

## Caloric Restriction – Scientific Abstracts

### **ABSTRACTS**

#### **The Benefits of Fasting.**

The Benefits of Fasting.

Christian Century. 1977.Mar.30

#### **Pale Reflections. Anorexia Nervosa.**

Pale Reflections. Anorexia Nervosa.

1998

#### **As We See It: Is conventional medicine finally catching up?**

As We See It: Is conventional medicine finally catching up?

*Life Extension Magazine*. 2002.Dec 8(2):13-5.

#### **Healing Celebrations. Fasting Instructions.**

Healing Celebrations. Fasting Instructions.

2002

#### **Health Agencies Update .**

Health Agencies Update .

*Life Extension Magazine 2002 Dec*. 2002.Sep.18 288(11):1342.

#### **Associated Press. Regular Fasting Seems to Improve Health.**

Associated Press. Regular Fasting Seems to Improve Health.

2004.Apr.30

#### **AFL (Ageless Foundation Laboratories): Fasting for Muscles and Health 2000.**

AFL.

2000

**How to Get Well 1977.**

Airola P.

1977;

**ANI (Asian News International): Measuring Leptin Levels Could Detect Breast Cancer Risk .**

ANI.

ANI. 2003

**Intermittent fasting dissociates beneficial effects of dietary restriction on glucose metabolism and neuronal resistance to injury from calorie intake.**

Anson RM, Guo Z, de Cabo R, et al.

*Proc Natl Acad Sci U S A.* 2003 May 13; 100(10):6216-20.

Dietary restriction has been shown to have several health benefits including increased insulin sensitivity, stress resistance, reduced morbidity, and increased life span. The mechanism remains unknown, but the need for a long-term reduction in caloric intake to achieve these benefits has been assumed. We report that when C57BL6 mice are maintained on an intermittent fasting (alternate-day fasting) dietary-restriction regimen their overall food intake is not decreased and their body weight is maintained. Nevertheless, intermittent fasting resulted in beneficial effects that met or exceeded those of caloric restriction including reduced serum glucose and insulin levels and increased resistance of neurons in the brain to excitotoxic stress. Intermittent fasting therefore has beneficial effects on glucose regulation and neuronal resistance to injury in these mice that are independent of caloric intake

**Prescription for Nutritional Healing.**

Balch JFBPA.

1997; 2

## **Adult-onset calorie restriction and fasting delay spontaneous tumorigenesis in p53-deficient mice.**

Berrigan D, Perkins SN, Haines DC, et al.

*Carcinogenesis*. 2002 May; 23(5):817-22.

Heterozygous p53-deficient (p53(+/-)) mice, a potential model for human Li-Fraumeni Syndrome, have one functional allele of the p53 tumor suppressor gene. These mice are prone to spontaneous neoplasms, most commonly sarcoma and lymphoma; the median time to death of p53+/- mice is 18 months. We have shown previously that juvenile-onset calorie restriction (CR) to 60% of ad libitum (AL) intake delays tumor development in young p53-null (-/-) mice by a p53-independent and insulin-like growth factor 1 (IGF-1)-related mechanism. To determine whether CR is effective when started in adult p53-deficient mice, and to compare chronic CR with an intermittent fasting regimen, male p53+/- mice (7-10 months old, 31-32 mice/group) were randomly assigned to the following regimens: (i) AL (AIN-76A diet), (ii) CR to 60% of AL intake or (iii) 1 day/week fast. Food availability on non-fasting days was controlled to prevent compensatory over feeding. Relative to the AL group, CR significantly delayed ( $P = 0.001$ ) the onset of tumors in adult mice, whereas the 1 day/week fast caused a moderate delay ( $P = 0.039$ ). Substantial variation in longevity and maximum body weight within treatments was not correlated with variation in growth characteristics of individual mice. In a separate group of p53+/- mice treated for 4 weeks ( $n =$  five mice per treatment), plasma IGF-1 levels in CR versus AL mice were reduced by 20% ( $P < 0.01$ ) and leptin levels were reduced by 71% ( $P < 0.01$ ); fasted mice had intermediate levels of leptin and IGF-1. Our findings that CR or a 1 day/week fast suppressed carcinogenesis-even when started late in life in mice predestined to develop tumors due to decreased p53 gene dosage-support efforts to identify suitable interventions influencing energy balance in humans as a tool for cancer prevention

## **Calorie Restriction with Adequate Nutrition-An Overview.**

Best B.

1995

## **Extended longevity in mice lacking the insulin receptor in adipose tissue.**

Bluher M, Kahn BB, Kahn CR.

*Science*. 2003 Jan 24; 299(5606):572-4.

Caloric restriction has been shown to increase longevity in organisms ranging from yeast to mammals. In some organisms, this has been associated with a decreased fat mass and alterations in insulin/insulin-like growth factor 1 (IGF-1) pathways. To further explore these associations with enhanced longevity, we studied mice with a fat-specific insulin receptor knockout (FIRKO). These animals have reduced fat mass and are protected against age-related obesity and its subsequent metabolic abnormalities, although their food intake is normal. Both male and female FIRKO mice were found to have an increase in mean life-span of approximately 134 days (18%), with parallel increases in median and maximum life-spans. Thus, a reduction of fat mass without caloric restriction can be associated with increased longevity in mice, possibly through effects on insulin signaling

### **A low-calorie diet as a model of life span expansion and study of mechanisms of aging.**

Bozhkov AL.

*Adv Gerontol*. 2001;(8):89-99.

none

### **Calorie restriction attenuates inflammatory responses to myocardial ischemia-reperfusion injury.**

Chandrasekar B, Nelson JF, Colston JT, et al.

*Am J Physiol Heart Circ Physiol*. 2001 May; 280(5):H2094-H2102.

