**TWENTY-THIRD ANNUAL MEETING** — American Aging Association
**EIGHTH ANNUAL MEETING** — American College of Clinical Gerontology
Friday through Tuesday
October 8-12, 1993
Four Seasons Hotel
1050 Sherbrooke Street West
Montreal, Quebec H3A 2R6

## MINISYMPOSIUM: "Nutritional Intervention in Aging"

*INVITED PAPERS*

1. Meydani, M.: **Overview: Nutritional intervention in aging**
2. Hoffer, L.J.: **Dietary protein requirements in relation to human aging**
3. Schaefer, E.J.: **Aging and plasma lipoproteins**
4. Buring*, J.E., Gaziano, M., Hennekens, C.H.: **Antioxidant supplementation on aging and related diseases**
5. Dawson-Hughes, B.: **Calcium and vitamin D nutrition and aging**

*SUBMITTED PAPERS*

6. Vilenchik, M.M.: **β-carotene, combined with other selected micronutrients, protects against mammary cancer and premature aging and increases life span of irradiated and of non-exposed rats**
7. Niedzwiecki*, A., MacEvilly, C., Pauling, L.: **Effect of megadoses of vitamin C on plasma risk factors for heart disease and structural changes in guinea pig aortas**

## MINISYMPOSIUM: "Intervention of Aging Process by Dietary Restriction"

*INVITED PAPERS*

8. McCarter, R.J.: **Metabolic consequences of dietary restrictions**
9. Richardson*, A., Takahashi, R., Pahlavani, M., Heydari, A.R.: **Mechanism of dietary restriction: transcription of heat shock genes**
10. Yu, B.P.: **How dietary restriction intervenes in age-related membrane deterioration**

*SUBMITTED PAPERS*

11. Lane*, M.A., Ingram, D.K., Cutler, R.G., Tilmont, E.M., Roth, G.S.: **Effect of long-term diet restriction on body composition in nonhuman primates as assessed by morphometry, isotopic dilution and dual energy x-ray absorptiometry**
12. Mervis*, R.F., Dry, J., Kuntz, N., Burton, D., Dvorak, R.M., Osoteo, M., Turturro, A., Lal, H.: **Life-long caloric restriction promotes stability of dendritic branching in the aging mouse neocortex: a quantitative Golgi study**

## MINISYMPOSIUM: "Exercise Intervention in Aging"

*INVITED PAPERS*

13. McCarter, R.J.M.: **Overview: Exercise intervention in aging**
14. Kirwan, J.P..: **Exercise and carbohydrate intolerance in the elderly**
15. Farrar, R.G.: **The effects of treadmill endurance training on aging in Fisher 344 rats**
16. Fiatarone, M.A., Kehayias, J., Roberts, S., Evans, W.J.: **The effects of exercise on frailty in the very old**
17. Nelson, M.: **The effects of exercise on bone health and body composition**
18. Evans, W.J.: **Summary and Concluding Remarks**

*SUBMITTED PAPERS*

19. Willis*, P.E., Parkhouse, W.S.: **Acute exercise restores skeletal muscle sensitivity to insulin-like growth factor**
20. Manfredi*, T., Fielding, R., Ding, W., Cosmas, A., Lee, H.Y., Fiatarone, M. Cannon, J, Evans, W.: **Quantification of exercise-induced muscle damage in older adults**

## MINISYMPOSIUM: "Immunodulators and Aging"

*INVITED PAPERS*

21. Roth, J.A.: **Cytokine influence on neutrophils in an animal model system**
22. Babiuk, L.A.: **Immunobiology of cytokines - their role in recovery from disease or immunopathology**
23. Marshall, G.D.: **Cytokine production in the elderly: implications for therapeutic manipulations**

24. Tizard, I.: **Use of immunomodulators to effect wound healing in an aging animal model system**
25. Busbee*, D., Merriam, E., Campbell, B.: **Immune function differences in aged and young rodents: effects of an acetylated β(1,4)-linked polymannose as an immunomodulator**
26. Daynes, R.A.: **The relationship between growth hormone responsiveness and steroid hormones in aging**

*SUBMITTED PAPERS*

27. Liu, Y., Cortopassi*, G.: **Somatic mutations at the BCL-2 locus occur more frequently among aged humans**
28. Joshi*, D., Lekhtman, I., Billiar, R.B., Miller, M.M.: **Luteinizing hormone (LH) responses to gonadotropin hormone releasing hormone (GnRH) and N-methyl D-aspartic acid (NMA) in young and old estrogen ($E_2$)-treated female C57BL/6J mice**

## SUBMITTED PAPERS
## Poster Session

33. Weinreb, O., Dovrat*, A.: **Ultra violet radiation promotes the aging process of the eye lens**
34. Verdon*, J., Kozak, J., Robertson, M.A.: **Body mass index, dementia, and severity of dementia in older aged Canadians: results from the Canadian study of health and aging**
35. King, G., Ordman*, A.B.: **Rate of excretion of vitamin C in human urine**
36. Millar*, J.S., Lichtenstein, A.H., Hachey, D.L., Cohn, J.S., Cuchel, M., Dolnikowski, G.C., Schaefer, E.J.: **Age-associated increase in very low density lipoprotein and low density lipoprotein apolipoprotein B-100 concentrations are due to changes in both production and catabolism**
37. Payette*, H., Gray-Donald, K.: **Adequacy of energy intake among elderly receiving community support services**
38. Cosmas*, A., Ding, W., Bronson, R., Manfredi, T.: **Age and diet effects on skeletal muscle tubular aggregates**
39. Pipkin*, J.L., Hinson, W.G., Lyn-Cook, L.E., Duffy, P.H., Feuers, R.J., Hart, R.W., Casciano, D.A.: **Induction of a 53KDa phosphoprotein in aged caloric restriction rats**
40. Forster, M.J., Lal*, H.: **Retardation of age-related declines in motor and cognitive functions by caloric restriction: longitudinal studies of inbred mice**
41. Chen*, L., Snyder, D.: **Effects of aging and moderate dietary restriction on blood parameters of rats**
42. Johnson*, C., Gerson, B., Jibrini, M., Podolsky, S.: **Longitudinal evaluation of long-term diabetes markers**
44. Fordyce*, D.E., Wehner, J.M.: **The effects of exercise on learning performance and associated hippocampal functioning: evaluation of young middle and old ages of initiation to life-long exercise**
87. Doubal*, S., Kucová, D.: **Growth factors and brain aging**

## MINISYMPOSIUM:
## "Current Pharmacological Strategies for Ameliorating Brain Aging"

*INVITED PAPERS*

46. Fanelli, R.J.: **Evidence for the efficacy of nimodipine in the treatment of disorders of brain aging**
47. Carney, J.M.: **Prevention and treatment of brain damage associated with Alzheimer's disease, Parkinson's disease, ischemic reperfusion injury, hyperoxia, and aging by nitron trapping compounds**
48. Williams, L.R.: **Oxidative stress, neurodegeneration, and neurotrophic therapy**
50. Ivy*, G.O., Rick, J., Murphy, P., Reid, C., Head, E., Milgram, N.W.: **Effects of l-deprenyl on manifestations of brain aging in the rat and dog**
51. Kitani*, K., Carrillo, M.C., Kanai, S., Sato, Y., Miyasaka, K., Ivy, G.W.: **Factors regulating the optimal dose of (-)diprenyl (DPN) for increasing antioxidant enzyme activities**

*SUBMITTED PAPERS*

52. Kitani*, K., Carrillo, M.C., Kanai, S., Sato, Y., Miyasaka, K., Ivy, G.O.: **The effect of a long term (6 months) treatment with (-)deprenyl on antioxidant enzyme activities in selective brain regions in old female Fischer 344 rats**
53. Carrillo*, M.C., Kitani, K., Kanai, S., Sato, Y., Miyasaka, K., Ivy, G.O.: **(-) Deprenyl (DPN) increases activities of superoxide dismutase (SOD) and catalase (CAT) in certain brain regions in old male mice**

## Annual Luncheon

Excellence in Journalism Award
Walter Nicolai Prize
Research Award
Appointment of Trustees
Presidential Address
Distinguished Achievement Award

56. **Walter Nicolai Lecture**

## Submitted Papers - Oral Presentations

57. Morgan*, D.G., Schreier, W.A., Holcomb, L.A., Gordon, M.N.: **Exaggerated glial reactions to deafferentation in aged rats**
58. Bétard*, C., Gee, M., Houde, L., Chagnon, P., Larrivée, D., Gauvreau, D.: **Apolipoprotein e4 allele frequency is increased in sporadic Alzheimer's disease patients**
59. Jarvik*, L.F., Matsuyama, S.S., Scheibel, A., Vinters, H.: **Autopsy diagnosis of Alzheimer disease**
60. Grad, B.R., Rozencwaig*, R.: **Role of melatonin and serotonin in aging: an update**
62. Camacho*, M.E., Crilly, R.G.: **Subjective sleep quality in a geriatric assessment unit (GAU)**
63. Hershey, D.: **Dynamic metabolic testing for longevity and fitness**
64. Huang, J., Davies, D., Cortopassi*, G.: **Detection of increased mtDNA damage in aging mice**
66. Meydani*, M., Martin, A., Ribaya-Mercado, J., Gong, J., Russell, R., Blumberg, J.: **Increase of antioxidant capacity of plasma by dietary β-carotene supplementation in older subjects**
68. Vogt, B., Leutzinger, Y., Richie, Jr.*, J.: **Fasting-induced depletion of glutathione in the aging mouse**
69. Schnaper*, H.W., Curry, C., Jain, A.K., Weidler, D., et al.: **Are all diuretics equally hazardous in older hypertensives?**
70. Vilenchik, M.M.: **Mechanisms of the premature/ accelerated and of delayed/retarded aging and their regulation for prevention of degenerative diseases**
71. Massie*, H., Aiello, V.: **Reducing exposure to visible light increases the life span of mice**

## MINISYMPOSIUM: "Genetic Regulation in the Study of Aging"

*INVITED PAPERS*

72. Baker, G.: **Types and modes of interventive strategies in the process of aging**
73. Chalifour*, L., Holder, E., Fahmy, R., Mou, L., Eddin, A., Moustafa, A., Ly, D., Dorrance, T., Bonyadi, S., Vestergaard, J., Salloukh, H.: **Characterization of hypertrophy-associated gene expression**
74. Hutchinson, T: **Molecular genetic analysis of genes for altered senescence**
75. Wang*, E., Lee, M.-J., Pandey, S.: **Cell cycle traverse, fibroblast senescence, and programmed cell death**
76. Mastrangelli, A.: **Direct in vivo gene transfer to the central nervous system using replication deficient, recombinant adenovirus vectors**
77. Vijg, J.: **Genetic instability, cancer and aging: new methods for disease gene identification and diagnosis**
78. Martin, G.M.: **Transgenic mouse models of longevity**

*SUBMITTED PAPERS*

79. Busbee*, D., Schroeder, M., Srivastava, V., Miller, S.: **DNA polymerase α accessory protein (αAP) enhances DNA binding and activity of enzyme isolated from aged human donors**

## MINISYMPOSIUM: "Mobility, Function and Aging"

*INVITED PAPERS*

80. Enesco, H.E.: **A biological perspective on mobility and aging**
81. Bickford, P.: **Alterations in neurophysiology and motor learning in aged rodents**
82. Bisson, M.S.: **Bipedalism, aging, and early hominid adaptations**
83. Tideiksaar, R.: **Assessment and measurement of human mobility: clinical and research perspectives**
84. Robbins, S.: **Somato-sensory aging in relation to proprioception and balance**
85. Trickey*, F., Gosselin, C., Maltais, D.: **Role of home environment in mobility and transfers with ageing**

*SUBMITTED PAPERS:*

86. Dixon*, L.K., Karkowski-Shuman, L.: **Age-related changes in horizontal locomotor activity in Drosophila inbred lines**

1

OVERVIEW: NUTRITIONAL INTERVENTION IN AGING. Mohsen Meydani*, Antioxidant Research Laboratory, USDA Human Nutrition Research Center on Aging at Tufts University. Boston MA 02111.

Aging is multifactorial and is dependent on genetic, life-style, and environmental factors. Nutrition may play a role in the progressive decline of several body functions with aging. Malnutrition is a common problem in both institutionalized as well as free-living elderly people. Age-dependent decline in energy intake is the most consistent finding in the population surveys. This is associated with a progressive decline in protein intake and lean body mass. Surveys also indicate that many of the elderly have vitamin and mineral intakes at 2/3 of the RDA. There is concern that many elderly are at risk of subclinical or marginal deficiencies of certain micronutrients such as, iron, calcium, zinc, thiamin, riboflavin, folic acid, niacin and vitamins A, D, and C. The manifestation of marginal deficiency of nutrients added to the normal effects of aging can undermine independence and predispose elderly to chronic diseases and diminish the quality of their life. Providing nutritional support and supplementation of the elderly with certain micronutrients have been shown to improve some of these age-associated conditions. Thus, nutritional intervention can be used as a practical and cost-effective way to improve health status of the elderly and reduce age-associated disabilities.

2

DIETARY PROTEIN REQUIREMENTS IN RELATION TO HUMAN AGING. L. John Hoffer, McGill Nutrition and Food Science Centre, McGill University, Montreal, QC.

Protein is an essential nutrient because the cyclic process of body protein breakdown and resynthesis is inherently inefficient. The N from nonreutilized amino acids is converted to urea and excreted, and hence must be replaced from the diet. Also, replacement amino acids entering the body from the diet are utilized with imperfect efficiency. Thus, the minimum protein requirement is determined by the maximum efficiency of endogenous amino acid reutilization and dietary amino acid conservation. There is considerable variability in protein requirement among individuals, but it is true in general that maximum efficiency of dietary and endogenous amino acid utilization can be attained only when concurrent energy and micronutrient provision are adequate and physiologic stress is absent. Existing data on protein needs of the elderly are limited and inconsistent; no data, however, convincingly demonstrate minimum protein requirements to be higher than that of young adults when expressed per kg of body weight. Since skeletal muscle mass is reduced in old age, this could indicate a slightly higher protein requirement per unit of active protein tissue in some elderly people. Perhaps this comes about simply because more rapidly turning over visceral proteins make a greater contribution to whole body protein metabolism when the mass of skeletal muscle is reduced. Protein nutrition in old age merits special attention, however. Severe protein malnutrition develops more readily and is more difficult to reverse in elderly patients. Also, eating difficulties are common in old age and may result in energy and micronutrient deficiencies which can impair the efficiency of amino acid utilization, thereby increasing the maintenance protein requirement.

