TWENTIETH ANNUAL MEETING — American Aging Association
FIFTH ANNUAL MEETING — American College of Clinical Gerontology
Wednesday through Saturday
October 3-6, 1990
Roosevelt Hotel
45th & Madison Avenue
New York, New York 10017

CLINICAL GERONTOLOGY

1. Spivack, B.: **Rheumatologic aspects of aging.**
   Chief of Medicine, New Britain Memorial Hosp. and Assist. Prof. Med., Univ. Connecticut School of Medicine, Farmington, CT
2. Gambert, S. R.: **Hormonal aspects of aging.**
   Prof. Med. and Director of Center for Study of Aging and Health Promotion, New York Medical College at Valhalla, NY
3. Tuckman, J.: **Treatment of spasm with alpha-2 adrenergic agonists in patients with central and spinal cord lesions.**
   Assoc. Medical Director, Bronx Veterans Admin. Med. Center, Bronx, NY
4. Tsitouras, P.D.: **Hormone "replacement" therapies in older men and women: An update.**
   Assoc. Chief of Staff, Bronx Veterans Admin. Medical Center and Dept. of Geriatrics, Mount Sinai Medical School, New York, NY
5. Starer, P.: **Urinary incontinence: basic and clinical aspects.**
   Chief, Geriatric Section, City Hospital Center at Elmhurst, Queens, and Assist. Prof. of Geriatric Med., Mount Sinai School of Medicine, New York, NY
6. Podolsky, S.: **The diabetic foot and other problems of older diabetics.**
   Chief, Metabolism/Endocrinology Section, Boston VA Outpatient Clinic, Dept. of Medicine, Harvard Medical School, Boston, MA

ANNUAL SYMPOSIUM
"Nutrition and Aging: Part A"

7. *Meydani, M:* **Protective role of dietary vitamin E on the oxidative stress in aging.**
8. Garry, P.: **Effect of aging on nutritional status of free-living elderly.**
9. Hallfrisch, J.: **Nutrition and aging in the Baltimore Longitudinal Study of Aging-Selected Mineral Intakes.**
10. Rivlin, R.: **Riboflavin nutrition, body composition and aging.**
11. **Dawson-Hughes, B.: Calcium and vitamin D nutrition in the elderly.**
12. Young, V.: **Protein and energy metabolism during human aging.**
13. Chandra, R.: **Nutritional regulation of immunity and the risk of illness in old age.**

Poster Session I

14. **Schultz*, B.M., Gupta, K.L., and Gambert, S.R.: Presentation of urinary tract infections (UTI's) in institutionalized elderly.**
15. **Sarma*, R.J., and Greenwood, J.: Exercise testing in elderly patients with myocardial infarction: differences in men versus women.**
16. Yang, Y.-C., Lin, A.-G., Liu*, E.-A., and Dai, Q.-S.: **Control study on the risk factors of cerebral vascular disease.**
17. Shindler*, O.I., Shindler, D.M., and Kostis, J.B.: **Does aortic insufficiency affect left ventricular compliance in the elderly heart?**
18. Miyamoto*, A., and Roth, G.S.: **Age-related decreases in α-adrenoceptor signal transduction in parotid cells.**
19. Tatariunas, A.B.: **Cardinal problems in the investigations of lipofuscin granules (LG) in modern experimental gerontology.**
20. Igarashi*, Y., and Takahashi, I.: **Lipofuscin pigment in the spiral ganglion of vitamin E deficient rats.**
21. Weiss*, A., Livne, E., and Silbermann, M.: **Hypertrophic layer of articular cartilage in aging mice is actively involved in bone remodeling.**
22. Prabhakaram, M., and Nath*, S.S.: **Selective regulatory effect of some hormones and neurotransmitters on the glutamate dehydrogenase from rats of various ages.**

MINISYMPOSIUM:
"Free Radical Reactions and Aging."

23. Kent, B.: **Effects of genotype and diet on metabolism and lifespan.**
24. Emerit, I.: **Increased oxyradical production in aging NZB mice.**
25. Sohal, R.S.: **Antioxidants or pro-oxidants as determinants of aging**
26. Alessio, H.: **Total antioxidant protection in different species and in humans after vitamin E and C supplementation.**
27. Richardson, A.: **Effect of dietary restriction on gene expression.**
28. Cohen, G.: **Peroxidative damage in Parkinson's disease.**
29. Ames, B.: **Oxidative DNA damage and aging.**

MINISYMPOSIUM:
"Recent Advances in the Neurobiology of Aging and Alzheimer's Disease."

30. Higgins, G.: **Increased protease inhibitor containing forms of APP in the aging CNS.**
31. Johnson, S.A.: **Neuronal APP-751/APP-695 mRNA ratio and plaque density in Alzheimer hippocampus.**
32. Slemmon, J.R.: **Endogenous peptide profiling in AD brain.**
33. Iqbal, K.: **Cytoskeletal protein pathology in aging and Alzheimer's disease.**
34. Kosik, K.S.: **The neuritic dystrophy of Alzheimer's disease.**
35. Marshak, D.R.: **Involvement in Alzheimer's Disease of S100 as a neurotrophic factor.**
36. Coleman, P.D., and Rogers, K.: **Molecular markers of intercellular signalling in normally aging brain and in Alzheimer's disease.**

ANNUAL SYMPOSIUM: "Nutrition and Aging, Part B"

37. Holt, P.: **Food restriction and the gut.**
38. Simic, M.: **Reduction of DNA damage by dietary restriction.**
39. Taylor, A.: **The relationship between age, nutrition and eye lens cataract formation.**
40. Mobarhan, S.: **The effects of aging on metabolism of vitamin A and beta-carotene.**
41. **Meydani, S.: Nutritional modulation of the immune system in the aged.**
42. Lipschitz, D.A.: **Aging, nutrition and hematopoiesis.**
43. Wood, R.: Mineral needs in the elderly: defining a research agenda for the 1990s.
44. Blumberg, J.B.: **The current status and future directions of nutrition and aging research.**

Luncheon (Friday)

Denham Harman: **Twenty years**

Video: Presentation of the 1989 Distinguished Achievement Award to President Ronald Reagan

Luncheon Speaker:
Bruce Ames, Ph.D.
"Prospects for Increasing the Functional Life Span"

Annual Awards:

Research Award —
Bruce N. Ames, Ph.D.

"This award is presented to Dr. Ames for his outstanding contributions to the role of free radical reactions in aging and disease. These contributions include: 1) development of an innovative method for measuring oxidative DNA damage in individual humans in a non-invasive manner, by measuring oxidative DNA damage products excreted in the urine after DNA repair; 2) demonstrating that the metabolic rate of various organisms is related to the oxidative DNA damage rate; 3) the discovery that uric acid, bilirubin and carnosine have significant antioxidant roles; 4) demonstrating that ascorbate is the most effective aqueous-phase antioxidant in human blood plasma, and 5) studies on the transcriptional regulator of oxidative stress-inducible genes. These contributions have significantly broadened knowledge of the action of oxygen-free radicals in living systems."

Clinical Gerontology Research Award —
Robert I. Gregerman, M.D.

"This award is presented to Dr. Gregerman for his major basic research contributions to the endocrinology and biochemistry of aging. These include: 1) studies on the age-related changes of thyroid function in man which underlie modern thyroid hormone therapy in the elderly; 2) elucidation of the pathophysiologic alteration of thyroid hormone secretion and metabolism, as well as the secretion of thyrotropin, during severe illness; 3) the first description of the drug-induced syndrome of inappropriate antidiuretic hormone secretion, a phenomenon which primarily affects the elderly, and 4) age-related alterations of hormone action at the membrane level.

"Dr. Gregerman has also contributed significantly to biomedical gerontology in his role over a span of more than 30 years as a teacher and mentor to young investigators."

Distinguished Achievement Award —
Miss Helen Hayes

"Actively involved in the theater since her first appearance on stage 84 years ago, our Distinguished Achievement Award recipient epitomizes the purpose of this award, established to call attention to the fact that chronological age is not a barrier to a full and productive life. Miss Helen Hayes first appeared on stage at age 6 and has earned acclaim in every dramatic media: stage, film, and television. Her appearances include *To the Ladies, Caesar and Cleopatra, Mary of Scotland, Farewell to Arms,* and *Victoria Regina.* In 1982 she received the Academy Award for the motion picture *Claudet* and in 1971 the Academy Award for Best Supporting Actress in *Airport.* From 1972-1973 she appeared in the television show, *The Snoop Sisters.*

Other activities that have helped to fill her busy life include the presidency of the American National Theater and Academy, chairperson of the women's activities of the National Foundation for Infantile Paralysis and, more recently, involvement in the restoration of a historic theater in Nyack, New York, as the Helen Hayes – Tappan Zee Performing Arts Center.

"Miss Hayes has extended her active productive life far beyond the usual retirement age. She serves as a wonderful role model for a long useful life. We are delighted to present this award to her just five days prior to her 90th birthday."

Paul F. Glenn Award —
Durk Pearson and **Sandy Shaw**

"The Paul F. Glenn Award was established to honor individuals who have made special contributions to biomedical aging research. Durk Pearson and Sandy Shaw are the 1990 recipients of this award.

"Through their book *Life Extension,* articles, and numerous radio and television appearances, they have significantly raised public awareness of the possibility that biomedical aging research will increase the functional life span.

"This award serves as an expression of our appreciation of the continuing advocacy by Durk Pearson and Sandy Shaw of the promise of biomedical aging research."

Special Service Award —
Bernadette L. McQueen

"Bernadette L. McQueen is the recipient of a logo of the American Aging Association. This logo is presented to her in recognition of twenty years of dedicated service to the American Aging Association. Since the inception of this association in 1970, she has ably handled its daily activities. We are grateful."