The life-prolonging effects of calorie restriction (CR) may be due to reduced damage from cumulative oxidative stress. Our goal was to determine the long-term effects of moderate dietary CR on the myocardial response to reperfusion after a single episode of sublethal ischemia. Male Fisher 344 rats were fed either an ad libitum (AL) or CR (40% less calories) diet. At age 12 mo the animals were anaesthetized and subjected to thoracotomy and a 15-min left-anterior descending coronary artery occlusion. The hearts were reperfused for various periods. GSH and GSSG levels, nuclear factor-kappaB (NF-kappaB) DNA binding activity, cytokine, and antioxidant enzyme expression were assessed in the ischemic zones. Sham-operated animals served as controls. Compared with the AL diet, chronic CR limited oxidative stress as seen by rapid recovery in GSH levels in previously ischemic myocardium. CR reduced DNA

binding activity of NF-kappaB. The kappaB-responsive cytokines interleukin-1beta and tumor necrosis factor-alpha were transiently expressed in the CR group but persisted longer in the AL group. Furthermore, expression of manganese superoxide dismutase, a key antioxidant enzyme, was significantly delayed in the AL group. Collectively these data indicate that CR significantly attenuates myocardial oxidative stress and the postischemic inflammatory response

### **Modulation of glutathione and thioredoxin systems by calorie restriction during the aging process.**

Cho CG, Kim HJ, Chung SW, et al.

*Exp Gerontol.* 2003 May; 38(5):539-48.

Accumulating evidence strongly suggests that oxidative stress underlies aging processes and that calorie restriction (CR) retards aging processes, leading to an extended lifespan for various organisms. Recent studies revealed that the anti-aging action of CR depends on its anti-oxidative mechanism. However, at present, the status of glutathione (GSH) and thioredoxin (Trx) system, two major thiol redox systems in animal cells during aging and its modulation by CR has not fully been explored. The purpose of this study is two-fold: one, to determine whether these two systems in rat kidney are altered as a consequence of aging; two, to determine whether these systems can be modulated by anti-oxidative CR. The results of our study showed that GSH and GSH-related enzyme activities decreased with age in ad libitum (AL)-fed rats, while CR rats consistently showed resistance to decreases in these activities. Data from the present data further showed that while Trx and Trx reductase (TrxR) in cytoplasm decrease with age in AL-fed rats, CR prevents these decreases. In contrast, we also found that the nuclear translocation of the redox regulators, Trx and Ref-1, increase with age, which was suppressed in CR rats. Therefore, increases in nuclear Trx and Ref-1 during aging may result in the up-regulation of redox-sensitive transcription factors, such as NF-kappaB or AP-1, via the interaction of Ref-1 and Trx in a redox-dependent manner. Our conclusion is that a redox imbalance occurs during aging and that redox changes are minimized through the anti-oxidative action of CR

### **Effects of age and dietary restriction on lifespan and oxidative stress of SAMP8 mice with learning and memory impairments.**

Choi JH, Kim D.

*J Nutr Health Aging.* 2000; 4(3):182-6.

This study was to evaluate the effect of dietary restriction (DR) on lifespan and oxidative stress of dementia mouse model SAMP8 with impaired learning and memory. SAMP8 female mice were fed either ad libitum (AL) or fed 60% of food intake of AL. Results showed that basal metabolic rates (BMR) were significantly lower (15 to 22%) in DR with increased median and maximum lifespans, suggesting feed and gross efficiencies were significantly lower in DR than in AL. Grading score of senescence resulted in a marked improvement about 2-fold by DR compared with AL. The amounts of lipofuscin at 12 months were significantly lowered 16% in DR than that of AL. Median and maximal lifespans significantly increased (28.5% and 16.4%, respectively) by DR, and also lowered superoxide radical about 15 approximately 45% in DR compared with AL at 4, 8 and 12 months of age. On the other hand, superoxide dismutase (SOD) activities were higher (about 15 approximately 30%) in DR than those in AL group of SAMP8 except for 4 months of age. Our results suggest that 40% calorie restricted SAMP8 can effectively suppress dementia-related abnormalities during aging

### **Drug May Ward Off Diabetes, Heart Disease.**

Christensen D.

United Press International UPI Science News. 2001.Nov.16

### **First Test-Tube Rhesus Monkey Healthy and Virile after 15 Years.**

Divett T.

Madison, WI. 1998

### **Dietary restriction reduces insulin-like growth factor I levels, which modulates apoptosis, cell proliferation, and tumor progression in p53-deficient mice.**

Dunn SE, Kari FW, French J, et al.

*Cancer Res.* 1997 Nov 1; 57(21):4667-72.

Diet contributes to over one-third of cancer deaths in the Western world, yet the factors in the diet that influence cancer are not elucidated. A reduction in caloric intake dramatically slows cancer progression in rodents, and this may be a major contribution to dietary effects on cancer. Insulin-like growth factor I (IGF-I) is lowered during dietary restriction (DR) in both humans and rats. Because IGF-I modulates cell proliferation, apoptosis, and tumorigenesis, the mechanisms behind the

protective effects of DR may depend on the reduction of this multifaceted growth factor. To test this hypothesis, IGF-I was restored during DR to ascertain if lowering of IGF-I was central to slowing bladder cancer progression during DR. Heterozygous p53-deficient mice received a bladder carcinogen, p-cresidine, to induce preneoplasia. After confirmation of bladder urothelial preneoplasia, the mice were divided into three groups: (a) ad libitum; (b) 20% DR; and (c) 20% DR plus IGF-I (IGF-I/DR). Serum IGF-I was lowered 24% by DR but was completely restored in the IGF-I/DR-treated mice using recombinant IGF-I administered via osmotic minipumps. Although tumor progression was decreased by DR, restoration of IGF-I serum levels in DR-treated mice increased the stage of the cancers. Furthermore, IGF-I modulated tumor progression independent of changes in body weight. Rates of apoptosis in the preneoplastic lesions were 10 times higher in DR-treated mice compared to those in IGF/DR- and ad libitum-treated mice. Administration of IGF-I to DR-treated mice also stimulated cell proliferation 6-fold in hyperplastic foci. In conclusion, DR lowered IGF-I levels, thereby favoring apoptosis over cell proliferation and ultimately slowing tumor progression. This is the first mechanistic study demonstrating that IGF-I supplementation abrogates the protective effect of DR on neoplastic progression

### **Your Solution 2002.**

FCI (Fasting Center International).