3

**AGING AND PLASMA LIPOPROTEINS**

E.J. Schaefer USDA Human Nutrition Research Center on Aging at Tufts University, Boston, MA 02111

Hypercholesterolemia due to elevations in plasma low density lipoprotein (LDL) cholesterol ($\geq$160 mg/dl or 4.1 mmol/l) has been identified as a major risk factor for coronary heart disease, and guidelines have been established for its management. The cornerstone of therapy is a diet restricted in total fat (<30% of calories), saturated fat (<7% of calories), and cholesterol (<200 mg/day). Such diets lower LDL cholesterol 15-20% in elderly men and women. It is well known that LDL cholesterol levels increase significantly with age due to decreases in LDL receptor mediated catabolism. More recently we have documented that aging is also associated with increases in very low density lipoprotein (VLDL) apolipoprotein (apo) B secretion rates and decreased conversion of VLDL apoB to LDL apoB. This results in increased deposition of lipid in the liver, presumably leading to down regulation of LDL receptor activity. Menopause results in significant increases in LDL cholesterol in females due to decreased LDL receptor mediated clearance. ApoE isoforms also play an important role in regulating LDL cholesterol levels. With aging there is a significant increase in central fat deposition and a decrease in body muscle mass. Available evidence suggests that a prudent diet and a significant exercise program can prevent the age related increase in VLDL and LDL. Such measures also reduce the age related increase in cardiovascular risk.

4

ANTIOXIDANT SUPPLEMENTATION ON AGING AND RELATED DISEASES. Julie E. Buring,* J. Michael Gaziano, and Charles H. Hennekens Harvard Medical School, Brigham and Women's Hospital, Boston, MA 02215

Recent evidence suggests that oxidative damage, particularly to low density lipoprotein, may be involved in the development and progression of atherosclerosis. Dietary antioxidants such as alpha tocopherol, ascorbic acid, and carotenoids represent one possible defense against oxidative stress, raising the possibility that these agents may prevent or delay the development of atherosclerotic disease. A growing body of observational data suggests inverse association between dietary intake or plasma levels of dietary antioxidants and cardiovascular disease. In addition, limited randomized trial data further suggest these agents may reduce the risk of subsequent cardiovascular events. While epidemiologic evidence supports the possibility that dietary antioxidants may play a role in the prevention of atherosclerosis, these agents represent a promising but unproven means of reducing the risk of cardiovascular disease. Definitive data await the results of ongoing randomized trials such as the Physicians' Health Study of beta-carotene among 22,071 US male MDs and the Women's Health Study of beta-carotene and vitamin E among approximately 40,000 US female nurses.

5

CALCIUM AND VITAMIN D NUTRITION AND AGING. Bess Dawson-Hughes, USDA Human Nutrition Research Center at Tufts University, Boston, MA 02111.

Calcium and vitamin D requirements of the elderly are the subject of considerable controversy. The effect of increasing calcium intake on rate of bone loss appears to depend on the usual calcium intake level and the stage in life. For example, in women within the first 5 years after menopause, supplemental calcium does not reduce the rate of bone loss. Women beyond this age are more responsive to supplemental calcium, particularly if they have low usual dietary calcium intakes. Calcium absorption efficiency declines with aging, so that the very elderly may require higher intakes. Recent estimates of the calcium requirement for adults range from 800 to 1,500 mg daily.

Defining optimal vitamin D is complex because vitamin D is acquired from solar-induced skin synthesis as well as from diet. Sun exposure stimulates both the synthesis and degradation of vitamin D in the skin. Synthesis of vitamin D is also influenced by latitude. With aging, both skin synthesis and intestinal absorption of vitamin D are reduced. Treatment with vitamin D is now known to reduce fracture rates in institutionalized elderly subjects who have low serum 25-hydroxyvitamin D levels. Among healthy ambulatory adult women, an intake of about 500 IU per day will prevent seasonal hormone changes and minimize wintertime bone loss from the spine, at least over the short term. Longer-term benefit in this population remains to be determined.

6

BETA-CAROTENE, COMBINED WITH OTHER SELECTED MICRONUTRIENTS, PROTECTS AGAINST MAMMARY CANCER AND PREMATURE AGING AND INCREASES LIFE SPAN OF IRRADIATED AND OF NON-EXPOSED RATS, M. M. VILENCHIK, CORNELL UNIVERSITY COLLEGE OF VETERINARY MEDICINE, ITHACA, NEW YORK 14853

A combination of non-toxic antimutagens was prepared using the fungus *Blakeslea trispora* mutant (M. M. Vilenchik et al., 1988, 1990, 9th International Congress of Radiation Research, Toronto, July 1991). This combination (1) protects rats against (a) liver DNA damage induced by hepatocarcinogen N-nitrosodimethylamine, (b) spontaneous and radiation induced mammary cancer, and (c) premature aging of thymus; (2) increases life span of control and of exposed rats; and (3) protects human skin against radiation-induced damage. Results of our clinical studies indicate also age-dependent depletion of certain carotenoids in the blood of humans who were under risk of accelerated aging. Our current research to optimize the delivery of avian retroviral vectors to the embryonic cells in vivo and the data from the literature suggest, that the mixture of selected micronutrients can be combined with molecular gene and/or tissue transplantation intervention into the aging process.

7

EFFECT OF MEGADOSES OF VITAMIN C ON PLASMA RISK FACTORS FOR HEART DISEASE AND STRUCTURAL CHANGES IN GUINEA PIG AORTAS. A. Niedzwiecki, C. MacEvilly, L. Pauling Linus Pauling Institute of Science and Medicine, Palo Alto, CA 94306

Importance of vitamin C in maintaining of vascular integrity and also the relation of majority of heart disease risk factors to ascorbic acid deficiency indicates the role of this vitamin in etiology of cardiovascular disease. The purpose of this study was to determine whether megadoses of vitamin C administered to guinea pigs have an antiatherogenic effects, compared to scurvy preventing supplements and to the recommended optimal doses of ascorbate for this animal. Guinea pigs (animals, that like humans, do not synthesize vitamin C) were divided into two diet groups (atherogenic and standard) supplemented with 1 mg, 25 mg, and 1000 mg of vitamin C per day. Histological changes in the aortic extracellular matrix proteins (collagen, elastin, mucopolysaccharides) observed in two low vitamin C supplemented groups but not in a high ascorbate group suggest, that suboptimal vitamin C level may promote the initiation of atherogenic process in the vessel wall. Moreover, the analysis of several plasma risk factors for heart disease in animals fed both atherogenic and standard diets shows their relation to vitamin C intake. The beneficial effects of megadoses of vitamin C on some plasma risk factors and their correlation with vitamin C tissue level is demonstrated. The results also suggest an increasing demand for vitamin C in atherogenic type of diet in guinea pigs.

8

METABOLIC CONSEQUENCES OF DIETARY RESTRICTION. Roger J. McCarter*, Physiology, Univ. of Texas Hlth. Sci. Ctr., San Antonio, TX 78284-7756.

Dietary restriction (DR) is the only manipulation known to consistently retard aging processes in mammals. This effect has been shown for DR initiated at weaning or during young adulthood. It is also well established that DR decreases metabolic rate (MR) per unit mass. We investigated the possibility that decreased MR is an important factor in the anti-aging action of DR. MR of male SPF Fischer 344 rats was measured under usual living conditions over 24-hour periods by analysis of air entering and leaving standard cages using rats fed ad libitum (A-S), fed 60% ad lib from 6 weeks of age (R-S) and with (A-E,R-E) or without (A-S,R-S) exercise wheels in cages. Results show MR of restricted rats is only lower for 6-12 weeks following initiation of restriction. R-E rats had significantly higher MR over most of the lifespan. Survival of rats was R-E>R>A,A-E. Maximum lifespans were R-E=R> A=A-E. These results show MR is not an important factor in the mechanism of DR. Recent reports show DR initiated during adulthood in rodents and non-human primates results in prolonged decrease of resting MR. This is consistent with earlier data showing only slow adaptation of body mass to DR when initiated in adulthood. However, taken together all data indicate that while DR does decrease MR, this is not a necessary condition for age retardation. Rather, other results show that DR improves survival by altering characteristics of fuel use, permitting adequate flux of nutrients under conditions less harmful to maintenance of cellular homeostasis.

9

**MECHANISM OF DIETARY RESTRICTION: TRANSCRIPTION OF HEAT SHOCK GENES.** A. Richardson*, R. Takahashi, M. Pahlavani, and A.R. Heydari, GRECC at Audie Murphy Memorial VA Hospital, and Department of Medicine, The University of Texas Health Science Center at San Antonio, San Antonio, TX, 7828.

Dietary restriction is the only experimental manipulation known to increase longevity and retard the aging of mammals, and our laboratory has proposed that changes in gene expression are an important component of the antiaging mechanism of dietary restriction. We have shown that dietary restriction alters the age-related changes in the expression of a variety of genes and that this alteration occurs at the level of transcription for many genes. To determine how dietary restriction alters the transcription of genes, we have studied the effect of age and dietary restriction on the expression of heat shock genes (hsp70, hsc70 and grp78) in suspensions of freshly isolated hepatocytes and spleen lymphocytes. The expression of hsp70 is induced markedly after hyperthermia. The induction of hsp70 transcription by hyperthermia (42.5°C) was approximately 50% lower for cells isolated from old rats (24 months of age) compared to cells isolated from young/adult rats (6 months of age). Studies with hepatocytes isolated from rats fed a caloric-restricted diet (60% of *ad libitum*) showed that dietary restriction resulted in a significantly higher level of hsp70 expression after hyperthermia, and this increased expression was due to an increase in the transcription of the hsp70 gene. HSF (heat shock transcription factor) plays a critical role in the regulation of hsp70 transcription. Immediately after heat shock, this protein oligomerizes, binds to the heat shock element on the promoter of the hsp70 gene and hsp70 transcription is initiated. Using a gel-shift assay, it was found that the amount of HSF in cell extracts capable of binding to the heat shock element decreased with age, and this decrease was reversed by dietary restriction. Therefore, our data suggest that the alterations in hsp70 transcription that occur with dietary restriction arise from changes in the level of a specific transcription factor, HSF.

10

HOW DIETARY RESTRICTION INTERVENES IN AGE-RELATED MEMBRANE DETERIORATION. Byung Pal Yu, Department of Physiology, University of Texas Health Science Center, San Antonio, Tx 78284-7756.

The susceptibility of membrane lipids to oxidative alterations is related to two inherent properties, the peroxidizability of lipids due to the degree of unsaturation, and membrane-mediated free radical generation. To assess the membrane alterations with age, hepatic mitochondrial, microsomal, and brain synaptosomal membranes were tested. The results show that changes in peroxidizability were caused by increased polyunsaturated fatty acids such as 20:4, 22:5 and 22:6, leading to loss in membrane fluidity due to increased peroxidation. Further tests on age-related changes in chol/phospholipid ratios revealed that cholesterol is not a factor in age-related membrane rigidity. Another factor contributing to age-related membrane rigidity may be the increased accumulation of endogenous 4-hydroxynonenal (4-HNE), a major peroxidation by-product. In the aged brain, similar membrane deteriorations were observed. The amount of isolated synaptosomal yield was significantly reduced in an ad libitum fed group after 12 months of age. The free radical generation by synaptosomes was much elevated in syanptosomes of 24 month old ad libitum fed rats. The significance of these studies is highlighted by the fact that these membrane deteriorations with age can be ameliorated by the protective action of dietary restriction. Results further support that the maintenance of cellular homeostasis is the underlying anti-aging action of dietary restriction. (Supported by AG0-1188)

11

**EFFECT OF LONG-TERM DIET RESTRICTION ON BODY COMPOSITION IN NONHUMAN PRIMATES AS ASSESSED BY MORPHOMETRY, ISOTOPIC DILUTION AND DUAL ENERGY X-RAY ABSORPTIOMETRY.**

Mark A. Lane*, Donald K. Ingram, Richard G. Cutler, Edward M. Tilmont, and G. S. Roth, Gerontology Research Center, National Institute on Aging, NIH, Baltimore, MD 21224.

In 1987 the NIA initiated a study to develop a primate model of diet restriction (DR). The objective was to determine if the rate of aging could be altered in long-lived mammalian species similar to the extensive results reported previously in a variety of shorter-lived animal models. Currently the colony consists of 57 male and 59 female rhesus monkeys and 29 male squirrel monkeys within selected age groups representative of the life span of each species. Diet restricted monkeys are fed at a level 30% below that provided to age- and weight- matched controls approximating ad libitum feeding. To reduce the risk of malnutrition in the restricted monkeys, diet premixes are supplemented with 40% greater vitamin, mineral, and trace element content. Diet composition does not differ between restricted and control animals. Several marked effects of age and DR on body composition have been noted using a wide variety of techniques. Previous reports have demonstrated the effect of DR on various morphometric measurements including body weight, crown-rump length, body mass index, skin fold thickness and various circumferential measurements. After more than 6 years on DR several of these measures exhibit continuing effects of reduced feeding. Isotope dilution studies have shown that DR reduced lean body mass, but surprisingly, not percent body fat in at least one subgroup of monkeys. Dual energy absorptiometry (DEXA) studies have confirmed the effect of DR on lean body mass and percent body fat. In addition, age- and diet- induced changes in total body and spine bone mineral content and bone density have been seen.

12

**LIFE-LONG CALORIC RESTRICTION PROMOTES STABILITY OF DENDRITIC BRANCHING IN THE AGING MOUSE NEOCORTEX: A QUANTITATIVE GOLGI STUDY.**

Ronald F. Mervis[1]*, Jessica Dry[1], Nick Kuntz[1], Diana Burton[1], Robert M. Dvorak[1], Maria Osoteo[1], Angelo Turturro[2], and Harbans Lal[3], [1]NeuroMetrix Imaging Research, Inc., Columbus, Ohio 43212, [2]National Center for Toxicology Research, Jefferson, Arkansas 72079, [3]Dept of Pharmacology, Texas College of Osteopathic Medicine, Ft. Worth, Texas 76107

The effects of life-long caloric restriction on neocortical dendritic branching in the aging and senescent mouse were evaluated in Golgi preparations. Methods. After weaning, female B6D2F1 mice were fed either a standard chow (Control) or 60% caloric restricted (CR) plus vitamin supplementation. Controls were sacrificed at 5, 10, 19, and 27 months-old. CR-fed groups were sacrificed at 5, 10, 19, 27, and 39 months-old. Using coded slides, camera lucida drawings were made of the basilar dendritic trees of randomly selected layer II/III pyramidal cells from the parietal cortex. They were quantified using Sholl analysis. Results. In aging control mice, there was a loss of branching from 5 to 10 months, a gain in branching from 10 to 19 months, and a final loss from 19 to 27 months (no control mouse survived to 39 months-old). The CR-fed group also showed a loss of branching from 5 to 10 months and then a stability in branching out to 39 months-old. Conclusions. In pyramidal cells of aging (control) mice, an initial loss of dendritic material is followed by dendritic hypertrophy (probably a compensatory response by surviving cells due to age-related loss of neighboring neurons). Ultimately, in the senescent controls there is a final involutional stage. By comparison, in caloricallly restricted mice, after an initial loss of dendritic material, there was neither hypertrophy nor atrophy even to very old age (39 months-old). This suggests that there was stability in both cortical neuronal population (no compensatory hypertrophy) and in dendritic membrane (no end-stage atrophy). The results strongly imply that life-long CR can attenuate normally-occurring age-related changes and maintain normal cortical circuity.

