non-Jewish citizens of Israel consume a diet rich in olive oil; their age-adjusted mortality from Western diseases is 50–70% lower than that of their Jewish compatriots (322).

Increasing the olive oil content of Western diets has the same favorable impact on serum lipid profile as does an increase in linoleic acid, but yields LDL that is less susceptible to oxidative damage (333–336); achieving a high proportion of oleic acid in tissue membranes and lipoproteins my be viewed as an antioxidant strategy. Within the context of the so-called 'high-carbohydrate' diet recommended by the American Diabetic Association (which modestly restricts animal fat), isocaloric substitution of monounsaturates for carbohydrate tends to have a slightly favorable impact on glycemic control, insulin sensitivity, and serum lipids in type 2 diabetics (336–344). Little information is available regarding the impact of dietary oleic acid on insulin sensitivity in non-diabetics. However, a recant study has correlated the fatty acid profile of plasma phospholipids with fasting insulin in 4304 middle-aged non-diabetics; percentage saturated fat correlated strongly with insulin levels, whereas a more modest negative association was noted between percentage oleic acid and insulin (345). A previous smaller study likewise found a strong association between percentage of saturated fat in serum phospholipids, insulinemia, and decreased metabolic clearance rate of glucose during euglycemic clamps (346). In overview, the picture which emerges is that saturated fat has by far the most negative impact on insulin sensitivity; high absolute intakes of linoleic acid may also be harmful in this regard, but oleic acid appears to be relatively innocuous, at least as a component of Western omnivore diets. (Evidently, fatty animal products, over-rich in saturated fats and essential amino acids, are 'tailor-made' to promote high IGF-I activity.)

These observations mesh well with the findings of the Seven Countries Study, a 15-year prospective cohort study that enrolled over 11 000 middle-aged men: 'All death rates were negatively related to the ratio of monounsaturated to saturated fatty acids. Inclusion of that ratio with age, blood pressure, serum cholesterol, and smoking habits as independent variables accounted for 85% of variance in rates of deaths from all causes, 96% coronary heart disease, 55% cancer, and 66% stroke… All-cause and coronary heart disease rates were low in cohorts with olive oil as the main fat (342)'.

Perhaps the true protective factor is not a high dietary intake of oleic acid per se, but rather a high fractional content of oleic acid in adipose stores, tissue membranes, and LDL. The insulin resistance and the cancer promotional impact of obesity and fatty diets are probably mediated by increased exposure of tissues to free fatty acids, giving rise to lipid mediators (such as diacylglycerol) that have adverse physiological effects (348–358); the activity of these mediators is likely to have marked stereospecificity. (The common notion that increased fat *oxidation* mediates the insulin resistance of Western society has been discredited (348,359).) In light of epidemiological and clinical evidence, it appears likely that mediators synthesized from saturated fatty acids are particularly aggressive in impairing insulin sensitivity and promoting cancer, whereas oleic acid gives rise to less active mediators and thus effectively act as a competitive

antagonist of saturated fat in this regard. Linoleic acid may have an intermediate impact. Thus, when oleic acid contributes a high fraction of the total free fatty acids to which tissues are exposed, the pathogenic impact of fat exposure is greatly lessened. Additionally, membranes and LDL particles enriched in oleic acid relative to polyunsaturates will be less prone to oxidative damage, thus lessening the pathogenic impact of lipid peroxidation.

A functional antagonism between oleic acid and saturated fats rationalizes the prognostic significance of the monounsaturate/saturate ratio in the Seven Countries Study, and confirms the wisdom of adding olive oil to Western diets that contain significant amounts of animal fat. However, within the context of very-low-fat vegan regimens exceptionally low in saturated fat such as those practiced by many rural Chinese and advocated by Pritikin and Ornish, what would be the impact of allowing a more liberal intake of olives, olive oil, and of nuts with a comparable predominance of oleic acid (almonds, pistachios, macadamias)? If these foods were used in moderation, such that total dietary fat did not exceed 20%, such a modification would not greatly increase risk for obesity or expose tissues to undesirably high free fatty acid levels, yet might markedly increase the fraction of oleic acid relative to other fatty acids in the body's tissue. Indeed, an advantage of a low-fat vegan diet is that a comparatively modest intake of oleic acid (equivalent to a tablespoon of olive oil daily) could be expected to have a notable impact on tissue lipid composition. Evidently, controlled studies are needed to assess the impact of adding extra oleic acid to a very-low-fat vegan diet. In the interim, lean vegans who choose to incroporate moderate amounts of monounsaturate-rich foods and oils in their diets probably won't hurt themselves, and may well do themselves some good.