2002

### **More Information on Fasting .**

FCI (Fasting Center International).

2003

### **The price of tumour suppression?**

Ferbeyre G, Lowe SW.

*Nature*. 2002 Jan 3; 415(6867):26-7.

### **Fasting and Eating for Health.**

Fuhrman J.

1998;

## **Mutations in the p53 tumor suppressor gene: clues to cancer etiology and molecular pathogenesis.**

Greenblatt MS, Bennett WP, Hollstein M, et al.

*Cancer Res.* 1994 Sep 15; 54(18):4855-78.

## **Alarming News on rBGH-IGF-1 Increases Cancer Risks.**

Hansen M.

2002.Sep.11;

## **Serum leptin levels in female patients with NIDDM.**

Haque Z, Rahman MA.

*J Coll Physicians Surg Pak.* 2003 Mar; 13(3):130-4.

**OBJECTIVE:** To compare serum leptin levels of diabetic and non-diabetic female subjects and also assess the relationship of hyperglycemia with serum insulin, C-peptide and leptin levels. **DESIGN:** It is a case control study. **PLACE AND DURATION OF STUDY:** The study was conducted at Medicare Hospital, Family Care Clinic and Baqai Institute of Diabetes and Endocrinology between December 1997 to September 1999. **SUBJECT AND METHODS:** One hundred and forty female subjects with different body mass indices and fasting blood sugar levels were selected from three different diabetic centers. A venous sample was drawn after an overnight fast (12 hours) for determination of blood parameters in all groups. Glycosylated hemoglobin, hexosamine, fructosamine, insulin and C-peptide were determined only in diabetic patients. Blood glucose, triacylglycerol (TAG), total cholesterol, HDL cholesterol, HbA1C, hexosamine and fructosamine were determined enzymatically. Serum leptin, C-peptide and insulin were measured using enzyme-linked immunoassay. **RESULTS:** Serum leptin levels of obese diabetic and non-diabetic subjects were significantly higher as compared with lean diabetic patients and non-diabetic subjects ( $P < 0.05$ ). Leptin levels were positively correlated with serum insulin and C-peptide levels. Serum leptin increased with increase in body mass index and waist hip ratio was strongly related with insulin resistance in NIDDM. **CONCLUSION:** Leptin levels are increased in obesity and may play a role in development of insulin resistance and NIDDM

## **A possible new role for the anti-ageing peptide carnosine.**

Hipkiss AR, Brownson C.

*Cell Mol Life Sci.* 2000 May; 57(5):747-53.

The naturally occurring dipeptide carnosine (beta-alanyl-L-histidine) is found in surprisingly large amounts in long-lived tissues and can delay ageing in cultured human fibroblasts. Carnosine has been regarded largely as an anti-oxidant and free radical scavenger. More recently, an anti-glycating potential has been discovered whereby carnosine can react with low-molecular-weight compounds that bear carbonyl groups (aldehydes and ketones). Carbonyl groups, arising mostly from the attack of reactive oxygen species and low-molecular-weight aldehydes and ketones, accumulate on proteins during ageing. Here we propose, with supporting evidence, that carnosine can react with protein carbonyl groups to produce protein-carbonyl-carnosine adducts ('carnosinylated' proteins). The various possible cellular fates of the carnosinylated proteins are discussed. These proposals may help explain anti-ageing actions of carnosine and its presence in non-mitotic cells of long-lived mammals

### **Fasting Instructions for Revitalizing Yourself and Reversing Diseases.**

Horowitz L.

2001

### **Recommendations for Fasting.**

Horowitz LS, V.

2002

### **The Latest research on Longevity Assurance Genes in Animals.**

infoaging.org.

2003

### **Dietary restriction increases insulin sensitivity and lowers blood glucose in rhesus monkeys.**

Kemnitz JW, Roecker EB, Weindruch R, et al.

*Am J Physiol.* 1994 Apr; 266(4 Pt 1):E540-E547.

Insulin sensitivity and glucose tolerance typically decline during later life. In a multidimensional randomized trial of the effects of dietary restriction started in adulthood on the processes of aging, we are studying insulin sensitivity and glucoregulation longitudinally in control (C, n = 15, fed a defined diet ad libitum for 6-8 h/day) and restricted (R, n = 15, fed 30% less than C) monkeys using the Modified Minimal Model method. Linear rates of change were calculated for individual animals through 30 mo of diet treatment and compared between treatment groups. Basal glucose, basal insulin, and insulin responses to glucose and tolbutamide increased for C and decreased for R animals ( $P < \text{or} = 0.002$ ), whereas insulin sensitivity decreased for C and increased for R ( $P = 0.008$ ). Glycosylated hemoglobin at 30 mo was marginally lower in R ( $P = 0.06$ ) and was positively correlated with fasting plasma glucose ( $r = 0.508$ ,  $P < 0.001$ ). Insulin changes were significantly correlated with changes in adiposity (weight and abdominal circumference). Identification of the mechanisms through which these effects are achieved may aid in ameliorating glucose intolerance, insulin resistance, and associated illnesses in older persons

### **BioMarker pharmaceuticals develops anti-aging therapy.**

Kent S.

*Life Extension Magazine 2003 Jun. 2003.Jun 9(6):56-7.*

### **Molecular exploration of age-related NF-kappaB/IKK downregulation by calorie restriction in rat kidney.**

Kim HJ, Yu BP, Chung HY.

*Free Radic Biol Med.* 2002 May 15; 32(10):991-1005.

Accumulating evidence strongly suggests that oxidative stress underlies aging processes, and that in a variety of organisms, calorie restriction (CR) retards these processes, thereby extending their lifespan. Recent studies revealed that the anti-aging action of CR depends on its anti-oxidative mechanism. In previous papers, we reported that aging activates the redox-sensitive transcription factor, NF-kappaB, and further reported that age-related NF-kappaB activation correlates with age-related oxidative stress. In the present paper, we present evidence that increased NF-kappaB binding activity during aging is elicited through the phosphorylation of IkappaB kinase (IKK), causing a degradation of IkappaBalpha and IkappaBbeta. We further show that CR inhibits IKK activation, down-regulating NF-kappaB activation as evidenced by increased bound IkappaBalpha and IkappaBbeta proteins in cytoplasm.