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EXERCISE AND CARBOHYDRATE INTOLERANCE IN THE ELDERLY. John P. Kirwan*, Wendy M. Kohrt and John O. Holloszy, Noll Laboratory, The Pennsylvania State University, University Park, PA 16802 and Section of Applied Physiology, Washington University School of Medicine, St. Louis, MO 63110.

Aging is frequently associated with the development of insulin resistance and the deterioration of glucose tolerance. Decreased physical activity with advancing age may contribute to the development of these defects in carbohydrate metabolism. In order to identify the role that exercise may play in ameliorating some of these abnormalities we have examined the effects of endurance exercise on insulin resistance and insulin action in older individuals. In one study, insulin resistance was examined using the euglycemic clamp procedure in a group of 8 mild non-insulin dependent diabetics (Age 64 $\pm$ 2 yr; BMI 33 $\pm$ 4 $kg \cdot m^{-2}$) before and after 7 d of intense exercise (30 min/d treadmill running + 30 min/d cycle ergometry, 75% $VO_{2max}$). Plasma glucose was maintained at 90 mg/dL and insulin was infused at 40 and 1000 $mU \cdot m^{-2} \cdot min^{-1}$ for two sequential 120 min stages. Steady state glucose infusion rates (SSGIR) were calculated for the final 30 min period of each stage of the clamp. SSGIR was significantly improved after compared to before the 7 d training period. In a separate study we evaluated the effect of a 9-month endurance exercise program on the glucose-stimulated insulin response and glucose disposal rate (M), using the hyperglycemic clamp procedure in 12 people aged 65 $\pm$ 1 yr with normal glucose tolerance. $VO_{2max}$ increased 23% in response to the exercise program. Plasma insulin concentration (I) during hyperglycemia (180 mg/dL) was lower (36 $\pm$ 6 $uU \cdot ml^{-1}$ vs 26 $\pm$ 5 $uU \cdot ml^{-1}$; $P<0.05$) after training. Insulin sensitivity was improved by exercise. During hyperglycemia the M was unchanged despite the blunted insulin response, resulting in an increase in the M/I ratio to a level similar to that found in young subjects. Thus, regular exercise was effective in reducing hyperinsulinemia and improving the insulin sensitivity of older individuals. Data from these studies strongly support the use of exercise as a stimulus to reverse some of the carbohydrate intolerance associated with aging.

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THE EFFECTS OF EXERCISE ON FRAILTY IN THE VERY OLD. Maria A. Fiatarone*, Joseph Kehayias, Susan Roberts, and William J. Evans, USDA Human Nutr Res Center on Aging at Tufts Univ, Boston, MA 02111.

Muscle weakness and atrophy have been linked to physical frailty in the elderly. Although disuse of skeletal muscle and undernutrition have been often cited as potentially reversible etiologies of this frailty, the efficacy of interventions targetted specifically towards these deficits has not been previously evaluated in a large controlled trial. We conducted a randomized, placebo-controlled clinical trial of high-intensity progressive resistance training and multi-nutrient supplementation in 100 nursing home residents. Individuals were randomized to a 10-week course of either lower extremity resistance exercise, nutritional supplementation, both active interventions, or a placebo-controlled condition. The primary outcomes of this trial were muscle strength, muscle cross-sectional area, and functional mobility. Ninety-four percent of the 63 women and 37 men of mean age 87.0 $\pm$ 0.4 yrs (range 72-98) enrolled completed the intervention. Exercise significantly improved muscle strength by 111.6% vs. no sig. change in the non-exercising subjects ($p<0.0001$). Gait velocity increased by 11% after exercise, while declining by 0.4% in the non-exercisers ($p=0.013$); and stair-climbing power improved by 27.6% compared to 4.4% ($p=0.003$). Muscle cross-sectional area by computerized tomography scanning of the mid-thigh increased after exercise. The nutritional supplement increased body weight, but had neither an independent nor additive effect on any primary outcome measure. Total energy intake was significantly increased only in those receiving both exercise and nutritional supplementation. We conclude that high-intensity resistance training is a feasible and effective means to counter muscle weakness, atrophy, and physical frailty in the oldest old. Multi-nutrient supplementation without exercise may reduce *ad libitum* food consumption, and does not further improve outcomes related to physical frailty over a 10 wk period.

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THE EFFECTS OF EXERCISE ON BONE HEALTH AND BODY COMPOSITION. Miriam Nelson, USDA Human Nutrition Research Center on Aging at Tufts University, Boston, MA 02111.

Osteoporosis is a major public health problem that is characterized by low bone mass and increased susceptibility to fractures, primarily in the hip, spine, and wrist. It is estimated to cause 1.3 million fractures annually in the United States in people aged 45 years and older. Physical activity and weight bearing are important mechanical stimuli for bone gain whereas physical inactivity has been implicated in bone loss. Indeed, both cross-sectional and longitudinal studies examining the effects of exercise and bone have for the most part shown positive results. In the literature there are both aerobic and strength training studies, with both types of exercise showing positive results. However, not all of the studies have been positive, probably because of differences in exercise protocols (either being more vigorous or less vigorous) and measurement techniques used. In addition, it is important to point out that strength training has the added benefit of improving strength which may be important for the maintenance of balance and the prevention of falls. Although the current research is far from conclusive, an exercise regimen should include vigorous exercise, including both strength training and aerobic exercise.

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QUANTIFICATION OF EXERCISE-INDUCED MUSCLE DAMAGE IN OLDER ADULTS. Thomas Manfredi*, Roger Fielding, Wenjing Ding, Arthur Cosmas, Ho Yong Lee, Maria Fiatarone and Joseph Cannon and William Evans, Univ. of Rhode Island, Exercise Science, Kingston, R. I. 02881; USDA Human Nutrition Research Center on Aging, Tufts Univ., Boston, MA. 02111; Univ. of Connecticut, School of Allied Health, Storrs, CT. 06269; General Hospital, Pathology, Cranston, R.I. 02920.

The purpose of this study was to compare the effects of exercise-induced muscle damage in older adults, ages 60 to 75 years, using stereological techniques. Needle biopsies were taken from the vastus lateralis before and immediately after eccentric cycling at a prescribed % $V02max$. Muscle samples were fixed for electron microscopy and micrographs taken at a magnification of 12,000X were analyzed for volume fractions of damaged Z bands ($V_Z$), focal damage ($V_{fd}$), I ($V_I$) and A ($V_a$) bands, and sarcoplasm ($V_S$). Compared to pre exercise samples, post samples showed evidence of mitochondrial and sarcolemma damage. Volume fractions of Z band damage and focal damage before and after exercise increased from 0.20% to 9.90% and 1.60% to 18.70% ($p<0.05$), respectively. We also observed a decline in $V_S$ ($p<0.05$) and an increase in $V_I$ ($p<0.01$), suggesting a stretching of the I band. We conclude that exercise-induced muscle damage in older adults results in quantitative increases in volume density of the I band associated with Z band and focal damage and a lessening of sarcoplasm volume.

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ACUTE EXERCISE RESTORES SKELETAL MUSCLE SENSITIVITY TO INSULIN-LIKE GROWTH FACTOR-1. Philippa.E.Willis* and Wade.S. Parkhouse. School of Kinesiology, Simon Fraser University, Burnaby, B.C. Canada, V5A 1S6.

The purpose of this study was to determine the effects of an acute bout of exercise on the responsiveness of skeletal muscle to insulin-like growth factor-1 (IGF-1) in animals of different ages. Mice (C57Bl/6) aged 4 and 12 months were divided into control or exercise groups. Exercised animals were sacrificed 12 hours following a low intensity treadmill run (12 m/min @ 8% grade for either 1 or 2.5 hours). Protein synthesis, degradation and net protein degradation were measured in an *in vitro* isolated muscle preparation in the absence or presence of different doses of IGF-1 in control and exercised animals. Results showed that protein synthesis rates decrease with increasing age with no change in the rates of protein degradation in control animals. In the soleus from the 4 month control mice, protein synthesis increased in response to a sub-maximal dose of IGF-1 (20nM), but this response was abolished in the 12 month old tissue. Following an acute exercise bout (2.5 hours), protein synthesis increased in the soleus of both age groups and net protein degradation only increased in the 12 month animals, with protein synthesis increasing to a greater extent than net protein degradation. The rates of protein synthesis of acutely exercised soleus of 12 month old animals increased in response to 20nM IGF-1. It was concluded that with increasing age protein synthesis decreases, with little change in degradation rates and that low intensity aerobic exercise of long duration increases protein synthesis rates and restores the sensitivity of slow twitch skeletal muscle to sub-maximal levels of IGF-1.

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CYTOKINE INFLUENCE ON NEUTROPHILS IN AN ANIMAL MODEL SYSTEM. James A. Roth, College of Veterinary Medicine, Iowa State University, Ames, Iowa 50011.

Neutrophils are important components of both native and acquired immunity. They are capable of responding rapidly to many infectious agents in the absence of a humoral and cell-mediated immune response and, thus play a major role in first line defense against infectious agents. Their activity can be enhanced by the presence of specific antibody or cytokines released during a cell-mediated immune response. Therefore they also play a role in acquired immunity. Aspects of neutrophil function have been shown to be decreased in the elderly. In addition, numerous factors have been shown to inhibit neutrophil function. These factors are associated with an increased susceptibility to infection. We have investigated several of these factors in cattle including viral infection, glucocorticoids, and bacterial virulence factors. In addition we have shown that young calves and cows at the time of parturition have decreased neutrophil function. These decreases in neutrophil function in cattle have been associated with increased susceptibility to bacterial pneumonia and mastitis. *In vitro* and *in vivo* studies have been conducted attempting to overcome the suppressed neutrophil function in cattle using recombinant cytokines and cytokine inducers. Recombinant bovine interferons (alpha and gamma), interleukin -1, tumor necrosis factor, granulocyte colony stimulating factor and granulocyte-macrophage colony stimulating factor have all been shown to enhance bovine neutrophil function *in vitro* and *in vivo.*

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IMMUNOBIOLOGY OF CYTOKINES - THEIR ROLE IN RECOVERY FROM DISEASE OR IMMUNOPATHOLOGY. Lorne A. Babiuk, Veterinary Infectious Disease Organization, Saskatoon, Saskatchewan, Canada S7N 0W0.

Cytokines are a family of molecules which are integral communication vehicles responsible for regulating specific and nonspecific defense mechanisms of the host. However, the application of these cytokines in medicine requires a thorough understanding of the interactions between the cytokines, the host, and the pathogen. Recent studies clearly indicate that the same cytokines can be produced by different cells, they have multiple activities, often overlapping between different cytokines, they can act synergistically or antagonistically and that different cytokines are produced at different stages of an infectious process (early and late cytokines). Furthermore, it is clear that the constellation of cytokines produced can dramatically influence the immune response such that it can primarily be a cell mediated or a humoral immune response. Depending on the specific host defense mechanisms required for recovery from the specific disease, shifting the immune response to either cellular or humoral immunity may exacerbate the disease or the cytokines themselves may actually induce immunopathology. Thus, the appropriate kinetics and balance of cytokines induced during the infection process is crucial for recovery from infection as well as for induction of immunity following vaccination. Following a general description of cytokines in infectious disease examples of their use in controlling viral or bacterial infections in a bovine respiratory, porcine respiratory and a mastitis model will be presented.

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CYTOKINE PRODUCTION IN THE ELDERLY: IMPLICATIONS FOR THERAPEUTIC MANIPULATIONS Galen D. Marshall, Division of Allergy & Clinical Immunology, University of Texas Medical School, Texas Medical Center, Houston, TX 77030

Increased incidence of and mortality from diseases associated with senescence of the immune response is an expected consequence of aging in humans. The exact mechanism associated with this is not fully understood, but includes a decrease in immunocompetent cell numbers vs function. Review of the literature suggests that the aging process is associated with decreased numbers of immunocompetent T cells. Residual T cells, both CD4+ ($T_H$) and CD8+ ($T_{S/C}$) tend to be of the memory rather than naive type. Cytokine production in rodent models shows general increases in inflammatory cytokines such as interleukins (IL)-1,6 and tumor necrosis factor alpha (TNFa) as well as T cell cytokines IL-3,4,5 and 10, while IL-2 responses decrease with aging. Human studies suggest these responses may be more variable depending upon the underlying health of the individual. IL-2 production by activated T cells is decreased in the elderly. However, addition of exogenous IL-2 increases a variety of immune repsonses *in vitro*. Memory T cell responses appear to be largely intact on an individual cell basis; however, the overall response is decreased, presumably due to impaired clonal expansion. These data suggest that healthy elderly humans produce adequate amounts of cytokine *in vivo* due to the expanded presence of multiple memory T cells. However, new antigen exposure is met with inadequate cytokine production resulting in impaired immune resonses. Confirming this hypothesis will allow the investigation of recombinant cytokine or cytokine modulators to enhance the immune response of elderly individuals.

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USE OF IMMUNOMODULATORS TO EFFECT WOUND HEALING IN AN AGING ANIMAL MODEL SYSTEM. Ian Tizard, Texas A&M University, College Station, Texas, 77843.

Wound healing is significantly impaired in the aged and obese. While the reasons for this are complex, one contributing factor is the relative decline in cytokine production by macrophages in aged animals. It was postulated that stimulation of macrophage function in aged animals could repair this cytokine deficit and enhance the rate of wound healing. Studies were therefore undertaken to determine if the complex carbohydrate, acemannan, a known stimulator of cytokine synthesis, had an effect on the rate of wound healing in old rats. Paired punch biopsy wounds were made in the backs of three groups of rats. One group consisted of 3 month-old rats. One group consisted of calorie-deprived old rats (24 months) and the third group consisted of old animals that had received food ad libitum. One wound was treated by local infiltration with acemannan while the paired control wound received saline. Acemannan treatment resulted in a statistically significant acceleration in the rate of wound healing in all three groups. The greatest increase was seen in the aged animals. The rate of wound healing in both groups of aged animals was bimodal. Some animals showed little impairment in their rate of healing while others were significantly delayed. (Research supported by Carrington Laboratories, Inc.)

