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Dietary Restriction, Tumors, and Aging in Rodents

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A chronic 30–50% restriction of dietary energy intake (but without malnutrition) typically and strongly lowers the incidence of most spontaneous and induced tumors, delays their onsets, and extends maximum life span in rodents. When compared to normally fed controls, animals fed these dietary restriction (DR) regimens show decreased rates of change for most (but not all) age-sensitive biologic indexes studied to date. DR's impact on chemically induced tumors appears to depend more on energy than on fat restriction, and result from less promotion (and not less initiation). The molecular and cellular events underlying these various outcomes of DR are unclear. Viable explanations include less cellular oxidative damage, a retardation in the age-related changes in the immune system, hormonal changes, less exposure to dietary carcinogens and promoters, less energy for tumor growth, less carcinogen activation, and better DNA repair. New findings are consistent with the notion that DR reduces cellular damage mediated by active oxygen. A lower production or higher detoxification rate of active oxygen species, which damages molecules and promotes tumor growth, could explain DR's effects on aging and tumors.

THE restriction of dietary energy intake without essential nutrient deficiency retards the rate of biological aging and opposes the development of late-life diseases in mice and rats (reviewed by Masoro, 1985; Merry and Holehan, 1985; Walford et al., 1987; Weindruch and Walford, 1988). Most of the work on diseases has involved tumors. Other interventions have not been found to influence aging so strongly or reliably.

Dietary restriction (DR) is most effective when started early in life at about 50% of the unrestricted intake level via diets providing adequate amounts of essential nutrients. DR started in midadulthood (e.g., 12-month-old animals) also retards diseases and aging, but to a lesser extent. An improved understanding of the molecular mechanisms underlying these various outcomes is the laudable goal of an increasing share of DR studies.

This article considers induced and spontaneous tumors and then aging processes in rodents on long-term DR. A complete survey is unneeded in view of the literature just cited and earlier reviews (Ross, 1976; Tannenbaum, 1947; Tannenbaum and Silverstone, 1957) and newer ones (Albanes, 1987a, 1987b; Pariza, 1986) on DR and tumors. Instead, an overview is provided underscoring aspects of probable importance.

Induced Tumors

There is a long history of interest in the effects of underfeeding on induced neoplasms. Moreschi (1909) observed that sarcoma grafts grew poorly in truly malnourished mice. Rous (1914) reported that mice fed an inadequate diet show slower growth of transplanted tumors and of surgically disseminated spontaneous mammary carcinomas. Bischoff and Long (1938) provided evidence for energy restriction being most important in opposing transplanted tumor growth. Tannenbaum's pioneering work during the 1940s and 1950s gave better evidence that induced tumor incidence was inversely related to dietary energy intake (Tannenbaum and Silverstone, 1957). In addition, DR started in midlife was effective.

After a hiatus of some 35 years, the DR model has recently attracted the interest of investigators of induced neoplasms in rats. The main focus here is on the importance of energy versus fat restriction in opposing chemically induced breast tumors (Boissonneault et al., 1986; Kritchevsky et al., 1984). Also studied in DR rats are intestinal tumors induced by chemicals (Pollard et al., 1984; Pollard and Luckert, 1986) and radiation-induced tumors (Gross and Dreyfuss, 1984). The data indicate that DR's anti-tumor actions appear to depend more on energy than on fat restriction, and result from less promotion (and not less initiation). A desirable development would be more interaction between gerontologic and oncologic "restrictionists" because DR may oppose the progression of aging and the growth of tumors by common mechanisms.

Spontaneous Tumors

Early evidence for DR retarding appearances of late-life tumors came from Tannenbaum (1940), who saw fewer and later breast and lung tumors in underfed mice from susceptible strains. These findings were soon confirmed and extended (Saxton et al., 1944; Tannenbaum, 1942; Visscher et al., 1942). Saxton (1945) also described diseases in rats from McCay's colony, in which the most common affliction was chronic pneumonia. He reported that pituitary chromophobe adenomas and lung lymphosarcomas occurred in about 50% of the control group but only rarely in rats on DR.