SUBMITTED PAPERS
Oral Presentations

45. Munkres, K.D.: Pharmacogenetics of superoxide dismutase isozymes in ***Neurospora.***
46. Vlassara*, H., Kirstein, M., Pasagian, A., and Harrison, D.: **Young marrow transplantation into old mice corrects aging-associated defect in macrophage receptors for advanced glycosylation endproducts.**
47. **Dixon*, L.K., and Kelly, J.G.: Drosophila as a model to study chemically induced porphyria and free radicals.**
48. Massie*, H., Whitney, S., and Sternick, S.: **The light theory of aging.**
49. Vydelingum, N. A.: **The influence of aging and obesity on ribosomal S6 phosphorylation in rat fat cells.**
50. Chung, M.H., Kasai, H., Nishimura, S., and Yu*, B.P.: Protection of nuclear DNA damage by dietary restriction in the aged liver.
51. Ingram*, D.K., Cutler, R.G., and Roth, G.S.: **Developing a model of dietary restriction in nonhuman primates.**
52. Fahy, G.M.: **A physiological view of aging and its implications for interventive gerontology.**
53. Niggli*, H. J., Rothlisberger, R., Bayreuther, K., and Francz, P. I.: **UV-induced ornithine decarboxylase as a marker of aging and differentiation in human skin fibroblasts.**
54. Kitani*, K., Ohta, M., and Zs.-Nagy, I.: **The effect of leupeptin on the lateral mobility of proteins in the plasma membranes of hepatocytes of C57BL/6 mice.**
55. Chatterjee*, B., and Roy, A. K.: **Loss of androgen responsiveness of rat liver during aging.**

Submitted Papers
Poster Session II

56. Enesco*, H.E., Bozovic, V., McTavish, A., and Garberi, R.: **Use of rotifers to test the rate of living theory of aging.**

57. Orentreich, N.D., Zimmerman*, J.A., and Matias, J.R.: **Lifespan extension produced by reduced methionine ingestion may be independent of caloric intake.**

58. Koltover, V.: **On the mechanism of life-span prolongation by antioxidant butylated hydroxytoluene.**

59. Lin, A.-G., Yan, Y.-C., Liu, E.-A., and Dai, Q.-S.: **Investigation on trace metal in hair of patients with cerebral vascular disease.**

60. Weiss*, A., Arbell, I., and Silbermann, M.: **Histomorphometry of age-related changes in the proximal femur of female CW-1 mice.**

61. Caprioli*, A., Ghirardi, O., Giuliani, A., Ramacci, M.T., and Angelucci, L.: **Rats exhibit age-related deficits in generalization but not in acquisition of active avoidance test.**

62. Ganguly*, R., Webster, T.B., Yangco, B.V., Sinnott, J., and Chmel, H.: **Influence of physicians' recommendation on influenza immunization acceptance among a group of institutionalized elderly.**

63. Pickart, L., Trachy, R.E., and Patt*, L. M.: **Stimulation of hair growth by peptide copper complexes.**

MINISYMPOSIUM:
"Mitochondria and Aging"

64. **Ames, B.: Oxidative mitochondrial DNA damage.**

65. Sohal, R.: **Role of mitochondria in age-associated oxidative stress.**

66. Fleming, J.: **Role of mitochondria in *Drosophila* aging.**

67. Nohl, H.: **Deviation of linear electron flow in mitochondria as ultimate cause of age-dependent oxidative stress.**

68. Shrago, E.: **Regulation of bioenergetics during aging in rats.**

69. Yu, B.P.: **Modification of mitochondrial aging by calorie restriction.**

SUBMITTED PAPERS
Oral Presentations

70. Sternick*, S., Massie, H., Shumway, M., and Whitney, S.: **Ascorbic acid is synthesized by *Drosophila.***

71. Johnson*, C., Gerson, B., and Podolsky, S.: **Correlation of fructosamine and HbA1c in older diabetic patients.**

72. **Healey*, J.H., Nuby, M., Gundberg, C., Godbold, J., and Bansal, M.: Evaluation of osteocalcin as a serum marker for osteoporosis.**

73. Koltover, V.: **Reliability of biological systems at different organization levels and the problem of molecular mechanisms of aging.**

74. Rosario*, P.G., Greenberg, M., and Weitz, S.L.: **Lymphocytic hypophysitis: a rare autoimmune disorder in the elderly.**

75. Nandy, K.: **Pharmacological manipulations of neuronal aging.**

76. Baird*, M.B., and Hough, J.L.: **Metabolic activation of 3,4-benzo(A)pyrene by hepatic nuclei isolated from young and old C57BL/6J male mice.**

77. Rothschild*, B.M., and Woods, R.J.: **Diffuse idiopathic skeletal hyperostosis (DISH) and arthritis in an early 20th century geriatric population.**

78. Young, Jr.*, R.C., and Rachal, R.E.: **Is tuberculosis in aging retired coal miners a threat to eradication?**

79. Tonna, E.A.: **Iconauthor/interactive videodisc computer programming for biogerontology and gerodontology.**

SUBMITTED PAPERS
Oral Presentations

80. Niedermuller*, H., Hofecker, G., and Skalicky, M.: **Modification of collagen aging.**

81. Kirstein*, M., Brett, J., Radoff, S., Ogawa, S., Stern, D., and Vlassara, H.: **Cell-receptor mediated interaction of glucose-modified proteins and the vascular wall: role in vasculopathy of aging and diabetes.**

82. Russo*, C., Cherniack, E.P., Wali, A., Schwab, R., and Weksler, M.: **Altered T cell repertoire in aging.**

83. Liu*, E.-Z., Yan, Y.-C., Zhao, T.-J, and Han, F.-P.: **The serum level of lipid peroxides as an aging substance in Chinese adults.**

84. Masini, M., Gori, Z., Masiello, P., Pollera, M., Del Roso, A., and Bergamini*, E.: **Age-related changes in the morphology of pancreatic beta-cells.**

85. Glaser, T., Schwarz-Benmeir, N., and Kosower*, N.S.: **Band 3 protein degradation by calpain is enhanced in erythrocytes of old individuals.**

86. Tatelman*, H., and Talan, M.: **Cold tolerance and metabolic heat production in adult and aged C57BL/6J mice at different levels of cold stress.**

87. Lui, E., Fisman*, M., Wong, C., and Diaz, F.: **Changes in the liver in Alzheimer's disease (AD): an investigation of hepatic zinc, copper, and metallothionein.**

88. Bickford-Wimer*, P., and Heron, C.: **Cerebellar noradrenergic function and motor learning impairments in aged F344 rats.**

89. Friedemann*, M., and Gerhardt, G.A.: **Age-dependent changes in the potassium-evoked release of dopamine in the striatum and nucleus accumbens of the Fischer 344 rat: an *in vivo* electro-chemical study.**

90. Spangler*, E.L., Garofolo, P., and Ingram, D.K.: **Effect of n-methyl-d-aspartate (NMDA) receptor blockade and age on acquisition (AQ) of a 14-unit t-maze in the rat.**

1

RHEUMATOLOGIC ASPECTS OF AGING. *B. Spivack,* 105 Longlots Road, Westport, CT 06880.

(Abstract appears on page 108)

2

HORMONAL ASPECTS OF AGING. *S.R. Gambert,* New York Medical College, The Center for Aging and Adult Development, Valhalla, NY 10595.

(Abstract appears on page 108)

3

TREATMENT OF SPASM WITH ALPHA-2 ADRENERGIC AGONISTS IN PATIENTS WITH CENTRAL AND SPINAL CORD LESIONS. *J. Tuckman,* Dept. of Geriatrics, Mount Sinai School of Medicine, New York, NY 10029.

(Abstract appears on page 108)

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HORMONE "REPLACEMENT" THERAPIES IN OLDER MEN AND WOMEN: AN UPDATE. *P. D. Tsitouras,* 115 Whitson Road, Briarcliff Manor, NY 10510.

(Abstract not available)

5

URINARY INCONTINENCE: BASIC AND CLINICAL ASPECTS. *P. Starer,* Chief of Geriatric Section, City Hospital Center at Elmhurst, Elmhurst, Queens, NY 11373.

(Abstract appears on page 108)

6

THE DIABETIC FOOT AND OTHER PROBLEMS OF OLDER DIABETICS. *S. Podolsky,* VA Outpatient Clinic, 17 Court St., Boston, MA 02108.

(Abstract not available)

7

PROTECTIVE ROLE OF DIETARY VITAMIN E ON THE OXIDATIVE STRESS IN AGING. *M. Meydani,* USDA Human Nutrition Res. Center on Aging at Tufts Univ., 711 Washington St., Boston, MA 02111.

Free radical reactions and peroxidation of membrane lipids have been implicated in the mechanism of age associated changes. Dietary vitamin E (E) appears to play a critical role in protecting the cell membrane from peroxy radicals produced from polyunsaturated fatty acids (PUFA) and maintaining membrane integrity. The protective role of E supplementation on exercise induced oxidative damage in 9 young (22-29 Y) and 12 older men (55-74 Y) was investigated. Older men supplemented with E for 7 wk, excreted a significantly lower level of TBARS in urine compared to placebo control following eccentric exercise. In conditions where the composition of membrane fatty acids change to more PUFA, older subjects may be at greater risk of oxidative damage. In a study of 15 young (22-35 Y) and 10 older (51-71 Y) women receiving fish oil capsules containing 1680 mg eicospentaenoic acid (EPA), and 720 mg docosahexaenoic acid (DHA) for 3 mo, older women were found to have greater increases of EPA ($p<0.001$) and DHA ($p<0.05$) in their plasma compared to young subjects. By substituting membrane fatty acids with potentially unstable n-3 fatty acids of fish oil, older subjects were found to be more at risk of oxidative stress than young subjects as indicated by decreased E/EPA+DHA (4.9 fold in older and 3.6 fold in young women) and presence of higher ($p<0.01$) lipid peroxides (6.23±0.75 nmol/ml in older vs. 4.05+0.45 nmol/ml in young women) in their plasma. These findings indicate that E plays an important protective antioxidant role in older subjects, particularly in conditions where oxidative stress and free radicals are potentiated.

8

EFFECT OF AGING ON NUTRITIONAL STATUS OF FREE-LIVING ELDERLY. *P.J. Garry,* Dept. of Pathology, Univ. of New Mexico School of Med., Albuquerque, NM 87131.

