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Undernutrition and chronic disease: cancer

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EARLY HISTORY: ANIMAL STUDIES

About 60 years ago McCay *et al.* (1935, 1939) showed that limiting the food intake of rats increased their life span and reduced symptoms of degenerative disease. Almost 30 years earlier Moreschi (1909) found that growth of transplanted tumours was severely inhibited when the mice bearing those tumours were underfed. A few years later Rous (1914) reported that neither spontaneous nor transplanted tumours grew well in rodents whose energy intake was restricted. There was considerable interest in the effects of dietary restriction on tumour growth in the second and third decades of this century. The early findings have been reviewed by Kritchevsky & Klurfeld (1986).

In the early 1940s two laboratories in the United States, those of Tannenbaum at the Michael Reese Hospital in Chicago and Baumann at the University of Wisconsin, began to investigate effects of diet on experimental tumourigenesis. Initially Tannenbaum (1940) found that underfeeding reduced the incidence of both spontaneous and chemically-induced tumours in mice. In underfeeding the same diet is fed to all the animals, some being allowed to feed freely and some being fed on a lower level of the same diet. The underfeeding is either designed to maintain the test animals at a predetermined weight or they are fed a proportion of the intake of the control group. Under conditions of underfeeding experiments, if the controls are ingesting the limiting amount of a necessary micronutrient the underfed group may become deficient in this nutrient with deleterious metabolic consequences. In the energy-restriction mode, the diets are designed to provide equal levels of vitamins and minerals and restriction is effected at the expense of a macronutrient. After his initial effort Tannenbaum (1942) formulated a diet of known energy content. Energy-restriction studies using this diet showed that incidence of spontaneous mammary or lung tumours or chemically-induced skin tumours was lowered significantly in several strains of mice (Tannenbaum, 1942). Incidence of spontaneous hepatomas was also affected by energy restriction (Tannenbaum & Silverstone, 1949).

Tannenbaum (1945) also showed that at the same level of energy intake a diet high in fat led to a higher incidence of mammary tumours than did one low in fat. Boutwell *et al.* (1949*a*) confirmed this observation in mice bearing chemically-induced skin tumours. Energy restriction was most effective during the progression phase of tumourigenesis; restriction during initiation followed by *ad lib.* feeding yielded results similar to those seen when the mice were fed freely throughout the experiment (Tannenbaum, 1944).

Lavik & Baumann (1943) studied dietary effects in mice treated with methylcholanthracene to produce skin tumours. The mice were fed on diets low in energy and low in fat (incidence 0%); low in energy and high in fat (incidence 28%); high in energy

but low in fat (incidence 54%); and high in both energy and fat (incidence 66%). Albanes (1987*a*) reviewed eighty-two studies involving energy restriction and tumourigenesis in mice and a low-fat, high-energy regimen (eighteen studies) was 56% more carcinogenic than a high-fat, low energy regimen (nineteen studies). Interest in energy restriction and cancer waned after 1950 being eclipsed by studies of the co-carcinogenic effects of dietary fat but was revived in the 1980s.

RECENT ANIMAL STUDIES

Kritchevsky *et al.* (1984) observed that 40% energy restriction completely inhibited the growth of 7,12-dimethyl-1,2-benz(a)anthracene (DMBA)-induced mammary tumours when the dietary fat was coconut oil (plus enough maize oil for essential fatty acid repletion). The energy-restricted rats were fed twice as much fat as the *ad lib.*-fed controls. Boissonneault *et al.* (1986) administered DMBA to female rats fed on a high-fat diet (300 g maize oil/kg), a low-fat diet (50 g maize oil/kg) or the high-fat diet restricted by 18·5%. Tumour incidence on the three diets was 73, 43 and 7% respectively. The daily energy intakes of the three groups were 170, 178 and 146 kJ/d. Klurfeld *et al.* (1987) showed that 40% energy restriction also inhibited 1,2-dimethylhydrazine (DMH)-induced tumours in rats. Rats fed on saturated fat exhibited a lower incidence of tumours than rats fed on an unsaturated fat confirming an earlier observation of Carroll & Khor (1971).