Much of what is known about influences of DR on spontaneous tumors in rats comes from Ross's work (Ross and Bras, 1971). In male Sprague-Dawley rats the incidences of the most common neoplasms (pituitary and pancreatic adenomas and lung reticulum cell sarcomas) were lowered by DR, while incidences of less common tumors were either unaffected (e.g., thyroid adenoma, urinary bladder papilloma) or increased (e.g., carcinomas, lymphoid reticulum cell sarcomas) by DR. But, when thinking about DR and neoplasia, one must consider both the incidence and onset of the neoplasm. Effects of DR on these parameters are shown in Figure 1 for 650 rats studied by Ross and Bras (1971). Tumor onset is, of course, difficult to determine precisely; however, based on the ages of death for tumor-bearing rats, onset and/or progression was markedly delayed by uninterrupted DR but not by DR terminated at 70 days of age. The final incidence of benign tumors fell with DR while malignant tumor incidence was less sensitive to diet.

Tumor incidence and longevity in female mice from a long-lived hybrid strain fed either 40 kcal per week (restricted) or 85 kcal per week (control) diets since 3 weeks of age are shown in Figure 2 (Weindruch et al., 1986). Circles show the ages of death for mice bearing a tumor at autopsy.

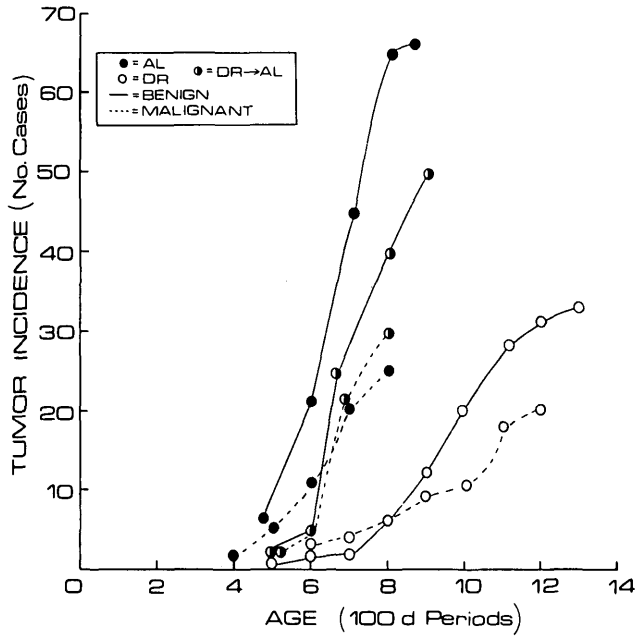

Figure 1: Tumor incidence in male Sprague-Dawley rats fed either ad libitum (AL, n = 250), restricted from weaning (21 d) to death (DR, n = 250), or restricted from weaning to 70 d of age and then fed ad libitum (DR → AL, n = 150). Redrawn from Ross & Bras (1971).

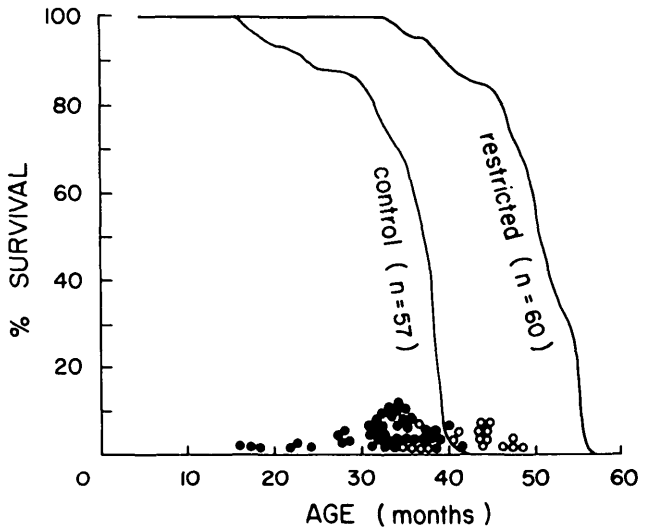

Figure 2: Longevity and tumor incidence in female mice from the long-lived C3B10RF$_1$ hybrid strain fed either a control or restricted diet. The filled circles show the age of death for tumor-bearing mice fed the control diet; open circles represent restricted mice.

Table 1. Delayed Development of Tumors in Mildly Underfed Mice[a]

	Incidence (%)		Age of Occurrence[c]	
Tumor[b]	AL	DR	AL	DR
Pituitary adenoma	33	8	25	31
Mammary	14	6	25	29
Lymphosarcoma	11	10	20	27
RCS–Type B	7	2	23	26
RCS–Type A	4	3	26	33
Lung–single adenoma	21	13	23	27
Lung–multiple adenoma	6	3	23	29
Lung–adenocarcinoma	11	15	24	28

[a]Data adapted from Rehm et al. (1985) using values for the subline not selected for body weight. The average life span for the ad lib (AL) fed group was 22 mo vs 26 mo for mice on mild DR (80% of the AL level).