In 1979, we recruited 304 healthy men (N=138) and women (N=166) from Albuquerque for a longitudinal study of nutrition and aging. Participation was entirely voluntary and limited to free-living men and women. Mean age of the population in 1980 was 72 years, ranging from 64 to 85 for males and 60 to 85 years for females. Each volunteer measured and recorded all food eaten for 3 consecutive weekdays. Dietary intake information was collected at 7 different periods over the past 10 years. Age-related changes in intake were assessed from cross-sectional and longitudinal perspectives using standard linear regression models to examine the relationship between intake and age and between intake and time.

The weights, as well as energy intake, remained relatively constant over time for males and females, 29 and 26 kcal/Kg, respectively. Mean cross-sectional analysis showed a decrease of 12 and 4 kcal/year with age for men and women, respectively. Longitudinal analyses showed a greater decrease in energy intakes over time, approximately 23 and 17 kcal/year for men and women respectively. Differences between the cross-sectional and longitudinal analyses has been attributed to a secular trend, i.e. lowering of fat intake over time in this population.

9

NUTRITION AND AGING IN THE BALTIMORE LONGITUDINAL STUDY OF AGEING-SELECTED MINERAL INTAKES. *J. Hallfrisch,* Metabolism Section, NIA-NIH, Baltimore, MD 21224.

Older people are at risk of inadequate intakes for a number of minerals (Ca, Fe, Mg, & Zn). The participants of the Baltimore Longitudinal Study of Aging are well-educated middle to upper middle class men & women ranging in age from 20-95. They provide 7-day diet records at their biennial visits to the Gerontology Research Center which include vitamin and mineral supplement intakes & over the counter medications such as antacids & laxatives. Median daily dietary intakes from diet alone in all 564 subjects & from diet plus supplements in those who use them were analyzed by age group & gender. More women than men took supplements. Median intakes of Ca from diet alone were below the RDA for women <60 & intake declined with age. With supplements, the median intake for women <45 just met the Osteoporosis Consensus Conference recommendation of 1000 mg and intakes of older women were far below the 1500 mg recommended for postmenopausal women. Approximately 25% of women <50 & 10% >50 consumed <2/3 RDA for Fe from diet alone. For both men & women, no age group had median intakes that met the RDA for Mg. For Zn, intakes were the most inadequate. For men, 40% consumed <2/3 the RDA. For women, 40-60% consumed <2/3 RDA. More women <60 had inadequate intakes than older women. These results indicate that many people in this well-educated, presumably well-nourished population did not consume adequate amounts of Ca, Fe, Mg, & Zn. For Ca & Zn the number may increase with age. More women than men are at risk. Even those taking supplements did not consume adequate levels of some minerals.

10

RIBOFLAVIN NUTRITION, BODY COMPOSITION AND AGING. *R.S. Rivlin, J.P. Pinto, and P. Dutta,* Dept. of Medicine, Memorial Sloan-Kettering Cancer Center and Cornell Univ. Med. College, New York, NY 10021.

To determine whether the binding of ligands to both beta-adrenergic and adenosine receptors in fat cell membranes is affected by the status of riboflavin nutriture, we performed experiments with (-)(3H)dihydroalprenolol (DHA) and (-)-N^6-(3H)phenylisopropyladenosine (PIA) in adipocytes isolated from normal and riboflavin-deficient rats of varying ages. Three-week-old female Holtzman rats were fed a riboflavin-deficient diet and age-matched controls were pair-fed an identical diet but supplemented with riboflavin for periods of three to forty weeks. At sacrifice, parametrial adipose tissue was excised and fat cell membranes prepared, followed by incubation with either DHA or PIA. In rats seventeen weeks and older consuming a normal chow diet, the binding of both ligands to receptors was markedly decreased compared to that in rats younger than seventeen weeks. Riboflavin deficiency did not have any effect on PIA binding in either young or old animals. Adenosine binding was lower in older than in younger animals regardless of riboflavin nutriture. By contrast, riboflavin deficiency diminished DHA binding in rats younger than seventeen weeks compared to the binding in age-matched controls. No decrease in binding of DHA occurred with advancing age in riboflavin-deficient rats. These results indicate that in fat cell membranes of young riboflavin-deficient animals, beta-adrenergic receptor binding is diminished compared to controls, and unlike that in controls is not influenced by age. It is concluded that both age and riboflavin deficiency may affect the ratio of B-adrenergic to adenosine binding capacity in fat cells, with possible implications for fat accumulation with aging.

11

CALCIUM AND VITAMIN D NUTRITION IN THE ELDERLY. *B.Dawson-Hughes,* USDA Human Nutrition Research Center on aging at Tufts Univ., Boston, MA 02111.

Despite extensive study, there is no consensus on how diet affects bone loss in elderly women. To address the relationship between calcium intake and rate of bone loss, we studied 360 healthy postmenopausal women with low (<400 mg/day) and moderate (400-650 mg/day) usual intakes of calcium in a 2-year, double-blind, calcium intervention trial. The women were treated with placebo (P) or 500 mg of calcium as either calcium citrate malate (TM) (CCM) or calcium carbonate (CC). In women within 5 years of menopause, added calcium had no effect on bone loss. In women 6 or more years since menopause who had low usual dietary intakes of calcium, CCM prevented bone loss from the spine, femoral neck, and radius. In women with moderate usual intakes, added calcium did not affect the rate of loss at any site. Because of the prevalence of low calcium diets, many women are expected to benefit from increased intakes of calcium.

During the winter, the women in this study with intakes of vitamin D under 220 IU/day had higher levels of serum PTH than those with intakes of vitamin D over 220 IU/day. PTH enhances bone resorption, and accelerated bone loss in the winter has been observed by several investigators. A role for vitamin D insufficiency in wintertime bone loss seems plausible but remains to be demonstrated.

12

PROTEIN AND ENERGY METABOLISM DURING HUMAN AGING. *V. Young,* Massachusetts Inst. of Technol., 77 Massachusetts Ave., Rm. E18-613, Cambridge, MA 02139.

(Abstract not available)

13

NUTRITIONAL REGULATION OF IMMUNITY AND THE RISK OF ILLNESS IN OLD AGE. *R. Chandra,* Janeway Child Hlth. Center, Dept. of Pediatric Med. and Immunol., St. John's, New Foundland, Canada.

(Abstract appears on page 108)

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PRESENTATION OF URINARY TRACT INFECTIONS (UTI'S) IN INSTITUTIONALIZED ELDERLY. *B.M. Schultz*, K.L. Gupta, and S.R. Gambert,* Center for the Study of Aging and Health Promotion, New York Medical College, Valhalla, NY 10595.

UTI's are a common problem in institutionalized elderly. Due to a variety of reasons, UTI's may present atypically making diagnosis difficult. Presenting signs and symptoms of UTI's were therefore studied in a 275 bed teaching skilled nursing home; correlation was made to 2 common age-prevalent diseases, diabetes mellitus (DM) and dementia. There were 144 UTI's in 65 persons (23.4%) between 1/1 and 6/30/89; mean, 2.2 per person (range 1-8). 47.2% of infections presented with fever; 7.6%, GU symptoms; 11.8%, altered mental status; and 42.4%, miscellaneous presentations. 8% of UTI's presented with more than one symptom. Although persons with DM and dementia did not differ in their incidence of UTI's, fever and altered mental status were more common in DM. Fever, however, was the only statistically significant finding ($p<0.03$). No presenting findings were significantly more common in persons with dementia. UTI's are common in institutionalized elderly. Close to half present without any evidence of fever and over 90% present without any GU symptoms. Any change in condition warrants a high index of suspicion for a UTI.

15

EXERCISE TESTING IN ELDERLY PATIENTS WITH MYOCARDIAL INFARCTION: DIFFERENCES IN MEN VERSUS WOMEN. *R.J. Sarma*, and J. Greenwood,* Rancho Los Amigos Medical Center, Downey, CA 90242.

To evaluate the safety and usefulness of exercise testing (ET) in elderly patients (EP) with myocardial infarction (MI), we analyzed the data on 46 men and 32 women with history of MI for >1 year. ECG showed MI in 69 patients (pts), bundle branch block 7 pts. Both treadmill (47pts) and bicycle (31pts) ET were used. ET was stopped due to extremity fatigue in 64, angina 3, dyspnea 4 and ventricular ectopy in 4 pts. Heart rate (HR), systolic and diastolic blood pressure (SBP,DBP) at rest, at peak exercise (EX) and change from rest to EX(DELTA) are:

	Males	Females	P
Age	71±6	71±7	NS
Rest HR	68±11	76±12	0.003
Ex. HR	127±22	116±21	0.02
DELTA HR	59±23	40±20	0.0002
% Predicted Max HR	85±14	79±14	0.06
Rest SBP	140±22	145±21	NS
Rest DBP	78±13	76±14	NS
MAX. EX. SBP.	179±31	189±26	NS
EX(HRxSBP)/100	230±64	218±45	NS
DELTA SBP	38±24	45±25	NS
Ischemia: (ANOVA NS)			
Positive (%)	26 (56)	11 (34)	
Negative (%)	3 (7)	5 (16)	
Equivocal (%)	6 (13)	4 (13)	
Indeterminate (%)	11 (24)	12 (37)	

Our results show that ET is safe in EP with old MI; women have significantly lesser HR at rest and at ET although the BP response is similar to men.

16

CONTROL STUDY ON THE RISK FACTORS OF CEREBRAL VASCULAR DISEASE. *Y.-C. Yand, A.-G. Lin, E.-A. Liu, and Q.-S. Dai,* Dept. of Neurosurgery, Harbin Med. University, Harbin, P.R.C. 150001.

This article studies the risk factors of cerebral hemorrhage and infarction in 194 no matched-pair cases. These factors include: 1) sex, 2) age, 3) marital history, 4) nation, 5) education level, 6) occupation, 7) years of work, 8) family income, 9) hypertension and cardiac disease history, 10) duration and therapical state of hypertension and cardiac disease, 11) diabetes history, 12) TIA history, 13) mood, 14) smoking history, 15) quantity and quality of smoking, 16) duration of smoking, 17) drinking history, 18) quality and quantity of drinking, 19) kinds of foods, 20) family history of hypertension and CVD, 21) died age of parents, 22) height and weight of body, and 23) systolic pressure and diastolic pressure. All of above factors were analyzed with Logress model. The results showing table below indicated that kinds and probability of CVD risk factors differs from literature.