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IMMUNE FUNCTION DIFFERENCES IN AGED AND YOUNG RODENTS: EFFECTS OF AN ACETYLATED ß(1,4)-LINKED POLYMANNOSE AS AN IMMUNOMODULATOR. David Busbee*, Elizabeth Merriam and Barbra Campbell, Department of Anatomy and Public Health, College of Veterinary Medicine, Texas A&M University, College Station, TX 77843.

As animals age their immune function changes, with a pattern of alteration typically characterized by the generalized loss of both humoral and cell mediated immune function. These losses have been proposed by a variety of investigators to be due to decreased macrophage activation, decreased cytokine synthesis, decreased receptor elaboration, decreased capacity for mitogenic stimulation and/or altered histocompatibility antigen complex presentation. The end results of age-related alterations in immune function are seen as increased susceptibility to bacterial, viral, fungal and parasitic diseases, and loss of immune surveillance protection against spontaneous neoplastic diseases. We have evaluated the use of a complex plant carbohydrate, randomly acetylated ß(1,4)-polymannose (ACM), as a potential immunomodulatory agent in a rodent model system for the study of aging. ACM stimulates phagocytic monocytes both in vivo and in vitro and increases secretion of IL-1, TNF, interferon and other cytokines. Treatment with ACM enhances antibody dependent cell mediated cytotoxicity, with lysis of EL4 and NMS cells in vitro, and the stimulation of immune attack on NMS cells in vivo. ACM apparently works via a mechanism similar to that of bacterial lipopolysaccharide, but has few of the toxic side effects of LPS. This immunomodulatory polysaccharide is under continuing investigation as a potential agent for upregulating the immune function of aged animals.

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THE RELATIONSHIP BETWEEN GROWTH HORMONE RESPONSIVENESS AND STEROID HORMONES IN AGING. Raymond A. Daynes*, Department of Pathology, University of Utah and the GRECC, Veteran's Affairs Medical Center, Salt Lake City, UT 84132.

The purpose of this study was to explore a number of physiologic consequences associated with the well understood age-associated loss in endogenous production of the steroid hormone, dehydroepiandrosterone (DHEA). Using quantitative ELISA analysis on serum and supernatants derived lymphoid cell cultures of young and old donors, it was discovered that the production of two important inflammatory cytokines, interleukin-6 (IL-6) and interferon gamma (IFNγ), become dysregulated as an apparently normal consequence of age. Because of the universal nature of the phenomena, the constitutive presence of these two cytokines might be considered normal, but by no means is a continual production of these cytokines a benign event. A dysregulated production of IL-6 has been linked to a variety of pathologic conditions, including a consistent acute phase response, elevated autoantibodies and an enhanced susceptibility to B-cell lymphoma. In the present investigation, we now demonstrate that the ability of T cells to respond normally to the immunoregulatory influences of platelet-derived growth factor (PDGF) is also depressed with age, and that this depression in responsiveness can be linked to the constitutive production of IL-6 by these animals. A dysregulated production of IFNγ in the aged may prove to have a tremendous number of physiologic ramifications. Many of these consequences appear to associate with IFNγ-induced depressions in cellular responsiveness to a variety of growth factors, including transforming growth factor β, interleukin-4, PDGF, and erythropoietin. Experiments employing aged animals provided with supplemental DHEAS have now established that the treated animals exhibit an apparently normal regulation of their inflammatory cytokine production. DHEAS supplemented animals also were also found to exhibit a concomitant return of normal cellular responsiveness to growth factor stimulation. Our results suggest that age-associated depressions in the production of a naturally occurring steroid hormone may be responsible for a dysregulation in inflammatory cytokine production. The continual presence of these cytokines could be responsible for depressions in normal cellular responsiveness to growth factor stimulation, responses important in wound healing, hematopoiesis, bone remodeling and immunologic function.

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SOMATIC MUTATIONS AT THE BCL-2 LOCUS OCCUR MORE FREQUENTLY AMONG AGED HUMANS, Yafei Liu and Gino Cortopassi, Institute for Toxicology, University of Southern California, 90033.

We have investigated the occurrence a particular class of somatic mutations, translocations of human chromosomes 14 and 18, in tissues from 31 individuals not known to have cancer. A nested polymerase chain reaction protocol was used to amplify rare t14;18 mutations in samples containing approximately 600,000 haploid genomes of DNA. All samples from 10 individuals under age 30 gave negative results, whereas 10 of 21 samples from individuals older than age 30 were positive for t14;18 translocations, a statistically significant correlation of translocation detection with age. The class of t14;18 mutations we detect are found frequently in Non-Hodgkin's Lymphoma (NHL), and are known to dysregulate the bcl-2 gene, which can delay B lymphocyte apoptosis, and could be a primary event in lymphomagenesis. Risk for NHL occurrence is about 100-fold higher in 70-year-olds than 5-year-olds. Our data support the notion that the bias in occurrence of NHL towards aged males may have at its root an age-specific bias in the occurrence of t(14;18) translocations.

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LUTEINIZING HORMONE (LH) RESPONSES TO GONADOTROPIN HORMONE RELEASING HORMONE (GnRH) AND N-METHYL D-ASPARTIC ACID (NMA) IN YOUNG AND OLD ESTROGEN ($E_2$)-TREATED FEMALE C57BL/6J MICE. D.Joshi*, I.Lekhtman, R.B.Billiar and M.M.Miller, Departments of Obstetrics and Gynecology, Experimental Medicine and Anatomy and McGill Center for Studies on Aging, McGill University, Montreal, Quebec H3A 1A1, Canada.

Hypothalamic GnRH stimulates pituitary LH release. There is an age-related loss of the preovulatory LH surge in female C57BL/6J mice. Changes in the pituitary responsiveness to GnRH and/or capacity of the hypothalamic GnRH neurons to release GnRH may contribute to this loss. We tested pituitary GnRH responsiveness by measuring the LH response to exogenous GnRH. Young (5-6 mo) normally cycling (n=6) and old (24 mo) acyclic constant diestrus (n=6) C57BL/6J female mice were ovariectomized (OVX) and $E_2$-treated for 7d. Following per cardia catheterization on d6, serum LH was measured in serial blood samples before and after an i.v. bolus of GnRH (5$\mu$g/5$\mu$l saline/kg BW and 15$\mu$g/15$\mu$l saline/kg BW 1 hr apart) on d7. Each challenge of GnRH evoked a significant release of LH in both young mice (0.3$\pm$0.04 ng/ml first challenge; 0.69$\pm$0.1 ng/ml second challenge) and old (0.78$\pm$0.1 ng/ml first challenge; 1.76$\pm$0.2 ng/ml second challenge). No LH response was observed in saline treated control mice. Thus pituitaries of old female mice are at least as capable of responding to exogenous GnRH as those of young ones. Next we tested the $E_2$ inhibition of hypothalamic GnRH neuronal function indirectly by measuring LH response to the excitatory amino acid NMA (20mg/4ml saline/kg BW and 40mg/4ml saline/kg BW 2hr apart). No response to NMA was demonstrated by young (0.23$\pm$0.1 ng/ml first challenge; 0.11$\pm$0.04 ng/ml second challenge) or old (0.25$\pm$0.09 ng/ml first challenge; 0.16$\pm$0.06 ng/ml second challenge) mice. A striking LH response was obtained in old (24mo) mice OVX at puberty (1.14$\pm$0.33 ng/ml first challenge; 0.99$\pm$0.29 ng/ml second challenge; $p<0.05$) as compared to saline treated mice. These results indicate that estrogen inhibits LH response to NMA in young and old mice but not in old mice OVX at puberty. Data from this study suggest that diminished LH secretion with age is likely to be due to changes of hypothalamic origin; the presence of ovaries may lead to alterations in regulation of GnRH neuronal function which can be reversed by long-term ovariectomy.

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ULTRA VIOLET RADIATION PROMOTES THE AGING PROCESS OF THE EYE LENS. **Orly Weinreb and Ahuva Dovrat*.** B. Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel 31096.

Solar radiation is one of the environmental cataractogenic agents of which their damaging effects accumulate with age. We followed the effect of ultra violet radiation at 365nm on the eye lens in long-term organ culture conditions. We irradiated bovine lenses in various amounts of radiation and followed the metabolism and optics of the lenses. Each lens tested was placed in a two-chamber cell and was maintained in the cell during irradiation. Following irradiation, lens optical quality was monitored during the culture period and lens epithelium samples were taken for enzyme analysis. It was found that irreversible damage to the lens was observed after irradiation of more than 5 J/cm$^2$. The activity of the enzymes hexokinase and catalase was reduced in lens epithelium 24 hours after irradiation. These two enzymes were affected 24 hours before optical damage was observed. On the other hand, at the same amount of radiation, glucose-6-phosphate-dehydrogenase activity was reduced only when lens opacity was observed (after 48 hours). It can be concluded that some enzymes are affected before the appearance of optical damage in the lens. These enzymes may demonstrate the first step of the chain leading to lens opacity.

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BODY MASS INDEX, DEMENTIA, AND SEVERITY OF DEMENTIA IN OLDER AGED CANADIANS: RESULTS FROM THE CANADIAN STUDY OF HEALTH AND AGING Josée Verdon*, Jean Kozak and Mary Ann Robertson Clinical Epidemiology Unit. Elisabeth-Bruyére Health Centre, Ottawa, Ontario, Canada, K1N 5C8.

Little is known in the research literature of the relationship between weight, body mass and the presence and severity of dementia. Furthermore, studies invariably sample only those individuals under the age of 65. This poster presentation examines the relationship of these factors in 2,914 seniors 65 years of age and older.

Body Mass Index (BMI) scores were derived (kg/m$^2$) for seniors who were assessed clinically as part of the recent national prospective Canadian Study of Health and Aging (CSHA). The CSHA sampling structure included cognitively intact and dysfunctional (Alzheimer's etc.) seniors residing in institutions and communities across 18 Canadian cities.

Analysis of variance indicated that both weight and BMI were significantly lower ($p<.001$) in demented than non-demented subjects residing in either the community or institution. BMI and weight decreased significantly ($p<.001$) in women as severity of dementia increased when age was covaried out. Only weight decreased significantly with severity in men in a similar analysis. Although overall BMI decreased with increasing age ($p<.001$), this was due primarily to age related changes in BMI among women.

Changes in weight and BMI are associated with the presence of dementia. However, the relationship between BMI, age, and severity of dementia appears to be different in men and women..

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RATE OF EXCRETION OF VITAMIN C IN HUMAN URINE. Gavin King and Alfred B. Ordman*, Beloit College, Beloit, WI 53511.

Vitamin C is a natural antioxidant which may protect humans against the harmful effects of free peroxide radicals. The major pathway for control of vitamin C levels in the body is urinary excretion. We investigated the regimen of vitamin C necessary to maintain elevated levels of vitamin C excretion in undergraduate students.

A class of 30 students took vitamin C tablets at 8 a.m. daily for one week. Urine samples were collected, and the concentration of vitamin C was assayed using the 2,6-dichlorophenolindophenol assay. In one group individuals took a daily dose of 0, 0.5, 1, or 2 g and all urine was collected and pooled during the first and last 24 hr. Total urinary excretion levels were 6+/-10, 60+/-70, 230+/-60, or 460+/-60 mg respectively on the first day, and 17+/-30, 45+/-60, 385+/-35, and 789+/-322 mg on the last day. The increased excretion on the last day is consistent with an accumulation of vitamin C in the body from one day to the next.

In the other group, a single dose of 2 g was taken daily for a week, and each urination during the first and last day was assayed. There was considerable variation between individuals in the rate of excretion of vitamin C in the urine. Excretion over the first 24-hr period rose significantly by noon in all individuals from near zero at 8 a. m. and all continued to excrete vitamin C throughout the remainder of the 24 hr. By the end of each 24 hr, the excretion rate had decreased significantly in most individuals. On the basis of these data a single daily dose will not maintain high vitamin C in the body over the following 24 hr.

The results are consistent with the hypothesis that to achieve a high enough vitamin C intake to keep urinary excretion levels elevated, a dose of more than 250 mg of vitamin C should be taken every 12 hr. This is substantially higher than the U. S. recommended daily allowance of 60 mg.

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**AGE-ASSOCIATED INCREASE IN VERY LOW DENSITY LIPOPROTEIN AND LOW DENSITY LIPOPROTEIN APOLIPOPROTEIN B-100 CONCENTRATIONS ARE DUE TO CHANGES IN BOTH PRODUCTION AND CATABOLISM.** John S. Millar*, Alice H. Lichtenstein, David L. Hachey, Jeffrey S. Cohn, Marina Cuchel, Gregory G. Dolnikowski, Ernst J. Schaefer, USDA Human Nutrition Research Center on Aging at Tufts University, Boston, MA, 02111.

In order to determine the mechanisms responsible for the age-associated increases seen in very low density lipoprotein (VLDL) and low density lipoprotein (LDL) apolipoprotein (apo) B-100 concentrations we conducted kinetic studies in 18 normolipidemic male subjects between the ages of 24 and 73. Subjects were maintained on similar diets consisting of 47-49% carbohydrate, 15% protein, and 36-40% fat (15-17% saturated, 15-17% monounsaturated, 6% polyunsaturated) with 180 mg cholesterol/1000 kcal for a minimum of 10 days. The metabolism of apo B-100-containing lipoproteins was studied in the fed state using a primed-constant infusion of $^2H_3$-leucine. Non-fasting apo B concentrations increased with age ($r=0.62$, $p=0.008$) in the triglyceride rich lipoprotein fraction ($d<1.006$ g/ml, approximately 95% of which is VLDL apo B-100 and 5% chylomicron apo B-48). Non-fasting LDL apo B-100 concentrations also tended to be increased with age ($r=0.48$, $p=0.054$). Data from the kinetic studies were analyzed using a multicompartmental model which derives LDL apo B-100 entirely from VLDL apo B-100 via intermediate density lipoprotein. Results from the kinetic analysis indicate that the fractional catabolic rates of both VLDL and LDL apo B-100 decrease with age ($r=-0.51$, $p=.036$; $r=-0.53$, $p=0.034$, respectively). Production rates of VLDL apo B-100 increased with age ($r=0.49$, $p=0.047$), but there was no increase in production of LDL apo B-100 with age ($r=0.03$, $p=0.905$). These results indicate that the age-associated increase in VLDL apo B-100 is due to both an increased production and decreased catabolism of VLDL apo B-100, whereas the age associated increase in LDL apo B-100 is due to a decreased catabolism.