[b]Most of the mammary tumors were nonmetastasizing carcinomas. RCS is reticulum cell sarcoma.

[c]Average age of death (in mo) of mice bearing that tumor.

DR increased average and 10th decile survival by about 35% and more than halved the overall tumor incidence. The longest-lived restricted mice (> 49 mo) were tumor free. Lymphoma (the most common neoplasm) was found in 46% of the control group versus 13% of the DR mice. The average longevity for lymphoma-bearing mice was 31 and 42 months for control and DR mice, respectively. The incidence of hepatoma, the next most common tumor, was insensitive to DR (about 20% of each cohort was afflicted), but hepatoma-bearing DR mice lived for an average of 44 months (about 10 months more than similarly afflicted controls).

Other reports (Rehm et al., 1985; Tannenbaum, 1945; Tucker, 1979) indicate that milder DR (approximately 20% restriction) significantly reduces late-life neoplasia. Data for outbred Han:NMRI mice are shown in Table 1. Neoplasia was judged to kill about 50% of the mice on either diet. Clearly, the incidence and onset of some tumors (pituitary

adenoma, mammary carcinoma, lung adenoma) were less and later for the restricted group. The average age of death for tumor-bearing mice was greater for DR than for control mice. These results are germane from the standpoint of potential human use, as many more people could adhere to mild than to severe DR.

In an informative exercise, Albanes (1987a) evaluated relations between energy intake, body weight, and cancer incidence using data from 14 reports (82 diet groups) on mice. Spontaneous and induced tumors were considered jointly. The average energy restriction was 29% less than the ad libitum level. Tumor incidence averaged 42% less in the restricted groups. Also, energy restriction appeared to be a more important factor than the level of fat intake in preventing/reducing neoplasia.

How does DR reduce the incidence and delay the onset of tumors? Reductions in initiation (e.g., less activation of carcinogens, more detoxification of activated carcinogens, less ingested dietary carcinogens, better DNA repair) and promotion (e.g., lower cellular levels of active oxygen species, more vigorous immune responses, less energy for tumor growth) may be occurring in DR. Research aimed at determining which (if any) of these factors may be involved in DR's antineoplastic actions needs to be carried out.

Active oxygen species (free radicals) may play a major role in neoplasia. Pryor (1986) suggests that active oxygen intermediates are involved in carcinogen activation and in the binding of activated species to DNA. Cerutti (1985) has discussed how cellular "prooxidant states" (i.e., increased levels of active oxygen, organic peroxides and radicals) may promote neoplastic growth in initiated cells. These same free radicals have long been implicated in aging processes (Harman, 1956). If active oxygen is indeed fundamental to both aging and tumor genesis and/or progression, then a reduction of active oxygen levels would provide a plausible molecular explanation for the action of DR. As discussed next, evidence is accumulating that lends indirect support for this premise.

Aging Processes

Gerontologic studies on DR have progressed from the early studies on longevity and diseases to newer studies on age-sensitive biological indexes. The large majority (but not all) of the biological indexes studied to date in DR rodents stay "younger longer." Currently, the emphasis is shifting to clarifying the *mechanism(s)* of DR's actions. Several possibilities (e.g., less damage by active oxygen species, retarded immunesenescence, neuroendocrine changes, altered gene expression, increased protein turnover) or combinations thereof are in the forefront of DR studies (Holehan and Merry, 1986; Masoro, 1985; Walford et al., 1987; Weindruch and Walford, 1988).

Establishing the mechanism(s) of DR's actions is no easy task when basic aging processes are so poorly understood. Generally, data are grossly lacking to allow one to strongly favor any one answer to the puzzle of what causes aging (or the retardation of aging by DR). With this caveat in mind, recent evidence is discussed which suggests that cellular damage usually attributed to active oxygen may be less in tissues from rodents on DR. This and other possibilities are more fully addressed elsewhere (Weindruch and Walford, 1988).

Mitochondria appear to produce free radicals during respiration (Loschen et al., 1974; Nohl and Hegner, 1978). Heart mitochondria from 23-month-old rats make oxygen radicals at a 25% faster rate than those from 3-month-old rats, and this is associated with a similar age-related increase in peroxidized lipids in the inner mitochondrial membrane (Nohl and Hegner, 1978). The suggestion has been made that mitochondrial active oxygen generation may be a primal cause of aging (Fleming et al., 1982; Harman, 1983). In line with this notion is the experimental evidence that mitochondrial numbers fall with age (Weindruch, 1984).