Probability	*Cerebral Infarction*	*Cerebral Hemorrhage*
Affirmatively effecting factors	1 hypertension history 2 TIA history	1 hypertension history 2 mood 3 drinking history 4 less vegetable in food
Probably effecting factors	1 nation 2 diabetes history 3 mood	
Suspect factors	1 cardiac disease 2 cigarette quality 3 drinking history 4 quantity of drinking 5 family history of CVD 6 systolic pressure	1 duration of work 2 family income 3 duration of hypertension 4 duration of drinking 5 quantity of drinking 6 family history of CVD 7 systolic pressure

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DOES AORTIC INSUFFICIENCY AFFECT LEFT VENTRICULAR COMPLIANCE IN THE ELDERLY HEART? *O.I. Shindler*, D.M. Shindler, and J.B. Kostis,* UMDNJ-Robert Wood Johnson Medical School, New Brunswick, NJ 08903-0019.

Elderly patients are often found to have altered diastolic left ventricular function on Doppler examination. This abnormal function is manifested as increased atrial contribution to diastolic filling of the left ventricle (A>E). Another common (hitherto considered unrelated) diastolic abnormality affecting the left ventricle in the elderly is aortic insufficiency (AI). Since AI may affect the abnormal left ventricular compliance manifested by A>E we decided to study the incidence of patients with both abnormalities. We reviewed 600 consecutive adult echocardiograms — 124 had AI. It was mild in 91 (73%), moderate in 21 (17%) and severe in 12 (10%). Seventy-seven patients had A>E. Twenty-eight had both AI and A>E. Their mean age was 66 s.d.10. A>E was not seen in any of the patients with severe AI. Our findings suggest that combined AI and A>E are common in elderly patients. The absence of A>E in severe AI may indicate that AI counterbalances the decrease in compliance associated with aging.

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AGE-RELATED DECREASES IN α_1-ADRENOCEPTOR SIGNAL TRANSDUCTION IN PAROTID CELLS. *A. Miyamoto*, and G.S. Roth,* Gerontology Research Center, NIA, Francis Scott Key Medical Ctr., Baltimore, MD 21224.

Experiments in parotid cells isolated from adult (6 mo.) and old (24 mo.) rats examined epinephrine (Epi) stimulated $^{45}Ca^{2+}$ efflux and inositol 1,4,5-trisphosphate (IP_3) formation characteristics of [^{3}H]prazosin binding, and the α subunit of the GTP-binding protein, as determined by immunoprecipitation. Compared with adults, Epi-stimulated $^{45}Ca^2$ efflux and IP_3 formation were reduced 31% and 36% in cells of old rats, respectively. There was a highly significant ($P<0.05$) correlation between Epi-stimulated $^{45}Ca^{2+}$ efflux and IP_3 formation, but there was no correlation between Epi-stimulated and IP_3-stimulated $^{45}Ca^{2+}$ efflux. Density of the α subunit of GTP-binding protein in the parotid cells did not show any significant differences between adult and old rats. In Scatchard analysis, no changes were observed in the Kd and Bmax for [^{3}H]Hprazosin. The GTP analogue, Gpp[NH]p decreased affinity of the agonist Epi in competing for [^{3}H]prazosin sites in membranes prepared from adult parotid. No effect of Gpp[NH]p on agonist binding in old membranes was observed. These results suggest that decreased signal transduction in parotid cells during aging is not due to loss of α_1-adrenoceptors and GTP-binding proteins. It appears that the age-related decline in α_1-responsiveness is mediated, at least in part, by the functional uncoupling of GTP-binding protein from α_1-adrenoceptors. The possibility exists that the membrane characteristics themselves may modify the receptor-effector coupling.

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CARDINAL PROBLEMS IN THE INVESTIGATIONS OF LIPOFUSCIN GRANULES (LG) IN MODERN EXPERIMENTAL GERONTOLOGY. *A.B. Tatariunas,* Lab. of Neuron Physiology, Kaunas Medical Academy, Kaunas 233000, Lithuania.

Three main problems exist in lipofuscinology today: 1) genesis of LG; 2) nature of autofluorescenting chromophore in LG, 3) action of centrophenoxine (CP) on/in LG. All these problems are closely connected and the solution of any of them would lead us to a powerful ideological progress. Now it becomes clear that LG are derived from endoplasmic reticulum and that autofluorescenting chromophore in LG exists in the form of pigment-protein complex. It is also supposed that CP could act on plasma membrane on receptor level. Based on these data further immediate tasks in lipofuscinology are the following — isolation of such a naturally existing covalent bound pigment-protein complex and analysis of chromophore of polyisoprenoid (retinoid) nature presumably. Another significant question is a target for CP action on/in cell, i.e. what and where hydrophobic landing ground for CP is. Solution of this question is complicated by significant degradation velocity of CP in alkali pH to dimethylaminoethanol and p-chloro-phenoxyacetic acid which is the basic compound of a majority of herbicides. For this reason we must know what the real concentration of CP action on/in cells is.

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LIPOFUSCIN PIGMENT IN THE SPIRAL GANGLION OF VITAMIN E DEFICIENT RATS. *Y. Igarashi* and I. Takahashi,* Yotsukaido Hospital, Chiba 284 and Central Lab. for Electron Microscopy, Teikyo Univ. School of Medicine, Tokyo 173, Japan.

Lipofuscin-Ceroid pigments generated in the spiral ganglion of two groups, the vitamin E deficient rats and the normal diet rats were observed and compared with respect to their shape and distribution between these two different feeding conditions. Five rats fed with vitamin E free diet for 6 months after birth and control five rats of same age were used for this study. Temporal bones were dissected and spiral ganglion were processed for electron microscopic observation. Result showed different patterns of lipofuscin distribution in both groups. Vitamin E deficient group had large aggregated lipoid, dark pigment so-called ceroid granules of irregular shape. In contrast, the normal diet group had small numbers of smaller homogenous lipofuscin granules, suggesting higher Schwann cell phagocytic activity. The present study has shown that lipofuscin/ceroid granules are generated in the non-dividing spiral ganglion cells much more in the vitamin E deficient group than control.

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HYPERTROPHIC LAYER OF ARTICULAR CARTILAGE IN AGING MICE IS ACTIVELY INVOLVED IN BONE REMODELING. *A. Weiss*, E. Livne, and M. Silbermann,* Faculty of Medicine, Technion, Haifa 31096, Israel.

Mouse mandibular condyles served as a model for studies on age-related changes in the metabolic activity of the hypertrophic layer in articular cartilage and its involvement in bone remodeling. In young animal the condylar cartilage is active in endochondral bone formation and is characterized by a well developed calcified hypertrophic layer. With increasing age the condylar cartilage acquired hyaline-like morphology, typical for articular cartilage. A clear tidemark separated the hyaline portion from the hypertrophic layer at 3 months of age and on. The hypertrophic zone was found to diminish gradually to one or two cell layers at 12 months. Silver staining of undecalcified sections revealed that even at 24 months the matrix in the vicinity of the hypertrophic cells was mineralized. Moreover, following in vivo tetracycline administration, an active mineralization in this area could be demonstrated. Alkaline phosphatase activity, determined histochemically in frozen sections, coincided with mineralization. ^{35}S-sulfate autoradiography revealed that hypertrophic cells were actively involved in the synthesis of glycosaminoglycans. Chrondroclasts and erosion cavities were frequently found along cartilage-bone interface, indicating towards an active phase of remodeling.

In conclusion, the present data provide evidence that in senescent mice, the hypertrophic layer of articular cartilage is highly metabolic and is actively involved in bone formation and remodeling.

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SELECTIVE REGULATORY EFFECT OF SOME HORMONES AND NEUROTRANSMITTERS ON THE GLUTAMATE DEHYDROGENASE FROM RATS OF VARIOUS AGES. *M. Prabhakaram[1] and S.S. Nath*,* [1]Mason Eye Inst., Univ. of Missouri, Columbia, MO 65212, USA; *Biochemistry Lab., Dept. of Zoology, Banaras Hindu University, Varanasi-221005, India.

Glutamate dehydrogenase (GDH) is a key regulatory enzyme in the ammonia metabolism of mammalian tissues and is greatly influenced by a variety of metabolites. With this aim, experiments were conducted to determine, whether the regulatory effect of some selected hormones and neurotransmitters on GDH is altered with respect to age, or not. Crystalline GDH was purified up to homogeneity, from different age groups of female rats (immature, 4-Weeks; young 22-Weeks; and old, 116-Weeks). Enzyme assays were carried out and the per cent activity of GDH remained, in the presence of different concentrations of selected hormones (steroids, anti androgens), and neurotransmitters was estimated. The obtained results show that some of the hormones/neurotransmitters, but not all, significantly and selectively, influence the activity of GDH *in vitro.* No age-related differences were observed among the three ages of enzymes, under the influence of these compounds. Thus, it appears that GDH is unaltered with advancing age of the rat, due to lack of structural differences, among the three ages of enzymes. The absence of age-related changes in GDH may be predominantly due to the mitochondrial origin of this enzyme, since it is well known that turnover of several mitochondrial proteins do not change with age in rat liver. It is also possible that post translational modifications may not effect the GDH in aging rats, as observed in the other mitochondrial enzymes of rat liver.

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EFFECT OF GENOTYPE AND DIET ON METABOLISM AND LIFESPAN. *B. Kent*, P.S. Tomlinson, J.M. Heneghen, J.R. Archer, and D.E. Harrison,* The Jackson Laboratory, Bar Harbor, ME 04609 & Dept. of Geriatrics and Adult Dev., Mount Sinai Med. Center, New York, NY 10029.