These findings led to the conclusions that age-related oxidative stress may be a primary cause of up-regulated and altered NF-kappaB activity in aged kidney, and that the anti-oxidative action of CR is a major force responsible for the maintenance of a properly functioning NF-kappaB/IkappaB-IKK signaling pathway, which might be involved in CR's life-prolonging action

### **Calorie restriction in nonhuman primates: effects on diabetes and cardiovascular disease risk.**

Lane MA, Ingram DK, Roth GS.

*Toxicol Sci.* 1999 Dec; 52(2 Suppl):41-8.

The effects of calorie restriction (CR) on life span, disease, and aging in physiological systems have been documented extensively in rodent models. However, whether CR has similar effects in longer-lived species more closely related to humans remains unknown. Studies of CR and aging using nonhuman primates (rhesus monkeys) have been ongoing for several years at the National Institute on Aging and the University of Wisconsin-Madison. The majority of data published from these studies are consistent with the extensive findings reported in rodents. For example, monkeys on CR weigh less and have less body fat. Monkeys on CR also exhibit lower body temperature, fasting blood glucose and insulin, and serum lipids. In addition, insulin sensitivity is increased in monkeys on CR. Recent efforts in the NIA study have focused on the effect of this intervention on risk factors for various age-related diseases, in particular for diabetes and cardiovascular disease. We have shown that monkeys on CR have lower blood pressure, reduced body fat, and a reduced trunk:leg fat ratio. Also, monkeys on CR have reduced triglycerides and cholesterol and have increased levels of HDL2B. Low levels of this HDL subfraction have been associated with increased cardiovascular disease in humans. In short-term studies, older (> 18 years) monkeys on CR exhibit reductions in insulin and triglycerides before changes in body composition and fat distribution became evident. These and other findings have suggested that CR might have beneficial effects on certain disease risk factors independent of reductions in body weight or prevention of obesity

### **Longevity Medicine. The Serious Search for an Anti-Aging Pill.**

Lane MARGS.

Longevity Medicine. 2002

## **Gene expression profile of aging and its retardation by caloric restriction.**

Lee CK, Klopp RG, Weindruch R, et al.

*Science*. 1999 Aug 27; 285(5432):1390-3.

The gene expression profile of the aging process was analyzed in skeletal muscle of mice. Use of high-density oligonucleotide arrays representing 6347 genes revealed that aging resulted in a differential gene expression pattern indicative of a marked stress response and lower expression of metabolic and biosynthetic genes. Most alterations were either completely or partially prevented by caloric restriction, the only intervention known to retard aging in mammals. Transcriptional patterns of calorie-restricted animals suggest that caloric restriction retards the aging process by causing a metabolic shift toward increased protein turnover and decreased macromolecular damage

## **Caloric intake and the risk of Alzheimer disease.**

Luchsinger JA, Tang MX, Shea S, et al.

*Arch Neurol*. 2002 Aug; 59(8):1258-63.

**BACKGROUND:** Diet may play a role in Alzheimer disease (AD). **OBJECTIVE:** To examine the association between caloric intake and AD. **METHODS:** Elderly individuals free of dementia at baseline (N = 980) were followed for a mean of 4 years. Daily intake of calories, carbohydrates, fats, and protein were recalled using a semiquantitative food frequency questionnaire administered between the baseline and first follow-up visits. Proportional hazards models were used to examine the associations of quartiles of intake and incident AD, adjusting for confounders. **RESULTS:** There were 242 incident cases of AD during 4023 years of follow-up (6 cases per 100 person-years). Compared with individuals in the lowest quartile of caloric intake, those in the highest quartile had an increased risk of AD (hazard ratio, 1.5; 95% confidence interval [CI], 1.0-2.2). Among individuals with the apolipoprotein E epsilon4 allele, the hazard ratios of AD for the highest quartiles of calorie and fat intake were 2.3 (95% CI, 1.1-4.7) and 2.3 (95% CI, 1.1-4.9), respectively, compared with the lowest quartiles. The hazard ratios of AD for the highest quartiles of calorie and fat intake compared with the lowest quartiles in individuals without the apolipoprotein E epsilon4 allele were close to 1 and were not statistically significant (P = .83 and P = .61, respectively). **CONCLUSION:** Higher intake of calories and fats may be associated with higher risk of AD in individuals

carrying the apolipoprotein E epsilon4 allele

### **Hormesis and the antiaging action of dietary restriction.**

Masoro EJ.

*Exp Gerontol.* 1998 Jan; 33(1-2):61-6.

Hormesis refers to the often encountered phenomenon of a beneficial biological action from a factor or agent that is generally viewed as detrimental. Beneficial actions that have been observed include life span extension. It is proposed that life span extension in rodents by dietary restriction is an example of hormesis and that sustained moderate hyperadrenocorticism underlies this life prolongation. Evidence supporting this concept is presented. The possibility is also suggested that whenever hormesis leads to an extension of mammalian life span, it is likely that moderate hyperadrenocorticism plays a major role

### **Caloric restriction and aging: an update.**

Masoro EJ.

*Exp Gerontol.* 2000 May; 35(3):299-305.

Restricting food intake to 50 to 70% of that eaten by ad lib-fed rats and mice markedly increases longevity, retards age-associated physiological deterioration, and delays and, in some cases, prevents age-associated diseases. These actions are due to the reduced intake of calories, and thus the phenomenon has been called the antiaging action of caloric restriction (CR). This article focuses on the possible biological mechanisms underlying the antiaging action. The following three proposed mechanisms are considered in depth: 1) attenuation of oxidative damage; 2) modulation of glycemia and insulinemia; 3) hormesis. The evolution of the antiaging action of CR is also considered. Based on this consideration, a scenario unifying the above mechanisms is presented

### **Calorie restriction in rhesus monkeys.**

Mattison JA, Lane MA, Roth GS, et al.

*Exp Gerontol.* 2003 Jan; 38(1-2):35-46.