Energy restriction is required if strong life span extension is to follow underfeeding. Why this is so is unknown, but it suggests that major energy-producing and -consuming metabolic processes as well as those involved in detoxifying noxious byproducts of energy metabolism merit close attention. Three nonmutually exclusive possibilities are that DR: (a) lowers metabolic rate at some important (but now unappreciated) level (e.g., per whole animal, brain, or physiologic "sensing center"); (b) increases metabolic efficiency with less free radical production and biological damage; and (c) increases detoxification of active oxygen.

Metabolic rate (O_2 consumption) per lean body mass of rat is unaltered by long-term DR (McCarter et al., 1985) leading Masoro (1985) to doubt a metabolic rate effect as being central to the action of DR. But, as just stated ("possibility a"), metabolic rate is lowered per whole animal and probably per brain (brain weight is quite insensitive to DR). If the number of active oxygen molecules produced is related to the total amount of O_2 consumed, then the total number of active oxygen molecules per body or brain should fall with DR.

Rodents subjected to short-term (< 2 months) dietary energy restriction use ingested energy-yielding food more efficiently than do controls (Boyle et al., 1978; Mohan and Rao, 1983; Hill et al., 1986). To my knowledge, similar studies of energy utilization after long-term DR have not been reported. It is possible that DR may raise coupled metabolism (i.e., that linked to ATP generation) and reduce uncoupled metabolism (i.e., that which does not generate ATP but makes free radicals and heat instead). Bray and Fisler (1985) discuss interrelated ways by which an energy-restricted organism may adapt metabolically: lower triiodothyronine levels, reduced brown fat mass and activity, less sympathetic nervous system activity, less operation of futile cycles (i.e., a cycle in which ATP is used to form a phosphorylated product that is then dephosphorylated with the loss of ATP's energy [e.g. the glycerolophosphate cycle]), less protein synthesis (an estimate is given that 20–50% of the basal metabolic rate in man goes toward the energy needed for protein synthesis). The coupling of oxidative phosphorylation to electron transport in rat liver mitochondria does appear subject to physiologic regulation (Klug et al., 1984). Perhaps DR induces energy-efficient mitochondria which convert more biological energy into ATP with less lost as heat and free radicals.

Unfortunately, very little is known about how long-term DR regimens impact on mitochondria. We studied iso-

Table 2. Effects of Dietary Restriction and Age on Activities of Superoxide Dismutase, Catalase and Palmitoyl CoA and on Lipid Peroxidation[a]

Diet	Age	SOD	Catalase	Palmitoyl CoA	Lipid Peroxidation
C	12	43 ± 14^{A}	210 ± 29^{C}	2.2 ± 0.8^{A}	27 ± 4^{AB}
R	12	43 ± 8^{A}	298 ± 31^{B}	1.7 ± 0.5^{A}	19 ± 2^{C}
C → R	12	41 ± 3^{A}	198 ± 31^{C}	ND	24 ± 3^{B}
C	24	39 ± 4^{A}	212 ± 15^{C}	ND	31 ± 6^{A}
R	24	39 ± 7^{A}	347 ± 67^{A}	ND	27 ± 5^{AB}

[a]Adapted from Koizumi et al., (1987). Values are means ± *SD*. Abbreviations: SOD, superoxide dismutase; ND, not determined; C, control; R, restricted; C → R, C diet until 1 wk before assay when switched to R. The number of mice studied in each diet-age group was: C-12mo = 10, R-12mo = 10, C → R-12mo = 6, C-24mo = 8, and R-24mo = 5. The values for SOD (units/mg protein), catalase (μmol/[mg pro·min]), and palmitoyl CoA (nmol/[mg pro·min]) are enzyme activities whereas those for lipid peroxidation (pmol/[mg pro·h]) give the amount of malondialdehyde formed in the thiobarbituric acid test. Means in each column not sharing a common superscript letter were significantly different ($p < .05$).

lated liver and brain mitochondria from young DR mice and found the recovery of liver mitochondria (protein/wet weight) to be 14–26% lower in DR mice based on protein and cytochrome *c* oxidase activity (Weindruch et al., 1980). Liver mitochondria from DR mice showed higher State 3 respiration rates (i.e., in the presence of ADP) than did mitochondria from controls for respiration supported by glutamate or pyruvate + malate, while State 4 rates were insensitive to DR. P/O ratios were largely uninfluenced by DR except for an 11% increase for respiration supported by malate plus pyruvate. The recovery and respiration of brain mitochondria were uninfluenced by DR.