One potentially serious drawback of a strict vegan diet is that it cannot supply the long-chain omega-3s (EPA/DHA) found in cold-water marine fish which, owing primarily to modulatory effects on eicosanoid metabolism, can inhibit cancer promotion and progression, and have favorable effects on cardiovascular risk, inflammation, brain myelin, and bone density (360). Unfortunately, ample intakes of alpha-linolenic acid (as from flaxseed oil) have a comparatively modest influence on tissue levels of EPA/DHA (361), and though they nonetheless may provide some physiological benefits (362,363), they entail ingestion of large amounts of readily oxidized oil. Fish oil concentrates, free of saturated fatty acid and cholesterol, and highly enriched in EPA/DHA, are now commercially available in supplement form; in the context of a low-fat vegan diet, four to six grams daily of such preparations might be sufficient to yield tissue levels of EPA/DHA comparable to those of Eskimos. For the sake of those who are vegan on ethical grounds, unicellular sources of these essential fatty acids are being developed, and hopefully will prove commercially feasible. (Whether or not one objects to the killing of fish, it can't be denied that the overharvesting of our oceans is an ecological tragedy in the making.)

PRACTICAL IMPLICATIONS

No diet or regimen can be expected to be free of *any* drawback. The fact that a low-fat, fiber-rich vegan diet is likely to reduce risk for most types of cancer, ischemic heart disease and its complications, obesity, diabetes, hypertension, osteoporosis, multiple sclerosis, gallstones, renal stones, appendicitis, diverticulitis, hiatal hernia, varicose veins, hemorrhoids, and possibly the chief metabolic complications of pregnancy – disorders which collectively are responsible for the majority of the deaths and hospitalizations in Western society – should be sufficient to recommend it. Those who are willing to make less striking changes in their lifestyle can be encouraged to reduce their consumption of animal products.

A vegan diet, aside from its deficit of vitamin B_{12} activity (readily compensated by supplementation), is typically more micronutrient-dense (per calorie) than the diets favored by omnivores (364), higher in protective phytochemicals and fiber, and usually somewhat lower in fat – especially saturated fat (46). Fears that a vegan diet may be inadequate in protein quality or quantity are unfounded. Advocates of veganism often cite the remarkable fact that human breast milk – presumably 'designed' to promote anabolism during a time of rapid growth – has a protein content that corresponds to only 5% of total calories (365). With the exception of fruit or refined sugar or oils, the protein content of vegan foods is considerably higher than this.

An important proviso is that, in areas of the world where soil selenium is low (such as New Zealand and large parts of Europe), a locally grown vegan diet may be a notably poor source of selenium (366). (Omnivores benefit from the efforts of animals to retain dietary selenium.) Since good selenium status may be particularly protective with regard to both cardiovascular and cancer risk (367,368), this poor selenium nutrition could have a countervailing negative impact on the health protection afforded by a vegan diet. Vegans would be well advised to include selenium in their supplementation program.

Clearly, vegan protein is not the only way to achieve a favorable balance of glucagon/insulin activity. Measures which promote the insulin sensitivity of skeletal muscle – and thus down-regulate insulin secretion – should have comparable benefit. A low-fat, fiber-rich diet, coupled

with regular exercise and avoidance of visceral obesity, should be useful in this regard. Carbohydrate foods of low glycemic index induce lower postprandial insulin excursions, and thereby prevent a down-regulation of insulin receptors that is inimical to insulin sensitivity (369–372); thus, whole foods containing their native fiber content and cell wall structure are preferable to highly refined flours and juices – though most fortunately, traditional semolina pasta has a relatively low glycemic index. (It may be noted that many of the recent studies that compare 'high carbohydrate' diets unfavorably with oleic acid-rich diets in diabetics, make no effort to use low glycemic index foods, and quite inappropriately insure that the two diets have equal fiber content.) Frequent feeding of small meals tends to improve insulin sensitivity and decrease LDL cholesterol (372), but also obviously entails a larger number of postprandial insulin surges that suppress IGFBP-1; how such a strategy might influence 24-hour IGF-I activity requires experimental evaluation. Chromium picolinate, recently reported to improve insulin sensitivity in type 2 diabetics and obese non-diabetics (373,374) may likewise complement the benefits of vegan protein, provided that it up-regulates IGFBP-1 (which presumably is contingent on not markedly sensitizing hepatocytes to insulin). Oral estrogen or tamoxifen can potentiate the down-regulation of IGF-I activity achievable with these measures. This perspective rationalizes a number of seemingly disparate epidemiological findings pertaining to risk for cardiovascular disease and cancer – most notably breast and colon cancer.