Based on the free radical theory of aging, we are testing the hypothesis that lifetime oxygen consumption is inversely related to lifespan in *Mus. musculus.* Lifespan in mice varies with genotype and caloric intake. To maximize divergence in lifespan, we are studying longitudinally two groups: (1) male mice of widely variable genetic backgrounds; (2) inbred and F1 hybrid males fed a defined diet either high or low in calories and housed singly or four to a side. At yearly intervals 24-72 hour oxygen consumption (V02) is measured on individuals for correlation with lifespan. Metabolic measurements are conducted in

chambers identical to the home caging of the animals and food delivery time is also similar. VO2 following a circadian pattern and did not differ between the first and third days of measurement. There was no significant difference in V02 or body weight between an average of 677 and 954 days of age in 106 mice of ten different genotypes. However, between genotypes, there was a significant difference in both parameters between Mol, the smallest in size, and the others. More than half the mice in the study are still alive and their lifespans are approaching three years. Of those which died, a significant inverse correlation was found between V02 and lifespan for mice selected for maximum genetic variability (het), but no correlation was found in inbred strains. As expected % mortality differs significantly between strains. Surprisingly, B6D2F1, B6/ob-ob, and C57BL/6 used significantly more oxygen on a low energy diet than a high energy diet. Singly housed mice had significantly higher VO2 than those housed four/side, although weights of the two groups was indistinguishable. Our results suggest a close link between genetic control of lifespan and consumption. The longevity achieved by mice fed a low calorie diet does not seem to be attributable to a decrease in metabolic rate, however temperature regulation may be a confounding factor as indicated by the higher V02 in the singly housed mice.

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INCREASED OXYRADICAL PRODUCTION IN AGING NZB MICE. *I. Emerit,* Institut biomedical des Cordeliers, Universite Paris VI and CNRS France.

Autoimmune manifestations increase with age. New Zealand Black (NZB) mice are a model for human autoimmune disease. They develop a lupus-like syndrome with hemolytic anemia and glomerulonephritis and are also characterized by a high frequency of lymphoreticular neoplasia, enhanced production of antinuclear antibodies and an increased frequency of chromosome breaks. Selective matings on the basis of chromosome breakage rates resulted in two NZB sublines, which differ with respect to neoplasia and autoimmune disease. Since superoxide dismutase suppresses chromosome damage in vivo after intraperitoneal injection, a role of the superoxide radical is suggested. Other indications for the involvement of activated oxygen species come from the beneficial effects of vitamin E on the life span of these mice.

A series of 124 NZB mice was studied for the production of superoxide and hydrogen peroxide, grouped according to age and subline origin. For the measurement of $0\bar{2}$, the cytochrome C reaction was used, for H_20_2 an assay in which phenol red is oxidized in presence of horse radish peroxidase to a product absorbing at 610 nm. In contrast to two non autoimmune strains used as controls, resident peritoneal macrophages from NZB mice showed increased spontaneous and stimulated $0\bar{2}$ and H_20_2 production. Oxyradical production was age-dependent and more important in the high breakage subline. A correlation between the severity of the disease and increased production of active oxygen was also documented by the higher values observed by class of spleen weight.

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ANTIOXIDANTS, PRO-OXIDANTS AND AGING. *R.S. Sohal,* Department of Biological Sciences, Southern Methodist University, Dallas, TX 75275.

In the absence of direct evidence linking oxygen free radicals with the aging process of animals, the alternative investigative approach has been to test the predictions of the free radical hypothesis of aging. If the hypothesis is correct, levels of antioxidant defenses and/or rate of pro-oxidant generation should be, respectively, directly and inversely correlated with the rate of aging. A comparison of antioxidant defenses (superoxide dismutase, catalase, glutathione reductase and glutathione) in liver, heart and brain of six different mammalian species (mouse, rat, guinea pig, rabbit, pig and cow), which have life spans ranging from 3.5 to 30 years, indicated that there was no clear-cut relationship between antioxidant defenses and the life span potential. In contrast, rates of 0_2 and H_20_2 generation by mitochondria were found to be inversely correlated to life span of the various species. Furthermore, antioxidant defenses of housefly and *Drosophila* were quite comparable to those in the mammalian tissues, but the rates of 0_2 and H_20_2 generation were much higher in the insects. Mutants of *Drosophila* with about 50% of normal SOD or catalase activity show no shortening of the life span. On the basis of such data it is hypothesized that rates of pro-oxidant generation rather than antioxidant defenses are reflective of the rate of aging process.

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NET PLASMA ANTIOXIDANT LEVELS IN SPECIES WITH DIFFERENT LIFE SPANS AND IN HUMANS FOLLOWING VITAMIN E AND C SUPPLEMENTATION. *H.M. Alessio* and R.G. Cutler,* Miami University, Oxford, OH 45056 and Gerontology Research Center, Baltimore, MD 21224.

The Longevity Determinant Gene Hypothesis predicts that aging is a result of long-term side-effects of normal endogenous biological processes essential for life. Differences in aging rates among mammalian species are accordingly predicted on how effectively an organism reduces these side-effects. Normal oxygen metabolism produces reactive oxygen species as a side reaction which could initiate aging processes. If this is true, then antioxidants acting to reduce these side-effects would determine aging rate. We have tested this hypothesis in previous experiments by measuring net sensitivity of total tissues to autoxidation and tissue and plasma concentrations of antioxidants, including superoxide dismutase, beta-carotene, and urate. Here we present results using an assay of net antioxidant protection in plasma taken from mammalian species of different life spans. Results indicate that the plasma of shorter-living mammals (i.e. mice) had 3-fold less protection than chimpanzee and 5-fold less than human. These results support our previous findings that tissues from longer-lived animals are more resistant to oxidative stress. We also report the effects on net plasma antioxidant protection of two antioxidant dietary supplements, vitamins E and C, in normal human subjects after a given exercise oxidative stress.

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EFFECT OF AGE AND DIETARY RESTRICTION ON THE EXPRESSION OF ANTIOXIDANT GENES AND FREE RADICAL DAMAGE. *A. Richardson,* Univ. of Texas Health Science Center and Audie Murphy VA Hospital, San Antonio, TX 78284.

An age-related decline in the activities of superoxide dismutase (SOD) and catalase (CAT) were found in liver from male Fisher F344 rats. The decline in SOD and CAT appears to arise primarily from a decline in the transcription of these genes. The decline in SOD and CAT was temporally correlated with an age-related increase in free radical damage as found by TBA-reactive material, lipofuscin, and dense bodies. Because dietary restriction is the only experimental manipulation that has been found consistently to increase the longevity of rodents, it was of interest to determine what effect dietary restriction (60% of the calories consumed by the rats fed *ad libitum*) had on the expression of the antioxidant genes: SOD, CAT, and glutathione peroxidase (GPX). Dietary restriction enhanced the expression of SOD, CAT, and GPX in liver tissue from old rats, and this increase in expression appeared to arise from an increase in the transcription of these genes. In addition, free radical damage in liver tissue from the rats fed the restricted diet was significantly lower than that observed in rats fed *ad libitum*. Subsequent experiments showed that dietary restriction also enhanced the activities of many of the antioxidant enzymes in heart, kidney, and brain tissue of male Fischer F344 rats. Free radical damage, as measured by TBA-reactive material, also was significantly lower in these three tissues of rats fed the restricted diet.

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PEROXIDATIVE DAMAGE IN PARKINSON'S DISEASE. *G. Cohen,* Dept. of Neurology, Mount Sinai School of Medicine, New York, NY 10029.

(Abstract not available)

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OXIDATIVE DNA DAMAGE AND AGING. *B.N. Ames,* Div. of Biochemistry and Molecular Biology, Univ. of California, Berkeley, CA 94720.

Progress in identifying the important endogenous processes damaging DNA and developing methods to assay this damage in individuals is presented. This approach may aid studies on modulation of the aging process and degenerative diseases associated with aging, such as cancer.

The endogenous background level of oxidant-induced DNA damage *in vivo* has been assayed by measuring 8-hydroxydeoxyguanosine (oh^8G), thymine glycol and thymidine glycol in urine and oh^8dG in DNA. Humans have greater than 10,000 oxidative hits/cell/day. Creatures with higher metabolic rates (and shorter life spans) have proportionally more damage. The level of oxidative DNA damage as measured by oh^8dG in normal rat liver is shown to be extensive, especially in mtDNA (1/130,000 bases in nuclear DNA and 1/8,000 bases in mitochondrial DNA). oh^8dG is one of about 20 adducts found on oxidizing DNA, e.g., by radiation.

We also discuss 3 hitherto unrecognized antioxidants in man and the role of various antioxidants in preventing lipid hydroperoxide formation in human plasma.

We will discuss the implications of these findings on the role of environmental toxins influencing aging and cancer.

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INCREASED PROTEASE INHIBITOR CONTAINING FORMS OF APP IN THE AGING CNS. *G. Higgins,* Univ. of Rochester Medical Center, Dept. of Neurobiol. and Anatomy, Rochester, NY 14642.

(Abstract not available)

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NEURONAL APP-751/APP-695 mRNA RATIO AND PLAQUE DENSITY IN AD. *S. A. Johnson,* Andrus Gerontology Center, University of Southern California, Los Angeles, CA 90089-0191.

The β-amyloid peptide that accumulates in plaques and cerebral blood vessels in Alzheimer's disease (AD) is derived from amyloid precursor proteins (APP). APP mRNAs in human brain consist of two major (APP-695 and APP-751) and additional minor (APP-714, APP-770 and APP-543) alternatively spliced or truncated forms. APP-543, -751 and -770 contain a Kunitz-type serine protease inhibitor (KPI) domain, that has serine protease (trypsin) inhibitory activity in extracts of transfected COS cells. The cellular distribution of major APP mRNA forms, prevalence changes during AD, and a possible role in β-amyloid accumulation are controversial. Initial studies failed to show changes in total APP mRNA prevalence in AD vs normal brain. However, we and others showed increased APP-751,770/APP-695 mRNA ratios in hippocampal and neocortical tissues during AD with probes specific for each APP mRNA. However, other studies have produced conflicting results. Moreover, the existing data does not show if there is a selective loss of neurons with high prevalence of a particular APP mRNA. Thus, it is crucial to establish if both mRNA forms are present in the same neurons to understand the possible relation of neuronal APP mRNA prevalence to β-amyloid deposition in plaques. We show by serial section in situ hybridization that any hippocampal pyramidal neuron contains both APP-751/770 and APP-695 mRNA species and that the APP-751/APP695 mRNA ratio is increased during AD as shown in previous studies. Moreover, we find a strong correlation between the increase in APP-751/APP-695 mRNA ratio and the density of neuritic plaques, which suggests a relationship of the APP-mRNA ratio to plaque formation.