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ADEQUACY OF ENERGY INTAKE AMONG ELDERLY RECEIVING COMMUNITY SUPPORT SERVICES H. Payette*, K. Gray-Donald Geriatric Research Center, D'Youville Hospital, Sherbrooke Canada J1H 4C4.

Inadequate total dietary intake and resulting weight loss are associated with declines in health status. **Objectives:** To assess dietary intake as compared to energy needs and to measure associated weight changes among elderly using support services. **Methods:** 145 subjects (mean age 78.8) receiving help with personal hygiene and housework were interviewed at home; 3 non-consecutive 24 hour dietary recalls, anthropometric measurements and lifestyle habits were recorded. The ratio of mean daily energy intake to resting energy expenditure (REE) (Harris-Benedict equation) was calculated for each subject. **Results:** The survey indicated very low intakes at all ages. The mean ratios for dietary intake to REE were similar in men and women (1.05 and 1.08 respectively), barely meeting basal requirements and inadequate for total needs. This ratio was negatively correlated with reported weight loss ($r=-0.63$; $p<0.01$) among underweight subjects. Weight change was not related to intake in normal and over-weight subjects. Important weight loss was evident in 27% of subjects; at highest risk were those with poor appetite ($p=0.02$), difficulty preparing meals ($p=0.01$) and getting groceries ($p=0.07$). **Conclusion:** Insufficient dietary intake and associated weight loss are prevalent and indicate the need for greater concern for nutritional intervention in home help programmes. Supported by MSSS and CRSSSE (Québec) and SIRP, Health & Welfare Canada

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AGE AND DIET EFFECTS ON SKELETAL MUSCLE TUBULAR AGGREGATES. Arthur Cosmas, Wenjing Ding, Roderick Bronson, and Thomas Manfredi, Univ. of Connecticut, School of Allied Health, Storrs, CT. 06269; USDA Human Nutrition Research Center on Aging, Tufts University, Boston, MA. 02111; Univ. of Rhode Island, Exercise Science Program, Kingston, R.I. 02881.

Although the pathophysiology of tubular aggregates (TA) has been identified in humans in a variety of skeletal muscle disorders, their origin is unknown. TA's have been reported in congenic male mice of the MRL+/+ substrain and have been found to increase in abundance with age. We examined the effects of 40% caloric restriction (CR) on TA accumulation and structure on young (19 month) and older (27 month) mice and found that the % of fibers with TA's increase with age in CR and ad libitum (AL) fed mice. However, within age groups, TA percentages were lower in the young (9.5% vs 59.5%) and older (22.1% vs 74.2%) restricted animals. Light microscopy revealed that many TA's may not have yet penetrated the sarcolemma in the young animals, especially the DR mice. The young DR animals also showed evidence of fiber splitting and round fibers compared to sparse evidence of pointed fibers in the young AL mice. In both groups of young mice the TA's appeared to be in high densities in some fasiculi and not in others. Fiber disarray was greater in the older AL mice than their age-matched DR counterparts. Electron microscopic examination of TA's showed no distinction in TA ultrastructure between age and dietary groups. Although there is considerable agreement that TA's arise from sarcoplasmic reticulum, we saw TA's in close approximation with mitochondria and some mitochondria showed evidence of internal vesicles. Results from this study suggest that diet restriction may minimize the formation of age-related TA's in skeletal muscle and that TA's may interact with mitochondria.

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INDUCTION OF A 53 KDa PHOSPHOPROTEIN IN AGED CALORIC RESTRICTED RATS. J.L. Pipkin*, W.G. Hinson, L.E. Lyn-Cook, P.H. Duffy, R.J. Feuers, R.W. Hart, and D.A. Casciano, National Center for Toxicological Research, Jefferson, AR 72079.

The quantitative and qualitative states of the p53 isoforms/isotypes were investigated in matrix proteins isolated from bone marrow of three groups of male Fischer 344 rats using two-dimensional $^{32}P$ fluorography and Western blotting with wild type (wt) antibody. Two groups were maintained *ad libitum*, young (Y/AL- 3 mo.) and old (O/AL- 28 mo.), while the third group of old rats maintained on a caloric restricted intake (O/CR- 28 mo.) of 60% of *ad libitum* rats. The quantity of $^{32}P$-incorporation into p53 isoforms seen in the Y/AL and O/CR were substantially reduced in O/AL rats at 18 and 36 hr of retinoic acid (RA) dosing, and in all cases, the amount of phosphorylation in isoforms of O/CR rats were increased from O/AL animals. Isotype #7 was absent from the fluorographs of O/AL rats under all conditions. Immunochemical conjugation of p53 wt Ab4 antibody for p53 isotypes was substantially reduced at 18 and 36 hr of RA dosing in O/AL as compared with Y/AL and O/CR rats. The phenol-soluble nuclear matrix proteins of which p53 was a member, showed additional phosphorylation in Y/AL in the $G_2$-phase of the cell cycle following 36 hr dosing with RA. The labeling and antibody binding levels of p53 isoforms in O/CR animals, altered by diet dependent factors, reflect a condition which is more reminiscent of Y/AL than O/AL animals.

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RETARDATION OF AGE-RELATED DECLINES IN MOTOR AND COGNITIVE FUNCTIONS BY CALORIC RESTRICTION: LONGITUDINAL STUDIES OF INBRED MICE. Michael J. Forster and Harbans Lal*, Department of Pharmacology, Texas College of Osteopathic Medicine, Fort Worth, TX 76107.

Longitudinal behavioral studies were conducted to determine if neural changes responsible for decline of cognitive or motor functions would be decelerated by long-term caloric restriction, a procedure which results in increased longevity in rodents. C57BL/6, B6D2F$_1$ and DBA/2 mice fed ad libitum or reared under caloric restriction (60% of ad libitum beginning at 4 months) were tested for recent memory and sensorimotor capacity at 10 and 22 months of age. Caloric restriction increased the lifespans of C57BL/6 and B6D2F$_1$ mice, but not DBA/2 mice. For measurement of motor function, the maximum speed at which a mouse could run on a treadmill was recorded independent of strength and endurance factors (Forster & Lal, *Biomed. Environ. Sci.*, 4, 144, 1991). When the levels of stable performance of ad libitum-fed and restricted mice were compared, it was observed that the restricted C57BL/6 and B6D2F$_1$ mice (but not DBA/2) failed to decline over chronological ages for which there was a clear decline in the ad libitum fed mice. Recent memory was measured using a delayed reversal procedure allowing longitudinal testing (Forster & Lal, *Behav. Pharmacol.*, 3, 337-349). The ad libitum- fed C57BL/6 and B6D2F$_1$ mice showed significant age-related decline in recent memory capacity, as evidenced by an increase in the rate of memory decay following information acquisition. In contrast, there was no change in memory performance of diet restricted mice of these genotypes as a function of age, although restriction conferred a slight performance disadvantage relative to ad libitum fed mice at 10 months of age. Overall, the results suggest that diet restriction may acutely influence the level cognitive and motor performance, as well as retard certain age-associated changes responsible for cognitive and motor declines.

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EFFECTS OF AGING AND MODERATE DIETARY RESTRICTION ON BLOOD PARAMETERS OF RATS. Linda Chen* and David Snyder, Dept. of Nutrition and Food Science, University of Kentucky, Lexington, Kentucky 40506 and Lobund Laboratory, University of Notre Dame, Notre Dame, Indiana 46556.

Effects of a 30 percent caloric restriction on hematocrits, levels of blood glycohemoglobin, serum glucose and serum protein at various ages throughout the life span were studied in rats. Eighty Lobund-Wistar male rats were divided into two groups: ad libitum (AL) or dietary restricted (DR). When compared to the AL group, the DR group received a 30 percent less diet per day. The rats were killed at 6, 12, 18, 24 and 30 months of age, and blood samples were collected. Hematocrits decreased with aging in both groups, and were higher in the DR group at 24 months of age. Blood glycohemoglobin levels increased with aging in the AL group, but not in the DR group, and were lower in the DR group at 30 months of age. Fasting serum glucose levels were not affected by dietary restriction or age. Serum protein levels were lower in the DR group than in the AL group at 30 months of age. It is concluded that aging affected hematocrit, blood glycohemoglobin levels and serum protein levels; while dietary restriction significantly decreased the levels of blood glycohemoglobin and serum protein in old age.

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LONGITUDINAL EVALUATION OF LONG-TERM DIABETES MARKERS. Crystal Johnson*, Benjamin Gerson, Majd Jibrini, Stephen Podolsky, VA Outpatient Clinic, Boston MA 02114.

Aging and diabetes mellitus have many interrelationships. Diabetes control is assessed from short term changes in serum glucose or longer term changes in glycosolated proteins (fructosamine and hemoglobin A1c). There is controversy over which assay provides the best information in the most reliable manner. We compared the three tests in 94 patients with diabetes over 49 weeks.

27 patients had Type I (insulin dependent) diabetes, aged 58$\pm$2.5 yrs; 67 pts had Type II (non-insulin dependent) diabetes, aged 67$\pm$1.2 yrs. All 27 of the Type I and 34 of the 67 Type II patients took insulin injections. Baseline data: glucose 221$\pm$9.0 (normal 61-137mg/dL); fructosamine 368$\pm$7.7 (normal 180-280umol/L); Hb A1c 7.6$\pm$0.2 (normal 3-5%). Results on week 49: glucose 206$\pm$7.7; fructosamine 371$\pm$7.5; Hb A1c 7.0$\pm$0.1.

Marked but transient glucose changes did not alter the other tests. Major events such as changes in therapy, development of infections or intercurrent illness were better reflected in gradual changes in glycosolated proteins, unlike the minute-to-minute serum glucose fluctuations.

Both major improvement or deterioration in diabetes control tended to be reflected sooner in fructosamine alterations than in Hb A1c changes. Our data suggests that both these tests provide reliable assessment of diabetes control, albeit somewhat differing periods of prior glycemia (i.e. 1-2 weeks for fructosamine compared to 1-2 months for Hb A1c). Fructosamine is a more cost effective test.

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THE EFFECTS OF EXERCISE ON LEARNING PERFORMANCE AND ASSOCIATED HIPPOCAMPAL FUNCTIONING: EVALUATION OF YOUNG MIDDLE AND OLD AGES OF INITIATION TO LIFE-LONG EXERCISE. Diana.E. Fordyce*[1] and Jeanne.M. Wehner[1,2]. [1]Institute for Behavioral Genetics and [2]School of Pharmacy, Univ. of Colorado, Boulder, CO 80309.

Previously, we have reported that physical activity enhances spatial learning performance in C57BL/6 and DBA/2 mice with associated alterations in hippocampal protein kinase C (PKC) (Fordyce and Wehner, Brain Res., In Press) and that aging results in a genetically-related decline in learning performance correlated to hippocampal bound PKC activity (Fordyce and Wehner, Neurobiol. Aging, 14: 309-317, 1993). Enhancement of learning performance with associated hippocampal alterations was also observed in F344 rats (Fordyce and Farrar, Behav. Brain Res., 43: 115-123, 46: 123-133, 1991), but these hippocampal neurochemical alterations ocurred only in rats initiated to lifelong exercise from a young age not an old age (Fordyce and Farrar, Brain Res. 541: 57-62, 1991).

From these investigations, it was of interest to systematically evaluate various ages of initiation to life-long exercise and examine subsequent alterations in learning performance and associated hippocampal neurochemistry. F1(B6xD2) and C57 mice which characteristically perform well and moderate, respectively, on spatial learning tasks were initiated to exercise at young (3 mos of age), middle-age (12 mos of age) and old (18 mos of age). All mice were spatial learning tested at 21 mos of age and hippocampal PKC was measured. The results of this investigation indicate that the benefits of exercise on cognition and associated hippocampal functioning during the aging process may be dependent on the age at which an exercise regime is initiated.

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EVIDENCE FOR THE EFFICACY OF NIMODIPINE IN THE TREATMENT OF DISORDERS OF BRAIN AGING Richard J. Fanelli, Institute for Dementia Research, Miles, Inc., West Haven, CT 06516

Nimodipine is a 1,4-dihydropyridine with L-type calcium channel antagonist properties. Electrophysiological studies have indicated that nimodipine blocks neuronal calcium current with high affinity, and reduces the calcium-dependent afterhyperpolarization recorded in hippocampal neurons from aged animals. In cultured hippocampal neurons, nimodipine potently inhibits the elevated intracellular calcium seen with potassium-induced depolarization. In behavioral studies, nimodipine has been shown to improve neuronal functioning in several aging and lesion models. Nimodipine prevents age-associated motor deficits in rats, enhances acquisition of conditioned eye-blink in aging rabbits, and improves recent memory function in aging primates. In rats with lesions of the medial septal nucleus, hippocampus or visual neocortex, nimodipine has been shown to enhance or preserve subsequent performance of selected behavioral tasks. In animal models of ischemia, nimodipine has been shown to have beneficial effects with respect to neurological indices and survival. Currently, nimodipine is approved for the treatment of neuronal deficits associated with subarachnoid hemorrhage in the USA, and for the treatment of age-associated dementia in several other countries. The results of a recent multicenter placebo-controlled trial, in which the efficacy of nimodipine in the treatment of dementia was evaluated, will be discussed. These findings, both from experimental animals and from clinical trials, support the therapeutic usefulness of nimodipine for the treatment of disorders of brain aging.

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PREVENTION AND TREATMENT OF BRAIN DAMAGE ASSOCIATED WITH ALZHEIMER'S DISEASE, PARKINSON'S DISEASE, ISCHEMIA REPERFUSION INJURY, HYPEROXIA AND AGING BY NITRON TRAPPING COMPOUNDS. John M. Carney, Dept. of Pharmacology, University of Kentucky, Lexington, KY 40536.