Calorie restriction (CR) extends lifespan and reduces the incidence and age of onset of age-related disease in several animal models. To determine if this nutritional

intervention has similar actions in a long-lived primate species, the National Institute on Aging (NIA) initiated a study in 1987 to investigate the effects of a 30% CR in male and female rhesus macaques (*Macaca mulatta*) of a broad age range. We have observed physiological effects of CR that parallel rodent studies and may be predictive of an increased lifespan. Specifically, results from the NIA study have demonstrated that CR decreases body weight and fat mass, improves glucoregulatory function, decreases blood pressure and blood lipids, and decreases body temperature. Juvenile males exhibited delayed skeletal and sexual maturation. Adult bone mass was not affected by CR in females nor were several reproductive hormones or menstrual cycling. CR attenuated the age-associated decline in both dehydroepiandrosterone (DHEA) and melatonin in males. Although 81% of the monkeys in the study are still alive, preliminary evidence suggests that CR will have beneficial effects on morbidity and mortality. We are now preparing a battery of measures to provide a thorough and relevant analysis of the effectiveness of CR at delaying the onset of age-related disease and maintaining function later into life

### **Overview of Nutrition: Disorders of Nutrition and Metabolism .**

Merck.

1999; Home Edition. section 12(Chapter 133)

none

### **Does Skipping Meals Make You Healthy?**

Mercola J.

2003

### **Low Insulin Not Calorie Restriction Lengthens Your Life.**

Mercola J.

2003

### **Juice Fasting and Detoxification.**

Meyerowitz S.

1998;

## **The connection between nutrition and tumor promotion. Z. Immunitaetsforsch.**

Moreschi C.

1909;(2):651.

## **Dietary restriction reduces angiogenesis and growth in an orthotopic mouse brain tumour model.**

Mukherjee P, El Abbadi MM, Kasperzyk JL, et al.

*Br J Cancer.* 2002 May 20; 86(10):1615-21.

Diet and lifestyle produce major effects on tumour incidence, prevalence, and natural history. Moderate dietary restriction has long been recognised as a natural therapy that improves health, promotes longevity, and reduces both the incidence and growth of many tumour types. Dietary restriction differs from fasting or starvation by reducing total food and caloric intake without causing nutritional deficiencies. No prior studies have evaluated the responsiveness of malignant brain cancer to dietary restriction. We found that a moderate dietary restriction of 30-40% significantly inhibited the intracerebral growth of the CT-2A syngeneic malignant mouse astrocytoma by almost 80%. The total dietary intake for the ad libitum control group (n=9) and the dietary restriction experimental group (n=10) was about 20 and 13 Kcal x day<sup>(-1)</sup>, respectively. Overall health and vitality was better in the dietary restriction-fed mice than in the ad libitum-fed mice. Tumour microvessel density (Factor VIII immunostaining) was two-fold less in the dietary restriction mice than in the ad libitum mice, whereas the tumour apoptotic index (TUNEL assay) was three-fold greater in the dietary restriction mice than in the ad libitum mice. CT-2A tumour cell-induced vascularity was also less in the dietary restriction mice than in the ad libitum mice in the in vivo Matrigel plug assay. These findings indicate that dietary restriction inhibited CT-2A growth by reducing angiogenesis and by enhancing apoptosis. Dietary restriction may shift the tumour microenvironment from a proangiogenic to an antiangiogenic state through multiple effects on the tumour cells and the tumour-associated host cells. Our data suggest that moderate dietary restriction may be an effective antiangiogenic therapy for recurrent malignant brain cancers

## **An Encyclopedia of Natural Medicine.**

Murray MPJ.

1991;

**Introduction to the Raw Life: Becoming Natural in an Unnatural World.**

Nison P.

2003

**Leptin and high glucose stimulate cell proliferation in MCF-7 human breast cancer cells: reciprocal involvement of PKC-alpha and PPAR expression.**

Okumura M, Yamamoto M, Sakuma H, et al.

*Biochim Biophys Acta.* 2002 Oct 21; 1592(2):107-16.

Glucose concentration may be an important factor in breast cancer cell proliferation, and the prevalence of breast cancer is high in diabetic patients. Leptin may also be an important factor since plasma levels of leptin correlated with TNM staging for breast cancer patients. The effects of glucose and leptin on breast cancer cell proliferation were evaluated by examining cell doubling time, DNA synthesis, levels of cell cycle related proteins, protein kinase C (PKC) isozyme expression, and peroxisome proliferator-activated receptor (PPAR) subtypes were determined following glucose exposure at normal (5.5 mM) and high (25 mM) concentrations with/without leptin in MCF-7 human breast cancer cells. In MCF-7 cells, leptin and high glucose stimulated cell proliferation as demonstrated by the increases in DNA synthesis and expression of cdk2 and cyclin D1. PKC-alpha, PPARgamma, and PPARalpha protein levels were up-regulated following leptin and high glucose treatment in drug-sensitive MCF-7 cells. However, there was no significant effect of leptin and high glucose on cell proliferation, DNA synthesis, levels of cell cycle proteins, PKC isozymes, or PPAR subtypes in multidrug-resistant human breast cancer NCI/ADR-RES cells. These results suggested that hyperglycemia and hyperleptinemia increase breast cancer cell proliferation through accelerated cell cycle progression with up-regulation of cdk2 and cyclin D1 levels. This suggests the involvement of PKC-alpha, PPARalpha, and PPARgamma

**Therapies of the Future: New Molecular Targets for Cancer Therapy.**

Oliff A.

1996

## **Calorie Restriction Slows Heart Genetic Aging .**

Parker R.

2002

## **Homo sapiens Genome Symposium.**

Pearson H.

2003.May

## **Effects of calorie restriction on thymocyte growth, death and maturation.**

Poetschke HL, Klug DB, Perkins SN, et al.

*Carcinogenesis*. 2000 Nov; 21(11):1959-64.