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ENDOGENOUS PEPTIDE PROFILING IN AD BRAIN. *J.R. Slemmon,* Dept. of Biochemistry, Univ. of Rochester Medical Center, Rochester, NY 14642.

Profiles of endogenous peptides from regions of human brain are being generated for the purpose of identifying possible alterations that are associated with AD. The analysis of naturally occurring peptides provides an approach for studying the biology of disease which compliments current RNA and DNA technologies. Whereas traditional molecular biology offers powerful approaches for characterizing protein expression, identifying and studying species that are products of post-translational processing initially requires purification and amino acid sequencing. This type of analysis also offers the advantage that the peptide can be detected at its final cellular location, which may be distant from its initial translation product or its message. As a class of molecules, peptides can also carry out important biological functions. Examples include peptide hormones, neurotransmitters, second messengers, toxins, allosteric modulators and more.

High performance liquid chromatographic (HPLC) technology developed over the last decade has provided rapid methodologies for simultaneously separating and quantifying hundreds of small proteins and peptides. Currently, we are employing a 2-D protocol which initially separates peptides on ion-exchange SPE cartridges followed by reverse phase-HPLC. Peak identification and quantification is performed with the model 727 Data Analysis Software from Axxiom Chromatography Inc.

Initial screening of 399 peptide peaks from three different brain regions (cortical areas 7,10 and 38; 9 AD, 5 Control) indicated that although most peptides do not display changes in their level of expression from case to case, a few species displayed regional alterations. Of these, the two most abundant peptides (which were specifically elevated in area 10) were subjected to amino acid sequencing. Data base searching identified the sequences obtained as belonging to human serum albumin and alpha hemoglobin. We are initially inclined to relate these data, indicating an apparent regionally selective increase in two components of blood, to data relating to potential alterations in the blood-brain barrier. Whether localization of these polypeptides is only to vessels or also the parenchyma, plaques or cells in AD brain is not yet know.

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CYTOSKELETAL PROTEIN PATHOLOGY IN AGING AND ALZHEIMER'S DISEASE. *K. Iqbal,* New York State Institute for Basic Research, 1050 Forest Hill Rd., Staen Island, NY 10314.

(Abstract appears on page 109)

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THE NEURITIC DYSTROPHY OF ALZHEIMER'S DISEASE. *K.S. Kosik,* Harvard Med. School and Brigham and Women's Hospital, Boston, MA 02115.

While numerous histological and biochemical lesions have been described in Alzheimer's disease, the correlation of any single lesion with the clinical dementia has been problematic. Recent data has demonstrated that the presence of dystrophic neurites reactive with antibodies to the microtuble-associated protein tau correlates very strongly with the occurrence of dementia. This association is considerably stronger than the deposition of β-amyloid protein, which is found in clinically spared brain regions and is a frequent concomitant of normal aging. Antibodies to ubiquitin and phosphorylated neurofilament also react with Alzheimer dystrophic neurites. The latter immunoreactivity is observed in denervating lesions, which may also occur in AD, perhaps due to the deposition of the β-amyloid protein within the synaptic space. It is unclear why a neuron that is not in contact with its target is unable to maintain its viability and undergoes a stereotypic cytoskeletal reorganization in the course of neuronal cell death. Following a denervating lesion, a crucial step in reinnervation is the formation of a growth cone. In AD, the dystrophic process may represent ineffective reinnervation due to neurite elongation in the absence of growth cones and the presence of a rigidified cytoskeleton.

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INVOLVEMENT IN ALZHEIMER'S DISEASE OF S100β AS A NEUROTROPHIC FACTOR. *D.R. Marshak* and W.S.T. Griffin+,* Cold Spring Harbor Laboratory, Cold Spring Harbor, NY 11724, and +The Univ. of Arkansas for Medical Sciences, Little Rock, Arkansas 72205.

The protein S100β is synthesized by astrocytes of the brain, is secreted during differentiation, and acts as a neurite extension factor on embryonic, cortical neurons during normal brain development. The gene for S100β is localized to human chromosome 21 near the telomere of the long arm, and levels of the protein increase slightly in aged rats and upon injury to the brain. We investigated the possibility of abnormal expression of S100β in Alzheimer's Disease (AD). Samples of temporal cortex, including hippocampus, from patients with AD or age-matched controls werre obtained on autopsy. These samples were extracted and analyzed by quantitative radioimmunoassay and by gel electrophoresis and immunoblots using rabbit antisera specific to S100β. In AD samples, the levels of S100β protein were 24-fold elevated, compared to controls. Levels of mRNA for S100β were found to be 10-fold or higher in AD samples by RNA slot blots using a full-length cDNA probe. Further, the neurite extension activity was assessed by bioassay on chick cerebral cortical neurons. The neurotrophic activity was 10-20 fold higher in AD samples compared to controls, and the activity could be blocked by specific antibodies to S100β. By immunocytochemistry, elevated S100β levels were observed in reactive astrocytes surrounding neuritic amyloid plaques in AD hippocampus. We suggest that S100β contributes to the neuropathology of AD, particularly abnormal neuritic growth.

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MOLECULAR MARKERS OF INTERCELLULAR SIGNALLING IN NORMALLY AGING BRAIN AND IN ALZHEIMER'S DISEASE. *P.D. Coleman,* Dept. of Anatomy, Univ. of Rochester School of Medicine, Rochester, NY 14642.

(Abstract appears on page 109)

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FOOD RESTRICTION AND THE GUT. *P.R. Holt,* Div. of Gastroenterology, St. Luke's Hospital Center, and Dept. of Medicine, Columbia Univ., New York, NY 10025.

The small and large intestine respond rapidly to acute changes in food intake by altering epithelial cell mass and proliferation, and the activity of epithelial digestive enzymes in the rat. Chronic food restriction is well recognized to delay many age-related phenomena, particularly in the post-mitotic parenchymal cells of the liver. The aging (21-27-mo) *ad lib* fed Fischer 344 rat demonstrates hyperplasia and hyperproliferation of epithelial cells in the small and large intestine and a delay in the expression of function of important small intestinal digestive enzymes. In addition, there is derangement of DNA synthesis in the intestinal crypts of the aging rat accompanied by evidence of nuclear and genomic damage. In rats fed at a level of 50% of *ad lib* controls, small intestinal hyperplasia and changes in enzyme specific activity are delayed until after 33 mo of age. Thus, food restriction has an age-delaying effect in rapidly replicating gut epithelial cells as it does in hepatic post-mitotic cells. Hyperproliferation is a feature of preneoplastic epithelia, epidemiologic studies suggest a positive association between caloric intake and colon cancer risk, and modest long-term caloric restriction reduces colonic proliferation and the number of chemically induced colon tumors. Because of these associations, the effect of food restriction on human colonic proliferation presently is under study.

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REDUCTION OF DNA DAMAGE BY DIETARY RESTRICTIONS. *M.G. Simic* and D.S. Bergtold,* 245/C214, NIST, Gaithersburg, MD 20899.

Urinary biomarkers of oxidative DNA base damage (UBODBD), such as thymidine glycol (dRTg) and 8-hydroxydeoxyguanosine (8-dRG-OH), are present at higher levels in short-lived than is long-lived species. The maximum life span (MLS) of mice, with a specific metabolic rate (SMR) of 180 cal/g/day, is 3.5 y, whereas for humans SMR = 25 cal/g/day and MLS = 100 y. The shorter MLS of mice has been rationalized by higher rate of DNA damage, i.e., higher UBODBD levels.

Human levels of UBODBD may differ between individuals and may fluctuate for a particular individual. We have discovered that human levels of UBODBD are both a function of total dietary energy intake (dRTg is 0.25 and 0.11 nmol/kg/day for 2,100 and 1,100 kcal/day, respectively) and the type of food. Apparent correlations among dietary energy intake, type of diet, UBODBD levels, longevity, and degenerative diseases, as well as plausible underlying mechanisms will be presented.

The role of certain food components in inhibiting DNA damage and reducing UBODBD, as well as the possible consequences of a reduced DNA damage on longevity and endogenous carcinogenesis, will be considered.

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RELATIONSHIP BETWEEN AGE, NUTRITION, AND EYE LENS CATARACT FORMATION. *A. Taylor*, P. Jacques, D. Nadler, F. Morrow, D. Shepard, and S. Sulsky,* USDA Human Nutrition Research Center on Aging, Tufts University, Boston, MA 02111.

Delaying cataract by only 10 years would eliminate the need for 1/2 of the cataract extractions. Blindness due to cataract afflicts 50 million persons worldwide. The prevalence of cataract in Americans aged 65-74, and 75 and over are 18% and 46%, respectively. More than $3.5 billion/year are spent on cataract exams and surgery in the U.S.

Cataract is due in part to modification of lens proteins, including oxidation, glycation, etc. Antioxidants can delay age-related changes to lens proteins in cell-free systems, and recent studies show that persons with 90uM, as opposed to 40uM plasma ascorbate and/or 1.7uM carotenoids, are better protected against some forms of cataract. As shown below, diet can be used to alter eye tissue levels of ascorbate.

	Mean Ascorbate Levels		
Tissue	Supplemented	Placebo	P-value
Plasma (ug/mL)	19.6	10.4	<0.001
Aqueous (ug/mL)	330.0	250.0	0.02
Lens (ug/lens)	182.1	130.6	0.002

Anticataract effects have also been found with the use of "sufficient" levels of tocopherol, industrial antioxidants such as BHT, and limiting dietary carbohydrate.

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THE EFFECTS OF AGING ON METABOLISM OF VITAMIN A AND BETA-CAROTENE. *S. Mobarhan* and H. Friedman,* Loyola University Medical Center, Maywood, IL 60153.