The processes of Alzheimer's Disease, Stroke, Multi-Infarct Dementias, Parkinson's Disease, Huntington's Chorea, Amyotrophic Lateral Sclerosis and the normal process of senescence are associated with significant functional, anatomical and biochemical changes. While the fundamental cause of these changes remains to be clearly elucidated, much progress has been made in this area. Important in this effort is the recognition that there is a significant role of reactive oxygen species and tissue oxidation in the process. A number of different lines of research support this concept. Studies of brain oxidation from autopsy material have indicated that there is a significant age-related increase in protein oxidation of the neocortex of both neurologically normal subjects and in patients with neurodegenerative conditions. In addition, there is regionalization to the rate of oxidation, involving the frontal cortex more than the occipital. In animals, there is a significant increase in protein oxidation following ischemia/reperfusion injury (IRI) and following inhibition of Complex-I mitochondrial respiration by MPTP and other mitochondrial poisons. In addition, there are significant decreases in enzyme activities (Glutamine synthetase [GS] and Creatine Kinase [CK] ) that parallel the increases in protein oxidation. In rodents, normal aging is accompanied by significant increases in the level of oxidized protein and decreases in neocortical GS and CK activities. Associated with these changes, there is a significant increase in susceptibility to ischemia/reperfusion injury of the brain (stroke) as a function of age in animals (and presumably in man). Nitrone trapping compounds (e.g. phenyl-butyl-nitrone, PBN) have the ability to covalently bind carbon-centered radicals. PBN can bind both lipid and protein radicals. In recent studies we have demonstrated that PBN and related compounds can alter the state of protein oxidation and enzyme activity when administered daily for 14 days. In addition to these biochemical changes, aged animals administered PBN made fewer errors in the radial maze test for temporal/spacial memory, compared to saline treated control aged gerbils. An additional aspect of brain aging is the enhanced risk to ischemic damage. PBN significantly protects the aged gerbil from lethal ischemia and reduces the degree of radial arm maze errors following non-lethal ischemia/reperfusion injury. When rats, gerbils, or mice are exposed to 100% oxygen at 1 atmosphere of pressure, there is an early decrease in both glutamine synthetase and creatine kinase activities in the neocortex. This decrease in enzyme activities can be prevented by pretreatment of the animals with PBN. Pre treatment and post-treatment with PBN and other NRT's also protect against chemically-induced Parkinson's disease and Huntington's disease in rodents. Thus, strategies designed to limit the production of free radicals and the secondary free radical production can produce beneficial effects both acutely and chronically in animal model systems and may ultimately be of clinical significance. (Supported in Part by AG 09690 and NS 23307)

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OXIDATIVE STRESS, NEURODEGENERATION, AND NEUROTROPHIC THERAPY. Lawrence R. Williams, Amgen, Inc., Thousand Oaks, CA 91360

Free radicals and reactive oxygen species normally and continually attack the molecular constituents of an organism. The brain is particularly vulnerable to oxidative damage, and age-related neurodegeneration may be caused by the temporal accumulation of oxidative injuries. Oxidative stress may also underlie the specific diseases of Charcot, Parkinson and Alzheimer. Alterations in the brain's endogenous antioxidant systems due to genetic or environmental predisposition could result in significant destruction of cellular membrane and DNA, and with increasing age, result in the death of the specific neuronal populations. These susceptible neurons might be protected from death by boosting the brain's ability to deal with oxidative stress. Such protection could be provided by treatment of patients with potent free radical-scavenging, antioxidant drugs, or with specific neurotrophic molecules which as part of their mechanism of action may stimulate the activity of the brain's endogenous antioxidants. We have begun to examine age-related alterations in endogenous antioxidant enzymes and the effects of exogenous neurotrophins in the Fischer 344 rat using quantitative in situ hybridization.

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EFFECTS OF l-DEPRENYL ON MANIFESTATIONS OF BRAIN AGING IN THE RAT AND DOG. *Gwen O. Ivy, John Rick, Paul Murphy, Chris Reid, Elizabeth Head, and N. William Milgram, University of Toronto at Scarsborough, Scarborough, MIC 1A4 Ontario, Canada

We have previously shown that treatment of aged rats with l-deprenyl increased both mean and maximum survival. Two subsequent studies have now been completed which were intended to establish: 1. Whether l-deprenyl affects age-dependent decline in cognitive and motor function in the rat, and 2., whether cognitive abilities of the aged dog are similarly influenced by treatment with l-deprenyl.

In the rat study male and female rats were given intragastric administration of saline or l-deprenyl at a dose of 1 mg/kg three times per week starting at 14 months of age. The Morris water maze was used to test cognitive function and groups were tested after 3, 6.5 or 10 months of treatment. Either short (2-4min) or long 23-33 min) intertrial intervals (ITI's) were used. We found that trials to criterion increased significantly as a function of age in the animals tested with the short ITI, but not in the animals tested with the long ITI. Deprenyl was without effect.

The rats were also tested on measures of motor function (tilting plane, wire suspension, horizontal bar) and in a novel open field arena. Deprenyl had no effect on motor performance, but did increase novelty-induced grooming in male rats. These results raise the possibility that chronic deprenyl treatment may result in a mildly elevated stress response in the rat.

The study with dogs examined the effect of oral administration of deprenyl on performance of a spatial memory test. The test required an animal to withhold responding during a time out period of either 20, 60, 110 seconds. Four aged dogs were used. All of the subjects showed improvement in performance at doses of 0.5 and 1.0 mg/kg when the time out period was 110 seconds.

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FACTORS REGULATING THE OPTIMAL DOSE OF (-)DEPRENYL (DPN) FOR INCREASING ANTIOXIDANT ENZYME ACTIVITIES. K. Kitani[1,2], M.C. Carrillo[3], S. Kanai[2], Y. Sato[2], K. Miyasaka[2] and G.O. Ivy[3], [1]Radioisotope Res Inst, Faculty of Medicine, Univ of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113, JAPAN; [2]Dept of Clin Physiol, Tokyo Metropol Inst of Gerontol, 35-2, Sakaecho, Itabashi-ku, Tokyo-173, JAPAN; [3]Div of Life Sci, Univ of Toronto, 1265 Military Trail, Scarborogh, Ontario, CANADA M1C 1A4.

Three independent studies have agreed that chronic treatment with DPN can prolong the life span of rats. The underlying mechanism(s) for this phenomenon, however, still remains totally unre-

solved. We have confirmed the initial contention by Knoll that this drug can significantly increase activities of superoxide dismutase (SOD) in rat striatum. Furthermore, we found that DPN treatment also significantly increases catalase (CAT) (but not GSH peroxidase) activities in selective brain regions such as striatum, s. nigra and cerebral cortices, where SOD activities are increased. We subsequently found that when animlas were treated with s.c. infusion of the drug for 3 wks, the optimal dose was 10 times lower in young females than males, while during aging, the dose decreases 4 fold in males but increases 5 fold in females. Further, we have recently found that longer term treatment reduces the optimal dosage found in our 3 wk study. Thus, with prolonged treatment, the dosage not only becomes less effective but even reduces the activities. We therefore suggest that the selection of an optimal dose of DPN is critically important for any long term treatment study, such as a life span study, if DPN's effect on antioxidant enzyme activities is causally related to its effect on the life span of rodents.

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THE EFFECT OF A LONG TERM (6 MONTHS) TREATMENT WITH (-)DEPRENYL ON ANTIOXIDANT ENZYME ACTIVITIES IN SELECTIVE BRAIN REGIONS IN OLD FEMALE FISCHER 344 RATS. K. Kitani[1], M.C. Carrillo[2], S. Kanai[2], Y. Sato[2], K. Miyasaka[2] and G.O. Ivy[3], [1]Radioisotope Res Inst, Faculty of Medicine, Univ of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113, JAPAN; [2]Dept of Clin Physiol, Tokyo Metropolitan Inst of Gerontol, 35-2, Sakaecho, Itabashi-ku, Tokyo-173, JAPAN; [3]Div of Life Sci, Univ of Toronto, 1265 Military Trail, Scarborogh, Ontario, CANADA M1C 1A4.

In order to ascertain the effect of the duration of (-)deprenyl (DPN) administration on the optimal dose for increasing antioxidant enzyme activities in rat brain, the effect of long term (DPN) treatment (s.c. injection 3 times/wk for 6 mo) on superoxide dismutase (SOD) and catalase (CAT) activities in selective brain regions was examined in old (22 mo) female Fischer 344 rats. All three doses of DPN tested (0.1, 0.25 and 0.5 mg/kg/ day) increased activities of both enzymes in s. nigra, striatum and cerebral cortices, mostly in a dose dependent manner. This was especially true for SOD activities, which showed the smallest effect with the lowest dose of 0.1 mg/kg/day. However, for CAT activities in cerebral cortices, the smallest dose of 0.1 mg/kg/day was most effective, while the highest dose (0.5 mg/kg/day) was non-effective. In contrast, in hippocampus and cerebellum there were no significant differences in enzyme activities between control and DPN-treated groups. It is suggested that for a long term study such as a life span study using this drug, a dose of 0.25 (or 0.5) mg/kg/day appears to be most appropriate. This is at least 4 times lower than the optimal dose of 1.0 mg/kg/day for successive 21 days suggested by our previous short term (3 wk) experiments.

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(-)DEPRENYL (DPN) INCREASES ACTIVITIES OF SUPEROXIDE DISMUTASE (SOD) AND CATALASE (CAT) IN CERTAIN BRAIN REGIONS IN OLD MALE MICE. M.C. Carrillo[1], K. Kitani[2], S. Kanai[1], Y. Sato[1], K. Miyasaka[1] and G.O. Ivy[3], [1]Dept of Clin Physiol, Tokyo Metropolitan Inst of Gerontol, 35-2, Sakaecho, Itabashi-ku, Toky-173, JAPAN: [2]Radioisotope Res Inst, Faculty of Medicine, Univ of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo-113, JAPAN; [3]Div of Life Sci. Univ of Toronto at Scarborogh, 1265 Military Trail, Scarborogh, Ontario, CANADA M1C 1A4.

Previous three studies have agreed that DPN can prolong the life span of rats. Also, increases in SOD and CAT activities in selective brain regions were demonstrated to occur by this drug and this phenomenon has been suggested to be causally related to the life prolonging effect of the drug. Thus far, no study has been reported with regard to the effect of the drug on antioxidant enzyme activities in animal species other than rats. The present study aimed to clarify whether a similar effect of DPN can be observed in mice. A s.c. continuous infusion of DPN for 3 weeks in old C57BL male mice increased SOD and CAT activities in s. nigra, striatum and cerebral cortex but not in hippocampus, cerebellum or the liver. The doses of 0.5 and 1.0 mg/kg/day were most effective, while with a higher dose (2.0 mg/kg/day), deprenyl tended to lose its effect slightly and with a lower dose (0.25 mg/kg/day) DPN was clearly less effective. The results suggest that deprenyl can increase antioxidant enzyme activities in certain brain regions in mice as was previously demonstrated in rats. The results coupled with our unpublished observations in dogs suggest that deprenyl has this particular effect in a variaty of different animal species.

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MODEL SYSTEMS TO STUDY THE B-AMYLOID PROTEIN OF ALZHEIMER'S DISEASE. Faheem A. Sandhu and Sayeeda Zain, Department of Biochemistry, University of Rochester, Rochester, NY 14642.

Alzheimer's disease (AD), a neurodegenerative disorder that severely impairs cognitive and memory function in elderly people, is partially characterized neuropathologically by extracellular deposits of *B*-amyloid protein. We were interested in studying how *B*-amyloid may be involved in aspects of AD pathogenesis. To do this, we expressed the last 100 amino acids of the amyloid precursor protein, which contains the entire *B*-amyloid region, in PC12 cells and in brains of transgenic mice. We found that expression of this fragment of APP altered cytoskeletal changes in PC12 cells following nerve growth factor treatment. Using both *in vitro* and *in vivo* systems of human APP expression, we can study the biology of APP and test hypotheses of how it may be involved in Alzheimer's disease.

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EXAGGERATED GLIAL REACTIONS TO DEAFFERENTATION IN AGED RATS. David G. Morgan*, Wayne A. Schreier, Leigh A. Holcomb & Marcia N. Gordon, Department of Pharmacology, University of South Florida, Tampa FL 33612-4799.

This purpose of this study is to identify age-related changes in the brain's reaction to injury. F344 rats of 6, 15 and 24 months

were injected unilaterally into the medial forebrain bundle with 8 μg of 6-hydroxydopamine to produce a modest deafferentation of the striatum (roughly 10% of synapses). Rats were sacrificed at 0 (no surgery), 2, 4, 7, 10, or 14 days after the lesion (n = 4-7 per group) and sections collected for histology. We report here on the striatal immunostaining for glial fibrillary acidic protein (GFAP) as an index of astrocyte reactivity. Staining intensity was evaluated by microscopic videodensitometry.

In young rats, the average O.D. increased slightly at 2-4 d and peaked at 7 d after the injection with a 50% elevation over un-injected rats. By 14 d, the staining intensity had returned to control values. In middle-aged rats, the staining intensity peaked between 4 and 7 d with a 75% elevation over control values. By 14 d values had returned to within 20% of baseline. For aged rats, the staining increased to almost 100% above control values 7 d after the inject-ion, and remained at this elevated level 14 d after the injection.

These results indicate that aged rats have an exaggerated reaction to deafferenting lesions. Both the magnitude of the response and its duration are greater in the 24 mo old rats than in 6 mo old animals. Importantly, the middle-aged rats exhibit an intermediate response. These data confirm earlier data we collected on the induction of GFAP RNA in aged mice following hippocampal deafferentation by fornix transection using in situ hybridization. An inhibitory role of this excessive astrocytic response on recovery of function is suggested. Supported by AG-07892 to DGM and AFAR to MNG.

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APOLIPOPROTEIN e4 ALLELE FREQUENCY IS INCREASED IN SPORADIC ALZHEIMER'S DISEASE PATIENTS. Christine Bétard*, Mark Gee, Louis Houde, Pierre Chagnon, Denis Larrivée, Denis Gauvreau. Projet IMAGE, Research Center, Côte-des-Neiges Hospital, Montreal (Quebec) H3W 1W5.

The frequency of three different apolipoprotein E (apo E) isoforms was studied in a group of 58 sporadic patients affected with late-onset Alzheimer's disease (AD).

Apo E was genotyped using a modified protocol of Wenham el al. (1991). After extraction from lymphocytes, genomic DNA was amplified by polymerase chain reaction using fluorescent oligonucleotides. Amplified fragments were digested with the restriction enzyme CfoI, separated on an automatic DNA sequencer (ABI, 373A), and analysed with the GeneScanner software (ABI 672). The apo E allele frequencies of the AD group were compared to a group of octogenerians free of cognitive symptoms from the Montreal area (Davignon et al. 1987) using a chi-square test.

The mean age in AD sample was 81 ± 7 years. The female:male ratio was 2.6. Apo E allele frequencies in AD sample differed significantly from those in the octogenerians sample (P< 0.001).

**Apo E allele frequencies in AD patients**

| Alleles | AD patients | | | Octogenerians | | |
|---|---|---|---|---|---|---|
| | All | Females | Males | All | Females | Males |
| *n* | *58* | *42* | *16* | *236* | *118* | *118* |
| e4 | 0.336 | 0.321 | 0.375 | 0.087 | 0.076 | 0.098 |
| e3 | 0.586 | 0.607 | 0.531 | 0.824 | 0.860 | 0.788 |
| e2 | 0.078 | 0.072 | 0.094 | 0.089 | 0.064 | 0.114 |

These results suggest that apo E gene is likely to be a susceptibility locus for AD. They are in agreement with a previous study performed by Strittmatter et al. (1993) on 30 unrelated AD subjects compared to age-matched controls.