In a study designed to determine the lowest degree of energy restriction required to inhibit DMBA-induced tumourigenesis Klurfeld *et al.* (1989*a*) restricted energy by 10, 20, 30 or 40%. All rats, including the controls, ingested 50 g fat/kg diet daily. At 10% restriction tumour incidence was the same as that seen in the controls (60%) but tumour multiplicity (tumours/tumour-bearing rat) was reduced by 32% and tumour burden (weight of all tumours/rat) was reduced by 47%. Restriction of energy by 20% reduced tumour incidence to 40% but tumour multiplicity and tumour burden were similar to those seen in rats whose energy was restricted by 10%. At 30% energy restriction tumour incidence, multiplicity and burden (compared with the controls) were reduced by 42, 72 and 91% respectively. Only one of the twenty rats whose energy was restricted by 40% exhibited a tumour. Plasma insulin levels in the rats subjected to 30 or 40% restriction were significantly lower than those observed in the other groups.

To determine whether a diet high in fat (oil) could override energy restriction, groups of female rats were given DMBA and fed on either 50, 150, or 200 g fat/kg *ad lib.* or 200 or 267 g fat/kg with a 25% energy restriction (Klurfeld *et al.* 1989*b*). The two energy-restricted groups ingested exactly the same amount of fat daily as did the *ad lib.*-fed groups fed on 150 or 200 g fat/kg. In the *ad lib.*-fed groups tumour incidence in rats fed on 50, 150 or 200 g fat/kg was 65, 85 and 80% respectively. Tumour multiplicity was 1·9, 3·0 and 4·1 and tumour burden 4·2, 6·6 and 11·8 g. Tumour incidence in the groups whose energy intake was restricted by 25% was 60% in rats fed on 200 g maize oil/kg and 30% in those fed on 267 g fat/kg. Tumour multiplicity in the two groups was 1·9 and 1·5 and tumour burden 1·5 and 2·3 g. Plasma insulin levels in the two restricted groups were significantly lower than those in the control groups. Welsch *et al.* (1990) fed DMBA-treated rats on 50 or 200 g fat/kg diets administered *ad lib.* or at 12% energy restriction. At 50 g fat/kg energy restriction reduced tumour yield by 29% and at 200 g fat/kg by 37%. Rats fed on 200 g fat/kg *ad lib.* exhibited 56% more tumours than those fed on 50 g fat/kg; at 12% energy restriction the difference was 38%. The incidence of colon

tumours induced by an indirect-acting carcinogen, methylazoxymethanol, is inhibited by energy restriction but tumours due to the action of N-methylnitrosourea, a direct-acting carcinogen are unaffected (Pollard & Luckert, 1985). This dichotomy merits further investigation.

The time in life at which energy restriction must be instituted to be effective was investigated by Tannenbaum (1947). The incidence of spontaneous breast tumours observed in 20-month-old DBA mice was zero when energy restriction was begun at 2 months. When restriction was begun at 5 or 9 months of age tumour incidence was reduced by 95 and 80% respectively. Weindruch & Walford (1982) restricted energy intake of cancer-prone mice by 44% when they were 1 year old. Incidence of hepatomas was reduced by 7%, lymphomas by 34%, and lung tumours by 50%. Life span of the mice bearing tumours was increased by 12% and that of the tumour-free mice was increased by 23%. Kritchevsky *et al.* (1989) tested effects of intermittent energy restriction on DMBA-induced mammary tumours and found a relationship between increasing feed efficiency and increasing tumour incidence. Ross & Bras (1973) and Ross *et al.* (1982) found that incidence of spontaneous tumours was increased by high feed efficiency and rapid growth. Ross & Bras (1971) found that lifelong dietary energy restriction (by 60%) of rats increased life span by about 40% and decreased incidence of spontaneous tumours by 90%. When rats were restricted for 7 weeks after weaning then returned to an *ad lib.* regimen life expectancy was not increased but incidence of spontaneous tumours fell by almost 40%.