Although the total dietary vitamin A (VA) intake is reduced with advanced age, there is a marked increase in the prevalence of VA supplementation, as well as changes in the metabolism and absorption of VA and beta-carotene (BC). We have shown that the rates of absorption of intact BC and its conversion to retinyl esters are higher in elderly subjects as compared to young controls when a single dose of BC (15 mg) is given with a 500 kcal diet. Fasting and post-prandial serum retinyl esters also increase with advancing age. This has recently been shown to be the result of reduced plasma clearance of retinyl esters in triglyceride-rich lipoproteins of intestinal origin. Other experimental studies conducted in our laboratory have suggested that old age is associated with decreased activities of hepatic retinyl ester hydrolase and cellular retinol-binding protein and increased activity of acyl coenzyme A:retinol acyl transferase. These changes may all contribute to increased hepatic VA stores, decreased mobilization of VA from the liver and altered intra-cellular transport of retinol. Therefore, long term use of VA supplementation in old age could result in excess hepatic VA accumulation and hepatic toxicity, which may be further aggravated by ethanol intake.

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NUTRITIONAL MODULATION OF THE IMMUNE RESPONSE IN THE AGED. *S.N. Meydani,* USDA Human Nutrition Research Center at Tufts University, Boston, MA 02111.

The age-associated changes of the immune response are well documented. However, the biochemical changes leading to these alterations are not well defined. A series of experiments, using dietary anti-oxidants and pro-oxidants were conducted in old mice and older adults to determine the contribution of lipid peroxides, especially that of oxidative products of arachidonic acid in the age-associated decline of the immune response. Splenocytes from old mice and peripheral blood mononuclear cells (PBMC) from older adults produced significantly more PGE_2 and their plasma had higher TBAR levels than their young counterparts. Vitamin E supplementation of both old mice and older adults decreased PGE_2 synthesis while increasing IL-2 production, mitogenic response to Con A and the delayed hypersensitivity skin test (DTH). Older adults supplemented with vitamin E showed a significant reduction in plasma TBAR. Supplementation with another dietary antioxidant, glutathione (GSH) (0.1 to 1% by wt of diet for 4 wk) significantly improved mitogenic response to Con A and PHA and DTH to DNFB in 17 and 24 mo old mice. This effect was due to an increase in spleen GSH level and not to a change in PGE_2 synthesis. On the other hand, supplementation of older women with fish oil containing highly unsaturated N-3 fatty acids, EPA and DHA (2.4 g/day for 3 mo) decreased cytokine production (IL-1, IL-2, IL-6, TNF), mitogenic response of PBMC to PHA and their production of PGE_2. Thus, supplementation with dietary antioxidants increases, and with dietary pro-oxidants decreases, immune responsiveness of aged. These effects are mediated via changes in the formation of PGE_2 and other lipid peroxides.

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NUTRITION AND THE AGING HEMATOLOGIC SYSTEM. *D. Lipschitz,* GRECC, VA Hospital, Dept. Medicine, Univ. Ark. Med. Sci., Little Rock, AR.

Studies in both animal and man reveal no age-related declines in the hematologic system. In longitudinal studies the prevalence of anemia does not increase with age and no decline in the number of bone marrow progenitor cells and differentiated cells occurs. Reserve capacity is compromised as evidence by a reduced ability of the aged bone marrow to respond to increased stimulation. There is also an increased susceptibility to hematologic pathology, which develops with

a level of stress that is not associated with abnormalities in the young. An example is the effects of housing aged mice in groups of 5 animal per cage which results in anemia and reductions in marrow erythroid and myeloid cells number. These changes are not noted when young animals are similarly housed. Evidence suggests that the mechanism is increased activity or increased competition for food. Nutritional changes may explain the etiology of the mild anemia frequently noted in the elderly. Unexplained anemia is common in low socioeconomic elderly, its prevalence correlating with measures of nutritional status including albumin, prealbumin, TIBC and serum folate. The biochemical parameters are not in the deficient range but at the lower end of normal. If nutrition does contribute to the high prevalence of anemia noted in low socioeconomic elderly, mechanisms other than simple deficiency must be considered. The elderly may be susceptible to more subtle deficiency than the young, or aging may interfere with nutrient delivery to target organ or nutrient-cell interactions.

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MINERAL NEEDS OF THE ELDERLY:DEFINING A RESEARCH AGENDA FOR THE 1990's. *R. J. Wood,* Mineral Bioavailability Laboratory, USDA Human Nutrition Res. Center on Aging at Tufts University, Boston, MA 02111.

Efforts are underway by the Food and Nutrition Board of the National Research Council to more precisely define the recommended dietary allowances (RDAs) for our elderly population. The success of this effort will depend greatly upon the availability of relevant research data concerning nutrient requirements of the elderly. Moreover, consideration needs to be given to changes in dietary patterns and intestinal function in the aged which may have significant impact on mineral bioavailability and dietary mineral recommendations. Discussion will focus on the currently available data on mineral requirements of the elderly. Particular attention will be placed on delineating the gaps in the human research data base regarding aging effects on phosphorus, magnesium and zinc metabolism and the definition of priority areas for future research.

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THE CURRENT STATUS AND FUTURE DIRECTIONS OF NUTRITION AND AGING RESEARCH. *J. Blumberg,* USDA Human Nutrition Research Center on Aging at Tufts University, Boston, MA 02111.

Nutritional components of the diet have been recognized to contribute to or ameliorate age-related losses of tissue structure and function. Nutritional intervention offers a practical approach to extending life expectancy and compressing the period between morbidity and mortality. High intakes of total and saturated fats and inadequate consumption of dietary antioxidants and fiber are associated with an increased risk for cancer, cardiovascular, and other chronic diseases. Dietary allowances currently assume levels of energy intake which exceed the amounts of food older adults actually consume; dietary quality becomes difficult to assure when caloric intake is low. Criteria used to establish nutrient requirements are largely inappropriate to aging concerns and/or lack the sensitivity to detect subtle biochemical alterations with significant consequences for the aging process. Recent evidence suggests a direct role for micronutrient status in maintaining optimal cognitive, immune, skeletomuscle, and visual functions and maximal responsiveness to exercise. Methods to identify the high risk for adverse drug-nutrient interactions in older populations can now be developed. Gene probes targeted to relevant metabolic pathways may allow for the individualization of nutrient requirements. New efforts are required to identify nutrient intakes sufficient to retard the rate of deterioration of physiological function with age and to protect against diseases common among the elderly.

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PHARMACOGENETICS OF SUPEROXIDE DISMUTASE ISOZYMES IN *NEUROSPORA*. *K.D. Munkres,* Molecular Biology Lab. and Dept. of Genetics, University of Wisconsin, Madison, WI 53706.

Three superoxide dismutase deficient mutants are respectively deficient in the exocellular — and the two mitochondrial isozymes at 24°. Their phenotypes are: 1) little or no growth at 35°; 2) hypersensitivity to paraquat or 100% oxygen; 3) female infertility; and 4) curtailed conidial lifespan. Tocopherol and ascorbate (or their esters), GSH, and the SOD-mimic Desferal-Mn are therapeutic for the first three phenotypes. The three putative structural genes are not closely linked to one another or their regulatory genes *Age*.

Conclusions: 1) Heat is a form of superoxide-mediated oxidative stress; 2) The isozymes confer resistance to oxidative stresses and capacity to express normal cellular differentiation and longevity; and 3) The results are consistent with the postulated existence of an oxy-regulon, a global genetic unit of regulation of antioxidant enzyme synthesis.

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YOUNG MARROW TRANSPLANTATION INTO OLD MICE CORRECTS AGING-ASSOCIATED DEFECT IN MACROPHAGE RECEPTORS FOR ADVANCED GLYCOSYLATION ENDPRODUCTS. *H. Vlassara*+, M. Kirstein+, A. Passgian+, and D. Harrison&,* +Laboratory of Medical Biochemistry, The Rockefeller University, New York, NY 10021, & Jackson Laboratories, Bar Harbor, ME 04609. Previous studies from this laboratory have shown that murine peritoneal macrophages (Mφ) possess a receptor for the removal of proteins modified by Advanced Glycosylation Endproducts (AGEs) shown to accumulate with time and being implicated in tissue damage in aging and diabetes. We have recently investigated the effect of aging on the Mφ AGE-receptor binding capacity from 2 groups of mice, a young (3 mos old, n=30) and an old (28 mos. old, n=30). The older group exhibited a 50% reduction in AGE-binding capacity, while analysis of the data demonstrated a marked reduction of both, number of sites/cell and binding affinity (Ka). The question was addressed whether this age-dependent decline in AGE-receptor activity was regulated proximally at the stem cell level or was due to environmental changes. Two groups of C57BL6 syngeneic mice (10 ea), one young and one old were lethally irradiated, after which young animals received a bone marrow transplant from healthy old mice, while the old animals received bone marrow transplant from the healthy young mice. Five weeks later peritoneal Mφ were tested for AGE-receptor binding capacity. Mφ from the old mice appeared to have recovered normal AGE-receptor function, while young ones demonstrated reduced function, almost to the level of the older group. These results suggest that 1) the reduction in both number and affinity of the AGE receptor could lead to a reduced rate of removal of AGEs from the tissues by aging Mφ and therefore contribute to the development of the complications associated with normal aging and, 2) the age-dependent alteration of the receptor function lies proximally within the stem cell and is not environmental.

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DROSOPHILA AS A MODEL TO STUDY CHEMICALLY INDUCED PORPHYRIA AND FREE RADICALS. *L.K. Dixon* and K.J. Gordon,* Dept. of Biology, Univ. of Colorado at Denver, Denver, CO 80217-3364.

Chemical induction of a porphyric condition by polyhalogenated aromatics (PHAs) has been accomplished in a number of mammalian species, in yeast, and in chick-embryo cultures. The development of such chemically induced porphyria also has been related to the formation of free radicals. Our goal was to induce a porphyric condition in *Drosophila* and to use the stock to study relationships between free radicals and porphyrin accumulation. We have to date only partially succeeded. In a pilot project adult flies of a wild type strain were fed on a medium containing hexachlorocyclohexane in concentrations ranging from 2×10^{-6} to 2×10^{-6} for three weeks; they were removed to untreated medium for 7 days. They were tested for porphyrins using a thin layer chromatography technique. To date sixteen cultures have been tested; one has shown a possible sign of porphyrin accumulation. Stocks of flies are being assayed for cytochrome isomers susceptible to PHA induction; more extensive testing and repeats of the feeding study are being carried out. We will use this chemical induction paradigm to study heme biosynthesis, porphyria, and free radical effects.