Wenham PR et al. Lancet 337: 1158-59; 1991.
Davignon J et al. Transac.Am. Clin. Climatotol. Assoc. 99: 100-110; 1987
Strittmatter et al. Proc. natl. Acad. Sci. USA 90: 1977-81; 1993

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AUTOPSY DIAGNOSIS OF ALZHEIMER DISEASE. Lissy F. Jarvik*[1,2], Steven S. Matsuyama[1,2], Arnold Scheibel[2], and Harry Vinters[3], [1]West Los Angeles VA Medical Center, and UCLA, Depts of [2]Psychiatry & Biobehavioral Sciences and [3]Pathology & Laboratory Medicine, Los Angeles, CA 90073

Confirmation of the clinical diagnosis of Alzheimer disease (AD) requires histopathologic examination. Slides obtained at autopsy were available for 17 probands who were participants in the UCLA/WLA VAMC longitudinal family study of AD. According to the routine autopsy reports (all emanating from major teaching hospitals) which accompanied the slides, the diagnosis was AD in 14 patients (82.4%), AD and arteriosclerotic vascular disease in one, multiple microinfarcts and marginal changes of AD in another, and focal atrophy without specific diagnostic features in the remaining one. An independent blind review of the slides by a neuroanatomist experienced in AD resulted in agreement with five of the 14 AD diagnoses, disagreement with seven and classification as questionable AD in the remaining five. The same slides are currently under review by a neuropathologist and preliminary results indicate further discrepancies. We conclude that even though neuropathologists are well aware of the diverse interpretations of the histopathologic findings in clinically diagnosed AD, other AD investigators are generally unaware of the substantial interpretive component in "definite" AD. Consequently, it would seem reasonable to explore the range of possible neuropathologic interpretations when assessing the validity of potential markers of AD.

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ROLE OF MELATONIN AND SEROTONIN IN AGING: AN UPDATE. Bernard R. Grad and Roman Rozencweig*, Montreal, Quebec, Canada H3X 1Y3.

In 1987, we proposed that aging is a pathological process resulting from a decline in the number of pinealocytes of the pineal gland resulting in a nightime deficiency of melatonin (M) synthesis from serotonin (S). The present paper reviews the pertinent literature since our first publication (Med. Hypotheses 23: 337-352, 1987).

Evidence is presented for the role of M and S in controlling the neuroendocrine system and immune network. Moreover, by acting to increase the intracellar cGMP to cAMP ratio, M provides widespread protection against free radical damage. Hence, a reduction of M leads to a cascade of aging processes, including increased cross-linkages which interfere with cellular metabolism throughout the organism. Also, a deficiency of M favors progressive arteriosclerotic changes and platelet aggegration which in turn promote the development of stroke and heart disease. The reduction of M has also been implicated in tumor formation and in Alzheimer's disease. The administration of M has been shown to increase life span in older animals and elevated M levels have been observed in longer-lived animals on calorie-restricted diets.

In conclusion, recent evidence supports the original hypothesis that a M deficiency, especially in relation to S, favors the promotion of aging in the organism.

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SUBJECTIVE SLEEP QUALITY IN A GERIATRIC ASSESSMENT UNIT (GAU). Maria E. Camacho* and Richard G. Crilly, Division of Geriatric Medicine, U. of Western Ontario, London, ON, Canada.

Poor sleep is frequently reported by patients admitted to the GAU. However routine assessment of sleep quality is not performed. The Pittsburg Sleep Quality Index (PSQI) was used to study 43 patients admitted to the GAU, excluding patients with clinical diagnosis of dementia or Folstein mini mental state examination less than 25. Mean age was 81 ± 8.7 (65 to 97), 13 men and 30 woman. PSQI mean score was 8.5 ± 5.0, 32 subjects (74%) scored over 5 (a score previously identified in poor sleepers). PSQI global score was highly correlated with sleep efficiency (r=0.70), subjective sleep quality (r=0.68), sleep disturbance (r=0.60), sleep latency (r=0.60) and total sleep time (r=0.55). Interestingly, although 56% realized they were taking sleeping medication, 70% actually were. In conclusion, poor sleep quality was frequently reported in this geriatric population. Routine evaluation of sleep quality is recommended to promplty identify sleep alterations in patients admitted to a GAU.

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DYNAMIC METABOLIC TESTING FOR LONGEVITY AND FITNESS. Daniel Hershey, M.L. #171, University of Cincinnati, Cincinnati, Ohio 45221-0171.

An evaluation of fitness and longevity has been developed, based on measurements of the basal metabolic rate and the metabolic response to exercise. The data is obtained in 22 minutes using a Basal-Tech whole-body calorimeter.

Recently seven marathon runners were tested in the calorimeter. The results were expressed as a Modified Overall Fitness Evaluation (MOFE). The subjects also had an independent fitness test (Profile 1000 program). The regression correlation was Profile 1000 = 21.5 MOFE + 717. This means the measurement technique using the whole-body calorimeter can be used to rank the fitness and longevity potential of persons according to their MOFE numbers. Longevity projections for the individual are accomplished from one set of dynamic metabolism data, obtained in 22 minutes, by converting the data to Excess Entropy Production (EEP), and establishing where the EEP values go to zero. Previously we produced longevity projections based on the EEP, but the data were obtained for static tests of metabolism over two, five, and even fifteen year durations.

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DETECTION OF INCREASED MTDNA DAMAGE IN AGING MICE. Janet Huang, Daryl Davies and Gino Cortopassi, Institute for Toxicology, Dept. of Molecular Pharmacology and Toxicology, University of Southern California, Los Angeles, CA 90033

It has been shown that a particular type of mitochondrial genetic damage can be amplified by the polymerase chain reaction in humans; this damage is most likely the result of deletion(s) of the mitochondrial genome. It is possible that such damage is deleterious--if so, one might want to study if particular interventions would decrease the age-related accumulation of such damage. We have found mtDNA damage does increase strikingly with age in a C57BL/6J mouse model system, and that the increased damage is likely the result of an increase in a particular deletion between two direct repeats of the mouse mitochondrial genome. Several similarities and some differences-- in structure, in tissue specificity, and in rate of accumulation exist between the mouse deletion and the human deletion that we have previously described (Cortopassi and Arnheim, 1990).

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INCREASE OF ANTIOXIDANT CAPACITY OF PLASMA BY DIETARY β-CAROTENE SUPPLEMENTATION IN OLDER SUBJECTS. M.Meydani*, A. Martin, J. Ribaya-Mercado, J. Gong, R. Russell and J. Blumberg. Antioxidant Research Laboratory, USDA Human Nutrition Research Center on Aging at Tufts University, Boston, MA 02111.

In a double-blind, placebo controlled study the antioxidant effect of dietary β-carotene supplementation on the potential of plasma peroxidation was investigated. 12 healthy women >65 y supplemented their usual daily diet with 90 mg β-carotene or placebo capsules for 3 wk. Plasma β-carotene and α-tocopherol and *in vitro* production of phospholipid hydroperoxide (PC-OOH) at 37°C in the presence of 50 mM 2,2'-azobis (2-aminopropane) hydrochloride (AAPH), a free radical generator, were measured before and after supplementation. Plasma β-carotene increased from 29±6 to 277±68 μg/dl ($p<0.05$) and α-tocopherol tended to rise (1368±279 vs. 1665±347 μg/dl, $p=0.08$) in supplemented subjects. β-Carotene supplementation did not effect basal levels of plasma PC-OOH as measured by HPLC postcolumn chemiluminescence (placebo: 45± 36, suppl: 103±47 pmol/ml), but did effect AAPH-initiated production of PC-OOH. Before supplementation, the lag phase of plasma PC-OOH production was 1 h with levels reaching to 5.0±3.4 nmol/ml after 6 h incubation. After β-carotene treatment, peroxidation was delayed with the lag phase increased to 4 h. Furthermore, plasma PC-OOH after 6 h incubation was significantly lower than before supplementation (2.0±2.0 vs. 5.0±3.4 nmol/ml) ($p<0.05$). In this system, plasma ascorbate levels were depleted first, followed by the sequential loss of α-tocopherol, γ-tocopherol, bilirubin, urate, and β-carotene. These results indicate that β-carotene supplementation increases the plasma antioxidant capacity of older women.

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FASTING-INDUCED DEPLETION OF GLUTATHIONE IN THE AGING MOUSE. Barbara Vogt, Yvonne Leutzinger, and John Richie, Jr.*, American Health Foundation, Valhalla, NY 10595.

Aging is associated with a general deficiency of glutathione (GSH). Since starvation is also known to lower hepatic GSH levels, we have investigated the combined effects of 24 hr food deprivation and aging on liver, kidney and blood GSH and cyst(e)ine levels in C57Bl/6N mice. No age-related differences in baseline hepatic GSH were observed between young (6 months), mature (12 months),

and old mice (24 months), consistent with previous findings that the deficiency in liver is not apparent until about 29 months of age. After six hr of fasting, an age-dependent reduction in hepatic GSH was already evident. After 24 hr, mature animals had a 4-fold greater decrease, and old animals had a 5-fold greater decrease in GSH ($P<0.001$) than the young animals. Liver weight also declined, decreasing total liver GSH content by 24% in young, 44% in mature, and 56% in old mice. Renal GSH and hepatic cyst(e)ine concentrations were unaffected by fasting. In young and mature mice, depletion of hepatic GSH was accompanied by a concomitant increase in blood GSH and kidney cyst(e)ine levels after 6 hr of fasting, suggesting enhancement of hepatic GSH efflux. However, in old animals, GSH depletion was associated with decreased blood GSH and kidney cyst(e)ine. These results demonstrate that under the stress of fasting aging changes in hepatic GSH homeostasis are revealed well before the GSH deficiency is observed. These aging changes may be due to decreased GSH turnover resulting from impaired biosynthesis.

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ARE ALL DIURETICS EQUALLY HAZARDOUS IN OLDER HYPERTENSIVES? Favorable Blood Pressure (BP) and Adverse Event Experience With A New Indoline-Derived Diuretic.

Harold W. Schnaper, Charles Curry, Adesh K. Jain, Donald Weidler, et al.

INDAPAMIDE (INDAP) is the first of a family of diuretics with an indoline base instead of the traditional thiazide chemical structure. Past studies suggest fewer and milder metabolic changes with blood pressure (BP) lowering doses than with some thiazide diuretics.

One hundred ninety five older patients (≥ 50 years) with mild to moderate hypertension were randomized, double blind [after 4 weeks of placebo (P) washout] either to low dose INDAP (1.25 mg daily) or P. One hundred sixty eight completed the 8 week parallel trial. The 81 INDAP treated participants showed a significant drop in sitting diastolic BP as early as 2 weeks into the double blind, compared with the P group ($p \leq .0015$). By 8 weeks, the difference was significant at the $p = 0.0001$ level. Secondary efficacy measures (sitting and standing systolic pressures, diastolic BP < 90, or > 10 mean drop) were also significantly improved for the INDAP group ($p \leq 0.0014$).

Incidence rates for all adverse events were equal in both groups (INDAP 41%, P 40%); as were drug related adverse events (INDAP 15%, P 13%). Drug related adverse events occurring in ≥2% of the INDAP group were headache (4%), dizziness (4%), asthenia (2%), pain (2%), visual problems (2%), and impotence (2%). Laboratory changes over baseline to 8 weeks in the INDAP group included potassium (-0.27 mEq/L); uric acid (+0.76 mg/dL), and BUN (+1.42mg/dL). None were clinically meaningful.

Older hypertensives tolerated INDAP treatment at least as well as placebo in this short term double blind trial, with significant benefits in blood pressure improvement.

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MECHANISMS OF THE PREMATURE/ACCELERATED AND OF DELAYED/RETARDED AGING AND THEIR REGULATION FOR PREVENTION OF DEGENERATIVE DISEASES. M. M. VILENCHIK, CORNELL UNIVERSITY COLLEGE OF VETERINARY MEDICINE, ITHACA, NEW YORK 14853

Using an improved method of alkaline sucrose gradient sedimentation (M. Vilenchik, Int. J. Radiat. Biol. 56, 685, 1989), the age-dependent decline of DNA repair and accumulation of DNA damage (DNAging) was found in "young" human fibroblasts (obtained from the skin of 25-30 years old donors). This DNAging can be a biomarker of premature aging of the skin, possibly connected with the exposure to mutagens. DNAging, measured using circular dichroism method and other methods, in rat brain is accelerated by radiation. This DNAging is connected with instability of brain DNA ( M. Vilenchik et al. J. Neurochemistry, 29, 1159) and determines rate of "normal" and radiation-induced aging of rats. In contrast, drastically increased resistance of the centenarians to diseases, such as cancer and Alzheimer's disease (M. Vilenchik, Biological Basis of Aging and Longevity, 3th edition in Spanish, pp. 321-328, 1989) can be connected with retardation of DNAging due to enrichment of the diet of this robust population in certain micronutrients.

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REDUCING EXPOSURE TO VISIBLE LIGHT INCREASES THE LIFE SPAN OF MICE. Harold Massie and Valerie Aiello, Masonic Medical Research Laboratory, Utica, N.Y. 13501

The purpose of the study was to establish the effect of visible light on the basic aging process. Young (57 days of age) male C57BL/6J mice were esposed to two different levels of low intensity light for their remaining life span. Each group of 25 mice were kept on a 12:12 hr light/dark cycle with overhead fluorescent lighting. During the 12 hr light cycle the experimental group were exposed to 1 lux or less of light. The control mice received 50-100 lux during the 12 hr light cycle. Both groups of mice were exposed to 400 lux of light for a period of 10 min/wk during routine examination, cage cleaning and food and water change. The entire survival curve was shifted to higher values in the dark group as compared to the control group with a 8.3% ($0.01 < P < 0.05$) increase in the mean life span for the mice shielded from low levels of environmental light. The increased survival of the "dark" group cannot be ascribed to dietary restriction since both groups had free access to food and water at all times. The dark group, in fact, gained more weight than the control group. We conclude that photoaging mediated through photodynamic action is an important aspect of the general aging process.

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CHARACTERIZATION OF HYPERTROPHY-ASSOCIATED GENE EXPRESSION. Lorraine Chalifour*, Emma Holder, Ramez Fahmy, Lunjun Mou, Ala Eddin Al Moustafa, Dao Ly, Tracey Dorrance, Sheida Bonyadi, Jeanne Vestergaard and Hashem Salloukh, Bloomfield Centre for Research in Aging, Lady Davis Institute for Medical Research, Sir Mortimer B. Davis - Jewish General Hospital, McGill University, Montreal, Quebec H3T 1E2.