We previously reported that calorie restriction (CR) significantly delays the spontaneous development of thymic lymphomas and other neoplasms in p53-deficient mice and their wild-type littermates. The purpose of the present study was to further characterize the anti-lymphoma effects of CR by assessing thymocyte growth, death and maturation in response to acute (6 day) and chronic (28 day) CR regimens. Male C57BL/6J mice fed a CR diet (restricted to 60% of control ad libitum intake) for 6 days displayed a severe reduction in thymic size and cellularity, as well as a decrease in splenic size and cellularity; these declines were sustained through 28 days of CR. Mice maintained on a CR diet for 28 days also displayed a significant depletion in the cell numbers of all four major thymocyte subsets defined by CD4 and CD8 expression. Analysis within the immature CD4(-)8(-) thymocyte subset further revealed an alteration in normal CD44 and CD25 subset distribution. In particular, CR for 28 days resulted in a significant decrease in the percentage of the proliferative CD44(-)25(-) subset. In addition, a significant increase in the percentage of the early, pro-T cell CD44(+)25(-) population was detected, indicative of a CR-induced delay in thymocyte maturation. Taken together, these findings suggest that CR suppresses (through several putative mechanisms) lymphomagenesis by reducing the pool of immature thymocytes that constitute the lymphoma-susceptible subpopulation

## **Researchers Discover Gene that Retards Aging in Mice.**

Premo D.

2001

**Leptin influences cellular differentiation and progression in prostate cancer.**

Saglam K, Aydur E, Yilmaz M, et al.

*J Urol.* 2003 Apr; 169(4):1308-11.

**PURPOSE:** Several studies have shown a positive association of dietary fat with prostate cancer. Leptin, a peptide hormone that has a role in the regulation of body weight, currently serves as a more accurate biomarker for total body fat. We designed a study to determine whether leptin influences cellular differentiation and the progression of prostate cancer. **MATERIALS AND METHODS:** In this study we investigated serum leptin in 21 patients with prostate cancer, 50 with benign prostatic obstruction and 50 healthy individuals matched for sex, body mass index and age. Patients with cancer were stratified into 2 groups by the disease spread, including groups 1--organ confined and 2--advanced disease, and into 3 groups by the differentiation degree, including groups 3--Gleason sum 2 to 4 or well differentiated, 4--Gleason sum 5 to 7 or moderately differentiated and 5--Gleason sum 8 to 10 or poorly differentiated. **RESULTS:** We noted significant differences in serum leptin in the cancer versus control and cancer versus benign prostatic obstruction groups. In addition, in the prostate cancer group serum leptin correlated with prostate specific antigen and biopsy Gleason score. We also observed significant differences in serum leptin in groups 1 versus 2, 3 versus 5 and 4 versus 5. **CONCLUSION:** Leptin may have roles in the development of prostate cancer through testosterone and factors related to obesity. It influences cellular differentiation and the progression of prostate cancer

**Immunological effects of low-fat diets with and without weight loss.**

Santos MS, Lichtenstein AH, Leka LS, et al.

*J Am Coll Nutr.* 2003 Apr; 22(2):174-82.

**OBJECTIVE:** The immunologic effects of isocaloric reduced- and low-fat diets and a voluntary calorie-restricted low-fat diet resulting in weight loss were compared to the immunologic effects of an average American diet in hyperlipidemic individuals. **METHODS:** Ten hyperlipidemic subjects were studied during three six-week weight maintenance phases: baseline (BL) [35% fat [14% saturated fat (SFA), 13% monounsaturated fat (MUFA), 8% polyunsaturated fat (PUFA)] and 147 mg cholesterol (C)/1000 kcal], reduced-fat (RF) [26% fat (4% SFA, 11% MUFA, 11%

PUFA) and 45 mg C/1000 kcal], and low-fat (LF) [15% fat (5% SFA, 5% MUFA, 3% PUFA) and 35 mg C/1000 kcal] diets followed by 12-week, low-fat calorie reduced phase (LFCR). RESULTS: During the last phase, the subjects' weight significantly decreased ( $p = 0.005$ ). Cholesterol levels were significantly reduced during all phases, compared to BL diet ( $p < 0.05$ ). Delayed-type hypersensitivity (DTH) was assessed using Multi-test CMI. Maximum induration diameters were 22.7, 25.4, 30.5, 34.5 mm for BL, RF, LF and LFCR diets, respectively. Subjects on the LFCR diets had significantly higher DTH compared to the BL diet ( $p = 0.005$ ). No significant effect of diet was observed on lymphocyte proliferation or interleukin (IL)-1, IL-2 and prostaglandin (PG) E(2) production. CONCLUSIONS: These data suggest that low-fat diets (15% energy), under conditions which result in weight loss, do not compromise and may enhance the immune response of middle-aged and elderly hyperlipidemic subjects. The results of this study provide support for the hypothesis that moderate caloric restriction in humans may have a beneficial effect on cell-mediated immunity such as those reported in calorie-restricted rodents

### **BioMarker Pharmaceuticals develops anti-aging therapy.**

Saul Kent S.

*Life Extension Magazine*. 2003 9(6):56-7.

### **Recommendations for Fasting.**

Saxion V.

2002

### **Therapeutic Fasting and Detoxification-Internal Cleansing-Optimum Health Through Natural Hygiene.**

Shirley's Wellness Cafe.

2003

### **Calorie restriction inhibits the age-related dysregulation of the cytokines TNF-alpha and IL-6 in C3B10RF1 mice.**

Spaulding CC, Walford RL, Effros RB.

*Mech Ageing Dev*. 1997 Feb; 93(1-3):87-94.

TNF-alpha and IL-6 are generally increased in the sera of aged humans and mice. The dysregulation of these cytokines may be critical in autoreactivity and immune dysfunction. In earlier studies we demonstrated that production of TNF-alpha and IL-6 following in vitro stimulation of peritoneal macrophages by LPS was reduced in old compared to young mice, and that dietary caloric restriction (CR) had no effect on the induction of TNF-alpha in this system. In the present study we examined the effects of age and calorie restriction on the constitutive production of both TNF-alpha and IL-6. Serum levels of both cytokines were significantly higher in old versus young mice. However, in old mice subjected to long term CR the serum levels were comparable to those of young mice. The potential involvement of normalization of TNF-alpha and IL-6 levels in the life extension effect of CR are discussed

### **Reversing aging rapidly with short-term calorie restriction.**

Spindler SR.