Human nature being what it is, many omnivores will be unwilling to relinquish dairy products, eggs, and flesh foods. Therefore, an alternate strategy is needed if the health benefits of increased hepatic glucagon activity are to be realized on a broad scale. In animal models of casein-induced hypercholesterolemia, enrichment of these diets with certain non-essential amino acids that are especially potent glucagon secretogogues – arginine, glycine, and alanine have been commonly used – is reported to lower serum cholesterol (375,376). By analogy, I propose that daily administration of multi-gram doses of such non-essential amino acids in palatable beverages or snack bars could be expected to improve the serum lipid profiles and decrease the cancer risk of omnivorous humans. In regard to reduction of elevated serum lipids, this hypothesis is readily testable. Such a strategy, however, would clearly be less protective than an optimal vegan diet.

Even if the ideas presented here regarding the impact of vegan protein on glucagon/insulin ratio, hepatic cAMP levels, and IGF-I activity prove to be substantially flawed, epidemiology as well as clinical experience make it clear that relatively unrefined predominantly vegan diets can provide remarkably versatile and profound health protection. From this perspective current official health recommendations to 'reduce' dietary fat to 30% fall wide of the mark. Campbell ruefully notes that the 30% figure was chosen because 'a dietary fat level of 30% of energy could be fairly easily achieved without significantly altering traditional dietary patterns, whereas increasingly lower levels of fat intake would require increasingly greater exchange of foods of animal origin with foods of plant origin' – the presumption being that most people would find such changes unduly irksome.

While it is certainly true that many people would be resistant to fundamental dietary changes, it is equally true that millions of intelligent people motivated to preserve their health are now taking half-way measures that my provide only modest benefit – choosing leaner cuts of meat, using reduced-fat dairy products, etc. – based on the recommendations of scientific and governmental authorities that they respect. Most of these people have neither the time nor the training to evaluate the biomedical literature themselves. Don't they deserve honest, forthright advice when their lives are at stake? Those who wish to ignore this advice, or implement it only partially, are at liberty to do so.

Admonitions to modestly reduce dietary fat are usually accompanied by earnest pleas for more fruit and vegetable consumption. The best way to achieve really substantial, meaningful increases in fruit and vegetable intakes is to convince people to minimize their intake of animal products; fruits and vegetables can then be used to help fill the resulting void. Otherwise, recommendations to increase fruit and vegetable intake are likely to meet with only token compliance.

The concept that the high intake of essential amino acids characteristic of Western diets, by colluding with high fat intake to induce excessive IGF-I activity, constitutes a grave risk factor for many deadly diseases, is not likely to be greeted with credence or warm approbation in many quarters. (Indeed, criticizing *essential* amino acids almost seems to be perverse blasphemy on its face.) Dairy, egg, and livestock interests fund a large part of the world's nutrition research, and devote a great deal of advertising revenue to reinforcing the fallacious notion that high protein intakes are desirable for health (365). Many if not most consumers accept this idea as gospel, and moreover are quite fond of the animal-derived foods in their diets. Yes, ample intakes of animal protein will help our children to grow and mature rapidly, and achieve excellence in sports requiring size and bulk. However, few seem to realize that the growth factor activity which makes this possible is the harbinger of occluded arteries and innumerable premature cancer deaths. It is undoubtedly no coincidence that massive American football players have a distressingly short life-expectancy; they would be well advised to turn vegan the day that they retire. Perhaps it

will come as some consolation that a number of the world's greatest *endurance* athletes are vegetarians.

Apparently, it has long been common knowledge among serious bodybuilders that a vegan diet, even if very copious in quantity, cannot build maximum muscle bulk. This accords well with the thesis that, as compared with omnivore diets of comparable caloric and protein content, vegan diets yield lesser IGF-I activity. Yet it appears that medical scientists have been slow to grasp this point. As of this writing, the entire biomedical literature accessible on Medline contains only one publication jointly mentioning 'vegetarian' and 'IGF-I' (*76*), and none at all co-citing 'vegan' and 'IGF-I'. This anomalous situation should not be too surprising. Bodybuilders have known for decades that a very-low-fat diet eaten ad libitum is inherently useful for minimizing body fat; medical scientists didn't begin to realize this until the mid 1980s.