RELEVANCE TO MAN

Hoffman (1913) urged the formation of a society to study cancer incidence in the United States and suggested that 'erroneous diet' was probably a factor in the aetiology of cancer. Hoffman (1927) later proposed that energy excess was an important factor in the cancer development. Berg (1975) also proposed that cancers prevalent in the United States might be related to high energy intake. Lew & Garfinkel (1979) and Garfinkel (1985) have shown relationships between overweight and cancer mortality in a cohort of over one million people.

The epidemiology of breast cancer suggests that early onset of menarche increases risk of breast cancer in women (Staszewski, 1971). Tall stature may also be a risk factor (DeWaard, 1975). Both age at onset of menarche and stature are influenced by nutritional status (Apter & Vihko, 1983). Swanson *et al.* (1988) assessed data from the first US National Health and Nutrition Examination Survey (NHANES I) and found that stature and frame size, but not body weight, were associated with increased risk of breast cancer in women. A prospective study of 23 831 Norwegian women (Vatten & Kvinnsland, 1990) found that women taller than 1·67 m displayed a greater risk for breast cancer than those shorter than 1·59 m. The association appeared to be confined to women whose prepubertal growth occurred between 1940 and 1945. Kritchevsky (1990) summarized international data relating to body weight and risk of breast cancer in women. In all, eleven studies were examined and nine of them found a positive relationship between breast cancer risk and body weight or height or body mass index, BMI (weight/height^2).

Albanes *et al.* (1988) correlated adult stature and cancer risk in men and women using data from NHANES I. They concluded that short stature was associated with reduced

cancer risk, especially in men. There is a strong genetic component to their findings but nutrition may also play a role. Albanes & Taylor (1990) examined the differences in height and weight with cancer incidence on an international scale. They found highly significant correlations between tumours at all sites and height for both women and men. Lindsted *et al.* (1991) found a significant negative trend between diminishing BMI and cancer risk in Seventh Day Adventist men. Albanes (1987*b*) reviewed the international data relating to energy intake, body weight and cancer. Increased body weight, high relative body weight or high energy intake were associated with increased risk of cancers of the breast, colon, rectum, prostate, endometrium, kidney, cervix, ovary, thyroid and gallbladder. There was an inverse correlation between cancers of the bladder, stomach and lung. Total energy intake has been shown to be related significantly to the incidence of colon (Jain *et al.* 1980; Lyon *et al.* 1987) or gastric (Graham *et al.* 1990) cancer.

EXERCISE

Increasing energy flux may be as effective as reducing energy intake. Rusch & Kline (1944) subjected mice bearing a transplanted tumour to enforced exercise (cage rotation) and tumour weight was reduced by about 30%. Vigorous treadmill exercise reduced incidence of DMH-induced colon tumours in rats by about 50%. The incidence of colon tumours in *ad lib.*-fed, exercised rats was about the same as that observed in sedentary rats subjected to 25% energy restriction (Klurfeld *et al.* 1988). Cohen *et al.* (1988) reported that voluntary exercise (activity cage) reduced mammary tumours in rats and voluntary exercise has also been shown to inhibit pancreatic cancer (Roebuck *et al.* 1990). Exercise has also been shown to inhibit growth of Morris hepatoma 7777 in rats (Baracos, 1989). On the other hand, Thompson *et al.* (1988, 1989) found that treadmill exercise actually enhanced the growth of DMBA-induced mammary tumours in rats. Their exercised rats ate more food and weighed more than the sedentary controls. Vigorous occupational physical activity has been shown to reduce the risk of colon cancer in men (Garabrant *et al.* 1984; Vena *et al.* 1985; Gerhardsson *et al.* 1988). In this regard it is interesting to note that over 70 years ago Sivertsen & Dahlstrom (1921) showed a relationship between energy expenditure and cancer risk; however, the group with lowest occupational activity and highest cancer death rate lived 10–15 years longer. Risk of cancer may also be reduced by regular exercise (Paffenbarger *et al.* 1987).

MECHANISMS

The mechanisms by which energy restriction affects carcinogenesis are moot. One probable reason for this is that the effects of energy restriction have not been regarded seriously. Other, more immediate effects on carcinogenesis have been studied in a reflection of the one disease, one cause, one cure paradigm.