*Life Extension Magazine*. 2001 7(12):40-61.

### **Calorie restriction enhances the expression of key metabolic enzymes associated with protein renewal during aging.**

Spindler SR.

*Ann N Y Acad Sci*. 2001 Apr; 928:296-304.

Our studies show that dietary caloric restriction (CR) alters the expression of key metabolic enzymes in a manner consistent with an increased rate of extrahepatic protein turnover and renewal during aging. Of the key hepatic gluconeogenic enzyme genes affected by CR, glucose 6-phosphatase mRNA increased 1.7- and 2.3-fold in young and old CR mice. Phosphoenolpyruvate carboxykinase mRNA increased 2-fold in young mice, and its mRNA and activity increased 2.5- and 1.7-fold in old mice. These changes indicate that CR enhances the enzymatic capacity for gluconeogenesis. The carbon required for gluconeogenesis appears to be generated from peripheral protein turnover. Muscle glutamine synthetase mRNA increased 1.3- and 2.1-fold in young and old CR mice, suggesting increased disposal of nitrogen and carbon derived from protein catabolism for energy. mRNA for the key liver nitrogen disposal enzymes glutaminase, carbamyl phosphate synthase I, and tyrosine aminotransferase were increased by 2.4-, 1.8-, and 1.8-fold in CR mice. Consistent with increased hepatic nitrogen disposal, hepatic glutamine synthetase mRNA and activity were each decreased about 40% in CR mice. Together, these and our other published data suggest that CR enhances and maintains protein turnover, and thus protein renewal,

into old age. These effects are likely to resist the well-documented decline in whole body protein renewal with age. Enhanced renewal may reduce the level of damaged and toxic proteins that accumulate during aging, contributing to the extension of life span by CR

### **Effects of caloric restriction on mitochondrial function and gene transcripts in rat muscle.**

Sreekumar R, Unnikrishnan J, Fu A, et al.

*Am J Physiol Endocrinol Metab.* 2002 Jul; 283(1):E38-E43.

Rodent skeletal muscle mitochondrial DNA has been shown to be a potential site of oxidative damage during aging. Caloric restriction (CR) is reported to reduce oxidative stress and prolong life expectancy in rodents. Gene expression profiling and measurement of mitochondrial ATP production capacity were performed in skeletal muscle of male rats after feeding them either a control diet or calorie-restricted diet (60% of control diet) for 36 wk to determine the potential mechanism of the beneficial effects of CR. CR enhanced the transcripts of genes involved in reactive oxygen free radical scavenging function, tissue development, and energy metabolism while decreasing expression of those genes involved in signal transduction, stress response, and structural and contractile proteins. Real-time PCR measurements confirmed the changes in transcript levels of cytochrome-c oxidase III, superoxide dismutase (SOD)1, and SOD2 that were noted by the microarray approach. Mitochondrial ATP production and citrate synthase were unaltered by the dietary changes. We conclude that CR alters transcript levels of several genes in skeletal muscle and that mitochondrial function in skeletal muscle remains unaltered by the dietary intervention. Alterations in transcripts of many genes involved in reactive oxygen scavenging function may contribute to the increase in longevity reported with CR

### **Aging alters the apoptotic response to genotoxic stress.**

Suh Y, Lee KA, Kim WH, et al.

*Nat Med.* 2002 Jan; 8(1):3-4.

### **The Famine of Youth.**

Taubes G.

2000

**Ask the experts. Wellness Letter.**

UCB (University of California B.

2002.Mar

**Calorie Restriction Reduces Age-Related Brain Cell Death 2002 Dec 30.**

UF (University of Florida.

2002

**The anti-ageing action of dietary restriction.**

Van Remmen H, Guo Z, Richardson A.

*Novartis Found Symp.* 2001; 235:221-30.

Over 60 years ago, McCay's laboratory showed that dietary or calorie-restriction dramatically increased the lifespan of rats. Since then, numerous laboratories with a variety of strains of rats and mice have confirmed this initial observation and have shown that reducing calorie intake (without malnutrition) significantly increases both the mean and maximum survival of rodents. Currently, dietary restriction is the only experimental manipulation that has been shown to retard ageing of mammals. Although mechanism whereby dietary restriction retards ageing is currently unknown, much of the emerging data suggest that the calorie-restricted rodents live longer and age more slowly because they are more resistant to stress and have an enhanced ability to protect cells against damaging agents

**Caloric restriction increases HDL2 levels in rhesus monkeys (*Macaca mulatta*).**

Verdery RB, Ingram DK, Roth GS, et al.

*Am J Physiol.* 1997 Oct; 273(4 Pt 1):E714-E719.

Caloric restriction (CR) prolongs the life of rodents and other small animals, but the benefits of CR for primates and people are as yet unknown, and mechanisms by which CR may slow aging remain unidentified. A study of rhesus monkeys, *Macaca mulatta*, is underway to determine if CR might prolong life span in primates and to evaluate potential mechanisms for life prolongation. Thirty rhesus monkeys in three age cohorts, restricted to 70% of ad libitum calorie intake for 6-7 yr, were compared with 30 controls. Plasma lipid, lipoprotein, and high-density lipoprotein (HDL)

apolipoproteins and subfractions were measured and compared with weight, percent fat, glucose, and insulin level. CR caused decreased triglyceride levels in adult monkeys and increased levels of HDL2b, the HDL subfraction associated with protection from atherosclerosis. Multivariate statistical analyses showed that differences in lipid and lipoprotein levels occurring with CR could be accounted for, at least in part, by decreased body mass and improved glucose regulation. These studies have used a novel dietary modification paradigm in nonhuman primates focused on calorie reduction. Results suggest that CR, as mediated by its beneficial effect on body composition and glucose metabolism, could prolong human life by decreasing the incidence of atherosclerosis

### **The Retardation of Aging and Disease by Dietary Restriction.**

Walford R.

1988;

### **The Anti-Aging Plan .**

Walford R.

1994;

### **The Vegetarian Guide to Diet & Salad.**

Walker N.