Recently, injections of growth hormone have become popular as a technique for restoring more youthful quantities of lean mass and boosting immune function in older people. Since these effects are mediated primarily by an increase in IGF-I production, the potential impact of injectible growth hormone on hyperplastic disorders such as cancer and atherosclerosis should be a matter of concern. Another currently popular 'anti-aging' strategy is the restoration of youthful levels of DHEA with oral replacement doses of this hormone. In a recent study in which daily oral doses of 50 mg of DHEA were administered to subjects aged 40–70 for six months, fasting serum IGF-I levels were up-regulated and IGFBP-1 levels were down-regulated such that the ratio of IGF-I/IGFBP-1 increased by about 53% (*377*); in a subsequent study, which documented broad immune stimulant effects for DHEA, this ratio increased by 32% (*378*). Thus, DHEA supplementation may also carry risks. Youthful growth factor activity may be cosmetically appealing, but its impact on elderly people who have had a lifetime to accumulate initiated pre-neoplastic cells may be hazardous. Except when growth factor activity is pathologically subnormal, it may be wise for us to let nature take its course, and strive for endurance and wiry strength as we age rather than muscle mass. And while promoting youthfully efficient immune capacity is a worthy goal, we should seek ways to achieve this that do not depend on up-regulation of a universal cancer promoter. (It is also relevant to note that the role of IGF-I as a growth factor for leukocytes can cut both ways – the lower incidence of leukemias in vegan rural Chinese has been noted, and it has recently been suggested that high IGF-I activity may mediate the epidemiological association of high birth weight with increased risk for childhood leukemia (*379*).)

It is often stated that the disorders of Western civilization are diseases of 'over-nutrition'. By and large this view is simply untrue. It *is* true that chronic gorging will strongly suppress IGFBP-1 and moderately up-regulate the synthesis of IGF-I, thereby promoting excess growth factor activity; caloric restriction can have the converse effect. But the large majority of overweight Western omnivores are *not* pathological gourmands – nor are most lean vegans subject to starvation or dedicated to self-abnegation. The fault in Western society lies in the *nature* of the food that is ingested, not in the quantity. Veteran Western dieters can tell you that the body can retain excess fat stores in the face of caloric deprivation; conversely, the experience of rural China shows that relatively high caloric intake need not translate into obesity. When people make a commitment to vegan eating, their weight and their health tend to take care of themselves. The 'over-nutrition' bromide is offensive because it is often used to justify the philistine and impractical suggestion that we need not change the nature of our diet, but rather consume it in 'more moderation'.

In regard to the practicality of a vegan diet, it may be germane to cite my own experiences. During the course of researching and writing this article, my findings impelled me to become a vegan. Having attempted to follow a low-fat diet for years, Asian foods have long been the staple of my diet. In the Asian restaurants I frequent, I now ask for vegetarian alternatives. In place of chicken, I now receive steamed vegetables and a little tofu – I don't miss the chicken. I long ago banished eggs and fatty dairy products from my diet; giving up the occasional non-fat yogurt hasn't been hard when so many delightful varieties of fruit are available. For lunch, I favor soup and salad restaurants – massive low-fat salads, vegetable soups, pasta, bread, and fruit leave me stuffed and quite satisfied. At home I often enjoy tasty soy burgers, filling bean soups, pasta, whole-grain breads, corn, fruit, beer, and various low-fat snacks, as well as take-out Asian food. In short, I am amply fed and enjoy my meals; my transition to veganism has been virtually effortless. (This should be viewed in the context of the fact that I am a bachelor inept in the culinary arts – one can only imagine the bounty if a real cook were in the house!) I offer my own experience to illustrate the point that, for people who have already adapted to low-fat eating, becoming vegan need not be a daunting ascetic challenge; subtracting animal flesh, dairy products, and eggs leaves a tremendous range of appetizing, satisfying foods. For those who wish to do their own cooking, books providing vegan or predominantly vegan recipes are of course available; in particular, popular books by Ornish and Robbins offer such recipes (*365*,*380*). (I perhaps should point out that I continue to use a supplemental fish oil concentrate of the type described above.)

As for the people whose diets are still centered on large slabs of animal flesh, bacon and eggs, cheese and other

dairy products, fried foods, etc. – these people either haven't been paying attention over the last decades, or their health is not a chief priority (at least until their first heart attack or cancer surgery). If people choose to 'live to eat' rather than 'eat to live', we should respect that – as long as the possible consequences are understood. For people eating typical 'Western' diets who *do* wish to become vegans, a gradual or partial transition may be more practical and less traumatic than a 'cold turkey' approach. And there is no reason to believe that veganism must be an 'all or nothing' commitment – cutting back on animal products such that vegan proteins become the predominant source of dietary protein, should be sufficient to achieve substantial health benefit.

I suspect that the simple injunction, 'Do not eat animal products' has the potential to do more for world health than all of the abstruse wisdom in all of the world's medical libraries. Not the least merit of this advice is that it is very easy to understand. Furthermore, encouraging the ethos that we should not harm our fellow creatures save in self-defense (construing legitimate medical research as a form of self-defense) would almost certainly have a favorable impact on interactions in human society. And many commentators have noted that a decline in the livestock industry would enable Third World nations to devote a higher proportion of their arable land to feeding their own people rather than to feeding livestock.

A low-fat, fiber-rich vegan diet, regular exercise, health-protective supplementation, clean drinking water, vaccination and better antibiotics, worthwhile employment and supportive relationships – these will be the fundamental bases of health in mankind's saner future.

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