Heart disease remains the most frequent single cause of death in people over 65. A common response to disease is hypertrophy of the heart. Normally cardiomyocytes will proliferate only in fetal and early neonate life. Further growth of the heart is the result of an increase in size of the cardiomyocytes. Adult cardiomyocytes are unable to proliferate. We isolated a line of transgenic mice which develop a hyper-trophic heart disease and die prematurely. Analysis of muscle and non-muscle gene expression has implicated an elevated early growth response-1 and a decrease in *junB* and heat shock protein 90 expression as early hypertrophy markers these mice. We found expression

of such transcription factor and signal trans-duction genes as c-*jun*, c-*fos*, p53, trans-forming growth factor-ß, c-*myc*, Ha-*ras* and Ki-*ras* to be increased later in hyper-trophy. The hypertrophy present in disease may be different than the normal hyper-trophy of growth as *junB* and HSP 90 were not found to be elevated in fetal or neonate rodent hearts. We have recently isolated novel genes which are differentially expressed in normal versus hypertrophied heart.

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**CELL CYCLE TRAVERSE, FIBROBLAST SENESCENCE, AND PROGRAMMED CELL DEATH.** Eugenia Wang,*Menq-Jer Lee and Siyaram Pandey, Bloomfield Centre for Research in Aging, Lady Davis Institute for Medical Research, Sir Mortimer B. Davis - Jewish General Hospital, McGill University, Montreal, Quebec, Canada H3T 1E2.

We have identified two proteins, statin and terminin, whose expressions are nonproliferation-specific. Recent results show that in nonreplicating cells, statin, a nuclear protein for both quiescent and senescent cells, is phosphorylated and is associated with a p45 serine and threonine kinase. In addition, a third protein, unphosphorylatd RB, is also present in the statin/p45 kinase complex. Biochemically the three proteins, statin, p45 kinase and unphosphorylated RB, form a trio-complex whose anchoring onto the nonproliferating cell nuclear matrix depends on the phosphorylated nature of statin. Characterization of the kinase action shows that statin may function to sequester the kinase phosphorylating action needed for the associated RB protein in its biochemical functional modes. Terminin is found in senescent cells as a 60 kda protein; its conversion to 30 kda signals the event of cell death. Neither the induction of programmed cell death (apoptosis), nor the conversion of terminin from 60 to 30 kda, is easily achieved in senescent cells; along with the finding of an unusually high level of *bcl2* in senescent fibroblasts, this result suggests that the failure to die is characteristic of the senescent state. However, in apoptotic 3T3 fibroblasts, one observes the typical DNA fragmentation preceded by the presence of terminin in the 30 kda form, as well as high c-*myc* and low *bcl2* presence. Emerging from these results is a picture describing the senescent state as a specialized status protecting cells from further proliferation, and from apoptosis.

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**TRANSGENIC MOUSE MODELS FOR β-AMYLOIDOSIS.** Kenichiro Fukuchi, Dennis D. Kunkel[1], Nils Eriksen, Charles E. Ogburn, Annette C. Smith, Clement E. Furlong[2], Samir S. Deeb[2], David Nochlin, S. Mark Sumi, Kenneth A. Walsh[3], Earl P. Benditt, and George M. Martin*, Depts. of Pathology, [1]Neurological Surgery, [2]Medicine, and [3]Biochemistry, Univ. of Washington, Seattle, WA 98195

**Seminal roles of the β-amyloid precursor protein (βPP) and the β-amyloid protein (Aβ) in the pathogenesis of Alzheimer's disease (AD) have been suggested. We (Fukuchi *et al.*, *Biochem. Biophys. Res. Commun.* 182, 165, 1992) and others (Yankner *et al.*, *Science* 245, 417-20, 1989; Maruyama *et al.*, *Nature* 347, 566-9, 1990) also demonstrated that the C-terminal regions of βPP is neurotoxic and amyloidogenic by overexpression of a cDNA in neuronal and COS cells. We therefore established transgenic mice bearing this cDNA (which included the signal sequence of βPP plus the 99 amino acid C-terminus of βPP) under the control of a cytomegalovirus enhancer and chicken β-actin promoter. High levels of expression of the transgene in all tissues of the transgenic mice were confirmed by Northern and Western blot analyses. By Tris-Tricine SDS-PAGE analysis, an 8-fold increase in the levels of the C-terminal fragments of βPP in the transgenic brain and at least a 50-fold increase in the transgenic intestines were observed as compared to control, nontransgenic tissues. Six- (n=1), 9- (n=1), 13- (n=1), 14- (n=4), and 16-month-old (n=4) transgenic mice were sacrificed for immunohistochemical and histopathological analyses. Using antibodies against Aβ, extensive β-amyloid deposits were found in the small intestines in 7 of 9 transgenic mice older than 12 months. These deposits were also characterized by Congo red birefringence. By electron microscopy, these β-amyloid fibrils were approximately 7-11 nm in diameter, comparable to the β-amyloid found in the brains of AD patients. No β-amyloid deposits were found in control nontransgenic sibs. Our transgenic mice have so far (up to 16 months) failed to produce pathological changes similar to those found in the brains of AD patients. Our transgenic mice, however, can be used for discovering factors that modulate the progress of β-amyloidosis, including drugs that might prevent deposition of Aβ.**

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DNA POLYMERASE α ACCESSORY PROTEIN (αAP) ENHANCES DNA BINDING AND ACTIVITY OF ENZYME ISOLATED FROM AGED HUMAN DONORS. David Busbee*, Matthew Schroeder, Vinod Srivastava and Susan Miller, Department of Anatomy and Public Health, College of Veterinary Medicine, Texas A&M University, College Station, TX 77843.

DNA polymerase α (pol α) isolated from fibroblast lines established from aged human donors (AG3529) exhibits decreased DNA binding and activity compared with fetal fibroblasts (WI38). WI38 and AG3529 cells transformed with pSV3.neo, an SV40-derived plasmid expressing large T antigen (T-ag), exhibit pol α with bound T-ag which has high specific activity and high affinity of binding to DNA templates. Transformed WI38 (2RA) shows two pol α peaks, each with approximately the same specific activity as the parent cell line. Transformed AG3529 (2-1) shows a single pol α peak which has about 15-fold higher specific activity and significantly higher DNA binding affinity than the parent cell line pol α. Pol α from these cells was treated with pol α accessory protein (αAP), isolated from the mouse transformed cell line L1210. Pol α from WI38, 2RA and 2-1 showed no enhanced DNA binding and increased specific activity in the presence of αAP. However, pol α from AG3529 showed significantly increased binding affinity for DNA in the presence of αAP, and exhibited about a 6-fold increase in enzyme activity. αAP was found to be an ATP-dependent helicase. We propose that a decrease in binding of αAP to pol α in old cells may account for a loss of pol α DNA binding affinity and specific activity which may be associated with the $G_1$/S replication block seen in aging cells. Preliminary data suggest that the age-related loss of pol α activity may be associated with decreased expression of αAP. Supported in part by AG06347 and an enhancement award from Texas A&M University.

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A BIOLOGICAL PERSPECTIVE ON MOBILITY AND AGING. Hildegard E. Enesco, Department of Biology, Concordia University, Montreal, Quebec

In humans, declining mobility levels with age are well documented. In this paper, we will examine whether animal models or evolutionary comparisons may teach us something about the mechanisms responsible for mobility loss. Decrease in spontaneous activity level with age is well documented in many animal species, including rotifers, nematodes, fruit flies, house flies, rats and mice. Some biologists interpret this loss of activity in terms of the "rate of living" theory of aging. While observations with some species suggest that increased activity level decreases lifespan, data from other species does not support this concept. Data from rotifers will be examined to illustrate this point. In physiological terms, a number of factors could account for the decreased mobility or activity level observed with increasing age. These include increased

collagen cross linkage in connective tissue, decreased coordination level of the nervous system, decreased muscle strength and decreased mitochondrial energy production. Most efforts at treatment, including growth hormone treatment and carnitine treatment, have focused in these latter two parameters.

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ALTERATIONS IN NEUROPHYSIOLOGY AND MOTOR LEARNING IN AGED RODENTS. Paula Bickford, Veterans Administration Medical Center, Denver, CO 80220.

Motor learning is fundamental to normal execution of movement because continual adaptation to change is required. Age-related declines in motor function are well documented for both humans and animals. Alterations in the ability to learn new motor skills, however, has not been studied extensively. In humans there is a decline in mirror tracking proficiency with advanced age suggesting that motor learning is altered. We have been examining the effect of age on acquisition of new motor skills using a rodent model. Fischer 344 rats are trained to perform a motor task that involves negotiating a runway with pegs placed in various patterns. Learning of this task is altered by manipulations of the noradrenergic system of the cerebellar cortex. This is observed with young animals treated with 6-hydroxydopamine(6-OHDA) to deplete NE, young animals treated with propranolol (10 mg/kg. i.p.), and 20 month old F344 rats that have age-related declines in cerebellar noradrenergic functions. Two weeks after training on a regularly spaced rod pattern, the animals were tested on a novel peg pattern. The young 6-OHDA lesioned, propranolol treated and aged rats all demonstrated deficits in acquisition of the novel motor task when compared to young control rats suggesting that a deficit in NE transmission in the aged rats may be important in the age-induced alterations in motor learning. Subsequent to behavioral testing extracellular recording from cerebellar Purkinje neurons in young control and aged rats demonstrated a correlation between performance on the motor task and the ability of NE to modulate the actions of GABAergic transmission ($r=.78$, $p<0.05$). This supports our hypothesis of a role for cerebellar noradrenergic function in motor learning deficits associated with aging.

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BIPEDALISM, AGING AND EARLY HOMININID ADAPTATIONS. Michael S. Bisson, Department of Anthropology, McGill University, Montreal, Quebec

The shift from quadrupedal to bipedal locomotion was a critical event in human evolution. Although the exact date and nature of this transformation is not known, the oldest hominid fossils (c. 4,000,000 BP) already possessed the anatomical specializations allowing habitual bipedalism together with more primitive characteristics including unusually long and strong forearms. Studies of Australopithecine and Homo habilis fossils and archaeological sites (c. 4-1,600,000 BP) indicate that early hominid adaptations differed significantly from both living non-human primates and human hunter-gatherers. Bipedal locomotion allowed energy efficient movement between widely scattered food sources in the arid African savannas, and strong arms aided frequent tree climbing for food and predator avoidance. Diets were gritty vegetal foods, fruit, and meat scavenged from defleshed predator kills. Evidence for food sharing and home bases is ambiguous. Maximum lifespan was c.30 years.

Anatomical changes related to bipedalism created stresses that in modern humans result in both injuries and chronic conditions particularly among the elderly. Hypermuscularity in early hominids probably prevented many injuries. Lifespans were too short for chronic or degenerative conditions to appear, and there is no evidence of the long term survival of severely injured or lame individuals. It is not until the Neanderthal period (c. 150-35,000 BP) that healed fractures as well as arthritis and extreme tooth loss become common. The appearance of disease associated with aging is one of the earliest indications that hominids were beginning to behave like humans.

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ROLE OF HOME ENVIRONMENT IN MOBILITY AND TRANSFERS WITH AGEING. F. Trickey*, C. Gosselin, D. Maltais, Public Health Unit, Montreal General Hospital, Montreal, Quebec, H3H 2K3.

Among the older population, because of increasing vulnerability, the home environment exerts strong influence on the individual's level of functioning, both in facilitating and hindering daily living activities. Mobility problems affect 81% of seniors reporting a disability. According to a large Canadian survey, close to 30% of community living seniors with disabilities, do not have the required equipment in their home to move about independently. Results of a study at the Public Health Unit of the Montreal General Hospital added more understanding about the obstacles to mobility and transfers in frail seniors' homes. The information is based on data collected among a group of 208 seniors who received an expert assessment of their homes by an Occupational Therapist (O.T.). Using a home assessment guide, the O.T. examined what characteristics in the individual's homes contributed to exacerbate difficulties in daily living activities. Of those activities under study, 14 related to mobility and transfers. Those activities were closely examined in order to better understand the elements in the structure of the home or in the choice of furniture and equipment that may become obstacles to senior's mobility and transfers. This presentation will examine the various barriers to mobility and transfers in frail seniors homes as well as the modifications that can be implemented to help seniors overcome those barriers.

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AGE-RELATED CHANGES IN HORIZONTAL LOCOMOTER ACTIVITY IN DROSOPHILA INBRED LINES. L. K. Dixon* and L. Karkowski-Shuman. CDHG, Penn State University, University Park, PA 16802.

Age-related declines in locomotor activity have been demonstrated in all Dipteran species studied to date. To investigate this age-related phenotype in more detail, we studied ten highly inbred lines of Drosophila at three ages: 7, 21, and 35 days. An automated activity recording device was placed horizontally in a light (12L:12D) and temperature (25oC) controlled incubator. Diurnal activity counts were obtained from 10-12 naive flies of each sex. Analysis of variance results indicated significant effects of Strain, Age, and Sex, as well as Strain x Age and Strain x Sex interactions. Although nine of the strains showed the familiar activity decline, one strain (12D) showed a slight increase in activity with age. It is possible that locomotor activity is not a good biomarker of aging for this strain; however, a decline in activity might be seen in this strain at ages greater than 35 days. This is currently being studied. All strains were most active during the light phase. Sex

differences were strain and light-condition dependent. Some strains showed no sex differences (C2), while others showed sex differences only in one light condition. When sex differences did occur, in all strains but one, females were most active. These results indicate that although locomotor activity clearly is related to age, the effect of genotype is important in its expression.

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GROWTH FACTORS AND BRAIN AGING. Ďoubal* S., Kučová D., Faculty of Pharmacy, Charles University, Hradec Králové, Czech Republic, 501 65.

Growth factors (GFs) are regulatory polypeptides which control, among others, synthetic activity, trophic conditions, differentiation and survival of target cells. From gerontological point of view, it is important that GFs influence processes of tissue repairs and regeneration. GFs are necessary for the maintenance of functional and differentiated state of tissues. An important role of GFs in mechanisms of brain aging is highly probable. The connection of GFs with an axis melatonin - growth hormone is important in this context. The prospects of using of GFs in the treatment of Alzheimer's and Parkinson's diseases and in the improvement of dystrophic changes in aging brain are particularly important from clinical standpoint.

The survey of main growth factors participating on the control of functions of CNS is presented in this work. Schemes of mechanisms of action of GFs in the brain are proposed, including the coupling of GFs with melatonin - growth hormone axis. The outline of prospects of treatment of age-related diseases is further presented. Possible role of positive feedbacks in the mechanisms of action of GFs is analysed and its influence on the dynamics of aging is discussed.