1940; First Edition 1940 (reprinted numerous times through 1986).

### **Plasma leptin and the risk of cardiovascular disease in the west of Scotland coronary prevention study (WOSCOPS).**

Wallace AM, McMahon AD, Packard CJ, et al.

*Circulation.* 2001 Dec 18; 104(25):3052-6.

**BACKGROUND:** Leptin plays a role in fat metabolism and correlates with insulin resistance and other markers of the metabolic syndrome, independent of total adiposity. Therefore, we hypothesized that raised leptin levels may identify men at increased risk of a coronary event in the West of Scotland Coronary Prevention Study (WOSCOPS). **Methods and Results-** Plasma leptin levels were measured at baseline in 377 men (cases) who subsequently experienced a coronary event and in 783 men

(controls) who remained free of an event during the 5-year follow-up period of the study. Controls were matched to cases on the basis of age and smoking history and were representative of the entire WOSCOPS cohort. Leptin levels were significantly higher in cases than controls (5.87±2.04 ng/mL versus 5.04±2.09 ng/mL, P<0.001). In univariate analysis, for each 1 SD increase in leptin, the relative risk (RR) of an event increased by 1.25 (95% confidence interval [CI], 1.10 to 1.43; P<0.001). There was minimal change in this RR with correction for body mass index (RR, 1.24; 95% CI, 1.06 to 1.45; P=0.006) or with further correction for classic risk factors, including age, lipids, and systolic blood pressure (RR, 1.20; 95% CI, 1.02 to 1.42; P=0.03). Leptin correlated with C-reactive protein (r=0.24, P<0.001) and, even with this variable added to the model, leptin retained significance as a predictor of coronary events (RR, 1.18; 95% CI, 1.00 to 1.39; P=0.05) at the expense of C-reactive protein. CONCLUSIONS: We show, for the first time, in a large prospective study that leptin is a novel, independent risk factor for coronary heart disease

### **God's Chosen Fast .**

Wallis A.

1993;

### **Influences of Calorie Intake on Aging and Cancer .**

Weindruch R, UW-Madison Institute on Aging.

2003

### **The retardation of aging in mice by dietary restriction: longevity, cancer, immunity and lifetime energy intake.**

Weindruch R, Walford RL, Fligiel S, et al.

*J Nutr.* 1986 Apr; 116(4):641-54.

We sought to clarify the impact of dietary restriction (undernutrition without malnutrition) on aging. Female mice from a long-lived strain were fed after weaning in one of six ways: group 1) a nonpurified diet ad libitum; 2) 85 kcal/wk of a purified diet (approximately 25% restriction); 3) 50 kcal/wk of a restricted purified diet enriched in protein, vitamin and mineral content to provide nearly equal intakes of these essentials as in group 2 (approximately 55% restriction); 4) as per group 3, but also restricted before weaning; 5) 50 kcal/wk of a vitamin- and mineral-enriched diet

but with protein intake gradually reduced over the life span; 6) 40 kcal/wk of the diet fed to groups 3 and 4 (approximately 65% restriction). Mice from groups 3-6 exhibited mean and maximal life spans 35-65% greater than for group 1 and 20-40% greater than for group 2. Mice from group 6 lived longest of all. The longest lived 10% of mice from group 6 averaged 53.0 mo which, to our knowledge, exceeds reported values for any mice of any strain. Beneficial influences on tumor patterns and on declines with age in T-lymphocyte proliferation were most striking in group 6. Significant positive correlations between adult body weight and longevity occurred in groups 3-5 suggesting that increased metabolic efficiency may be related to longevity in restricted mice. Mice from groups 3-6 ate approximately 30% more calories per gram of mouse over the life span than did mice from group 2. These findings show the profound anti-aging effects of dietary restriction and provide new information for optimizing restriction regimes

### **Posttranslational quality control: folding, refolding, and degrading proteins.**

Wickner S, Maurizi MR, Gottesman S.

*Science*. 1999 Dec 3; 286(5446):1888-93.

Polypeptides emerging from the ribosome must fold into stable three-dimensional structures and maintain that structure throughout their functional lifetimes. Maintaining quality control over protein structure and function depends on molecular chaperones and proteases, both of which can recognize hydrophobic regions exposed on unfolded polypeptides. Molecular chaperones promote proper protein folding and prevent aggregation, and energy-dependent proteases eliminate irreversibly damaged proteins. The kinetics of partitioning between chaperones and proteases determines whether a protein will be destroyed before it folds properly. When both quality control options fail, damaged proteins accumulate as aggregates, a process associated with amyloid diseases

### **The slimming new water cure.**

Woman's World.

*Women's World Magazine*. 2001

### **Calorie restriction and spontaneous hepatic tumors in C3H/He mice.**

Yoshida K, Inoue T, Hirabayashi Y, et al.

*J Nutr Health Aging.* 1999; 3(2):121-6.

Caloric restriction started at the young adult (YA) stage and the full adult (FA) stage in mice was compared, specifically focussing on whether there would be a delay in the onset time of spontaneous hepatoma or a reduction in its frequency. Caloric restriction lengthened the life spans of both groups, the YA, and FA. Both groups showed striking reductions of spontaneous hepatomas, from 70.9 +/- 3.5% for non-restricted controls down to 35.7 +/- 5.7 and 30.4 +/- 4.0%, for mice restricted from young adult, and from full adult stages, respectively; further, the numbers of tumor-free mice in the restricted groups increased by 45.7% and 38.5%, respectively, from 11.5%, in the non-restricted control. The cumulative incidences of hepatoma in the caloric restricted groups showed a delayed and lower incidence compared with those of the non-restricted group; a parallel delay might result from a weakened activity in tumor-promotion, whereas a lower frequency, might reflect a possible reduction of target cells for hepatomata development. Both effects can be assumed to have resulted from caloric restriction. When cumulative incidences of small hepatomas were compared between the two restricted groups, restriction started at the young adult stage is assumed to have caused fewer initiation stresses, as well as to have delayed promotion, as clearly evidenced by a flatter curve of incidence with a lower total incidence. Thus, the time at which caloric restriction is started plays a critical role in its subsequent effects