Lipid peroxidation and lipofuscin content are indicators of cellular peroxidative damage. Measure of lipid peroxides in tissue samples has been most frequently made by the thiobarbituric acid (TBA) assay which, as a sensitive and specific assay of lipid hydroperoxides, has severe shortcomings (Marshall et al., 1985). Evidence is accumulating to suggest that long-term underfeeding reduces levels of lipid peroxides and lipofuscin. Dietary protein restriction (with energy restriction) in mice lowered lipofuscin levels in brain (Enesco and Kruk, 1981) and lipid peroxides in several other tissues (Chipalkatti et al., 1983a). A 50% restriction of a complete diet imposed on weanling mice reduced heart lipfuscin content and liver lipid peroxidation at 12 months of age (Chipalkatti et al., 1983b).

We studied livers of 12- and 24-month-old mice fed control (C, 95 kcal/wk) and restricted (R, 55 kcal/wk) diets from 3 weeks of age (Koizumi et al., 1987). Short-term DR (1 week only) was also tested. Our intent was to screen for influences of DR on several enzymes having possible relevance to aging processes. The enzymes included several xenobiotic metabolizers, radical scavengers (catalase, superoxide dismutase, glutathione peroxidase), superoxide sources (xanthine oxidase, peroxisomal β-oxidation of palmitoyl-CoA), and glucose 6-phosphatase. Lipid peroxidation was also measured. Certain of these data are summarized in Table 2. Comparing 12- and 24-month-old mice, the strongest diet or age effect observed was an increased catalase activity for group R (42% higher at 12 months, 64% at 24 months). Lipid peroxidation was clearly lower (30%) in group R than in group C mice at 12 months but was only marginally lower (13%) at 24 months. Similarly, in 12-month-old C and R mice injected with the P-450 inducer β-naphthoflavone, mice from group R showed higher catalase activity (40–44%) and lower lipid peroxidation (43–46%) in both β-naphthoflavone-injected and vehicle-injected groups. These data suggest that if free radical damage is involved in aging, it may be a particular kind of damage, i.e., that prevented by a selective increase in catalase activity.

How DR increases catalase activity in rodent livers needs further investigation. It may not be simply a response to increased H_2O_2 production because most agents that increase H_2O_2 cause peroxisomal proliferation, and, based on the lack of effect on β-oxidation, this was not observed. Also, it is important to see if other tissues are influenced like liver and to pinpoint subcellular sites involved.

Other investigators have found liver catalase activity to fall with aging and to be sensitive to DR. Ross (1969) observed that catalase activity fell with aging in rats and that DR attentuates this decline. The DR rats at 33 months of age showed an 18% increase in activity when the basis of expression was nitrogen. Richardson et al. (1987) describe a 50% increase in catalase-specific mRNA in old rats on DR since weaning. Levels of superoxide dismutase-specific mRNA also rose sharply with DR.

Data recently reported as meeting abstracts (Laganiere and Yu, 1986; Laganiere et al., 1987) confirm and extend these findings. Studies of liver subcellular fractions from DR and control rats showed that: (a) membrane lipid hydroperoxide content increased with age in both groups but was reduced about 2-fold at 6 and 24 months of age by DR; (b) the ratio of unsaturated/saturated fatty acids in membranes decreased with age and this was prevented by DR; and (c) cytosolic levels of antioxidants (glutathione, ascorbic acid) and activities of protective enzymes (catalase, glutathione reductase and transferase) fell with aging in the control group. DR arrested the loss in glutathione and raised the activities of all three enzymes during the second year of life.

More recently, Laganiere and Yu (1987) fully reported some of this work. Mitochondrial and microsomal membranes from livers of DR rats showed much lower levels of enzyme-dependent and endogenous lipid hydroperoxides. Both parameters rose with aging.

The case for DR acting via free radical-related mechanisms is rapidly gaining strength. A clear picture awaits the use of assays providing precise detection of the radical species produced and the nature, site, and significance of any damage inflicted. Such studies would permit more precise

statements for several sensible notions which can only now be stated in vague terms. Inquiry also needs to be directed toward better defining the impact of DR on cellular protection against these insults. The present results support but certainly do not prove an important role for free radicals in aging processes.

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