Free radicals derived from oxygen have been implicated as possible factors in tumourigenesis and there has been much activity in the cancer field related to anticancer effects of antioxidant vitamins such as A, E and C as well as of carotenoids. Rao *et al.* (1990) showed that energy restriction increased the activities of superoxide dismutase (*EC* 1.15.1.1), catalase (*EC* 1.11.1.6) and glutathione peroxidase (*EC* 1.11.1.9) in livers of aging rats. Yu (1991) reported that the activities of superoxide anion, hydroxyl anion and hydrogen peroxide fell by 27, 28 and 6% respectively in the livers of energy-restricted rats.

Boutwell *et al.* (1949*b*) suggested that energy restriction of female rats resulted in 'pseudohypophysectomy' reducing the size of the ovaries and uterus. They also observed adrenal hypertrophy. Energy restriction has been shown to reduce levels of circulating mammotrophic hormones in rats and mice (Sylvester *et al.* 1981, 1982; Sarkar *et al.* 1982).

Energy restriction in mice, whether instituted early or late, prolongs life, reduces lympho-proliferative disease, stimulates immunological responses and increases the interleuken-2 productive capacity of lymph nodes but not spleen cells (Kubo *et al.* 1984).

The influences of energy restriction on aspects of DNA metabolism are positive in the direction of cancer control. Energy restriction leads to enhanced DNA repair (Lipman *et al.* 1989) and reverses to a degree the age-related loss of specific activity and fidelity of DNA-polymerases (Srivastava *et al.* 1991). Energy restriction increases formation of DNA adducts called I compounds (Randerath *et al.* 1991). Oncogene expression in rats (Fernandes *et al.* 1987) and mice (Nakamura *et al.* 1989) is reduced by energy restriction. Himeno *et al.* (1992) find that energy restriction inhibits expression of *c-fos* and *c-ki-ras* mRNA in mice.

Koizumi *et al.* (1992) studied body temperature in two strains of mouse whose weekly energy intake was reduced by 49%. Energy restriction extended life span drastically in both male and female mice and reduced spontaneous tumourigenesis by 55% in the males and by 96% in the females. Mitotic activities in the intestine of energy-restricted female mice housed at 20–22° were reduced by 73% but when the mice were housed at 30° the mitotic index was only 21% lower. The authors concluded that the severe reduction in mitotic activity is due to energy restriction-induced torpor.

Insulin deprivation will inhibit tumour growth and cell division (Cohen & Hilf, 1974; Taub *et al.* 1987). When tumour-bearing rats are made diabetic the tumours stop growing (Heuson & Legros, 1972). Plasma insulin levels fall significantly in rats subjected to energy restriction (Klurfeld *et al.* 1989*a*,*b*). Insulin levels fall immediately upon institution of energy restriction in rats and remain low throughout the restricted regimen. The levels of insulin-like growth factor I (IGF-I) also fall at first but rebound to normal within a few weeks; levels of IGF-II are unaffected (Ruggeri *et al.* 1989). Both IGF-I and II have been shown to stimulate the growth of human breast cancer cells in culture (Osborne *et al.* 1990). Aging results in a slight decrease in plasma IGF-I concentrations in rats and the decrease is accelerated significantly in energy-restricted animals. Aging also results in reduction of IGF-I mRNA and this reduction is prevented by dietary restriction (Breese *et al.* 1991). In mice both insulin receptor and glucocorticoid receptor mRNA increase with age. The latter is not influenced by dietary restriction but the former is increased about 20% in 52% energy-restricted mice (Spindler *et al.* 1991). Hepatic insulin receptors are also increased in energy-restricted rats (Balage *et al.* 1988) and binding of insulin to rat liver nuclei is increased by food restiction (Venkatraman & Fernandes, 1992). How these events affect tumour growth is unclear.

Holehan & Merry (1986) published an extensive review of dietary manipulation of aging. Many of the mechanisms discussed in detail by them are applicable to the present presentation.

CONCLUSION

In conclusion it seems abundantly evident that reduction of energy intake and, to a lesser degree, increased energy output inhibit tumourigenesis (spontaneous, induced or

transplanted) in rodents. A modest reduction in energy intake appears to be a simple and inexpensive approach to reduction of cancer risk in man.

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