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THE LIGHT THEORY OF AGING. *H. Massie*, S. Whitney, and S. Sternick,* Masonic Medical Research Laboratory, Utica, NY 13501.

The effect of visible light on the life span of *Drosophila melanogaster* was studied at 30, 35 and 37°C on a 12:12 light:dark cycle. As would be expected for a photochemical process, greater decreases in life span induced by light were observed with increasing temperature. The changes in life span at 30°C exceeded 100% and those at 35°C exceeded 500% within a range of lux values from 7000 to 0.3 lux. The relative decrease in life span changed slowly between 0.3 and 400 lux. Above 400 lux a faster rate of change was observed. We conclude that light is one of the most important factors yet observed in the aging of Drosophila. We proposed that aging in general may be a photochemical process.

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THE INFLUENCE OF AGING AND OBESITY ON RIBOSOMAL S6 PHOSPHORYLATION IN RAT FAT CELLS. *N.A. Vydelingum,* Sloan Kettering Cancer Center, New York, NY 10021.

Insulin (INS) has been shown to stimulate the phosphorylation of a single ribosomal protein (S6,Mr=32.5KDa) in rat adipocytes. To further examine the effects of INS on S6 phosphorylation, adipocytes were isolated from the epididymal fat pads of young, lean (YR, 140g) and older, obese, litter mates (OR,600g), male Sprague Dawley rats that had been fasted for 24 Hr. The adipocytes were equilibrated for 2 hr. in a phosphate-free buffer containing 32p orthophosphate (0.2mCi/ml), glucose (5mM) and a mixture of amino acids. The cells were incubated for a further 20 min +/- INS (0.1mU/ml). Ribosomes were isolated and incorporation of 32p into S6 protein was determined by PAGE and autoradiography. In cells from YR, INS increased both total ribosomal protein labeling (TRPL, mean +/- SE; INS 3759 +/- 97 vs Cont. 1359 +/- 121 dpm/1A 260 unit; $p<0.02$, $n=8$) and 32p specific activity of S6 (PSA; INS 1.32 +/-0.05 vs Cont. 0.51 +/- 0.07 dpm/Unit protein, $p<0.02$). In contrast, in OR, INS stimulation of both TRPL (INS 1674 +/- 58 vs. Cont. 1042 +/- 67 dpm/1A 260 Unit, $p<0.05$, $n=8$), and PSA of S6 (INS 0.52 +/-0.04 vs Cont. 0.38 +/- 0.03, dpm/Unit protein, $p<0.05$), was decreased. Hence, the stimulation of S6 phosphorylation by INS is diminished in fat cells from OR. Insulin resistance associated with aging and/or obesity may explain these changes.

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PROTECTION OF NUCLEAR DNA DAMAGE BY DIETARY RESTRICTION IN THE AGED LIVER. *M.H. Chung[1], H. Kasai[2], S. Nishimura[2], and B.P. Yu[3]*,* [1]Dept. of Pharm. Coll. of Med., Seoul Natl. Univ., Korea, [2]Biol. Div. Natl. Cancer Ctr. Res. Inst., Tokyo, Japan, [3]Dept. of Physiol., UTHSC, San Antonio, TX 78284-7756.

It is generally accepted that DNA molecules undergo continuous modification during aging. Since the cell function and survival depend on the genomic integrity, it is important to maintain the DNA structural integrity throughout their life span. Our investigation was to assess the extent of DNA modification by age and to explore the possible protective action of dietary restriction. Male Fischer 344 rats were maintained under specific barrier conditions. Dietary restriction (DR) was imposed by a 40% reduction of the average food intake of *ad libitum* fed (AL) controls. The endogenous DNA damage in liver was estimated by quantifying 8-hydroxy-deoxyguanosine (8-OH-dG) by HPLC. The results show that the amount of 8-OH-dG/10^5dG at 18 mos of age was 2.65±0.2 in AL rats compared to 2.43+0.2 in DR rats, with no significant differences. However, at 24 mos, the values for AL and DR rats were 2.31±0.2 and 1.64±0.1, respectively, making significant differences of $p<0.05$. Our data on DNA damage shows no age-related increase between 18 and 24 mos. The significance of our findings is that DNA damage can be attenuated by the anti-radical actions of dietary restriction, thereby protecting the genomic integrity against oxidative threat which occurs throughout the life span of organisms.

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DEVELOPING A MODEL OF DIETARY RESTRICTION IN NONHUMAN PRIMATES. *D.K. Ingram*, R.G. Cutler, and G.S. Roth,* N. W. Shock Laboratories, Gerontology Res. Center, NIA, NIH, Baltimore, MD 21224.

Dietary restriction (DR) is a potent modulator of aging processes in laboratory rodents and lower species. Beyond epidemiological evidence relating caloric intake as a risk factor in various age-related human diseases, little is known about the relevance of DR to nonhuman primates. We have now developed a nonhuman primate model for assessing the effects of DR on general physiology of higher species, for determining whether aging processes can be retarded by dietary restriction in monkeys, and for testing various hypotheses related to mechanisms for the anti-aging effects of DR as addressed in rodents. At ages ranging from 1-9 years, different groups of rhesus and squirrel monkeys were provided a diet (fortified with recommended vitamins and minerals) on a regimen that slowly reduced their intakes to 30% less that of comparable, weight-matched controls. After 3 years on the regimen, the body weight growth of the DR group is clearly less than that of controls. Other morphometric measurements indicate the DR regimen has produced lean monkeys without markedly stunting skeletal growth. Based on a range of clinical markers and veterinary evaluation, there was no evidence of detrimental effects of the DR regimen, and both control and DR monkeys appear very healthy. We maintained groups of old monkeys for making cross-sectional comparisons on parameters of interest, and recently we have placed an old (>18 y) group of rhesus monkeys on the same DR regimen. Along with many collaborators, we are currently assessing a wide range of biochemical, cellular, and physiological parameters in a longitudinal manner to determine their utility for determining whether DR has altered developmental and/or aging rates in these monkeys.

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A PHYSIOLOGICAL VIEW OF AGING AND ITS IMPLICATIONS FOR INTERVENTIVE GERONTOLOGY. *G.M. Fahy,* American Red Cross Jerome Holland Lab., Transplantation, Rockville, MD 20855.

A physiological view of aging is discussed which holds that aging is primarily the result of regulated changes in genetic expression that affect a small number of key cellular activities as well as a number of key neuronal, immunological, and endocrine pathways. The failure of exhaustive attempts to demonstrate mis-synthesis of proteins with aging and the discovery of clearly regulated repression of essential genes with aging suggest that aging is genetically regulated and not primarily driven by random damage. The most compelling evidence supporting this hypothesis is the striking reversibility of age-related changes in response to physiological stimuli. For example, appropriate physiological interventions can reverse immunological aging by regenerating the thymus gland, reverse the decline of lean body mass and the buildup of adipose tissue in man, reverse age-related losses of neurotransmitter receptors, and reverse "*in vitro* aging." Single pharmacological agents are able to increase maximum lifespan and reverse age-related declines in protein synthesis, and transgenic *Drosophila* carrying extra elongation factor one live longer than controls. Calorie restriction elevates growth hormone (whose actions are primarily "gerolytic"), whereas aging itself is accompanied by reductions in growth hormone. The physiological hypothesis of aging explains most data easily and has exciting implications for clinical gerontology.

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UV-INDUCED ORNITHINE DECARBOXYLASE AS A MARKER OF AGING AND DIFFERENTIATION IN HUMAN SKIN FIBROBLASTS. *H.J. Niggli[1]*, R. Rothlisberger[1], K. Bayreuther[2], and P.I. Francz[2],* [1]Cosmital SA, Rte de Chesalles 21, CH-1723 Marly, [2]University of Hohenheim, Institute of Genetics, D-7000 Stuttgart 70 FRG.

Hayflick's pioneering work in the early sixties entailed that human diploid fibroblasts had become a widely accepted in vitro model system for gerontological research. Bayreuther and co-workers have extended this model based on morphological and biochemical data. They showed evidence for the theory that cellular senescence is a process of terminal differentiation. Using this model, we have shown that mitomycin-C (MMC) accelerates the differentiation pathway from mitotic (MF) to postmitotic fibroblasts (PMF) using 2-dimensional gel electrophoresis. As shown previously UV-induced ornithine decarboxylase (ODC) can be activated by ultraviolet light in human skin fibroblasts. We tested this interesting enzyme in the fibroblast system for a possible role in differentiation and aging. Indeed, we were able to demonstrate that UV-induced ODC-response is significantly reduced in the MMC-induced postmitotic stage of fibroblasts. We compared this finding with previous results from our laboratory, where we have found that ODC in human skin fibroblasts from younger donors can be significantly more stimulated by UV compared to the enzyme activities in fibroblasts from older donors. We conclude that ODC is an excellent marker of differentiation and aging.

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THE EFFECT OF LEUPEPTIN ON THE LATERAL MOBILITY OF PROTEINS IN THE PLASMA, MEMBRANES OF HEPATOCYTES OF C57BL/6 MICE. *K. Kitani, M. Ohta, and I. Zs.-Nagy,* Dep. Clin. Physiol. Tokyo Metropol. Inst. Gerontol., Tokyo, Japan, 173.

Leupeptin (a thiol protease inhibitor) has been shown to induce ceroid-lipofuscin in the brain as well as other internal organs including the liver in young rats and mice. Since the lateral diffusion of hepatocyte surface membrane proteins has been shown to decrease with age, the present study aimed at clarifying how the diffusion constant will be affected by pretreatment of leupeptin.

Male C57BL/6 mice of different ages (2 to 24 months) were ip infused for 2 wks at a rate of 5 mg per 100 g body weight/day of leupeptin. Another group of adult (12 months old) male mice were treated for 2,4,8,11 and 14 days, respectively with the same daily dose. The average lateral diffusion constant (D) and the fractional recovery (FR) of surface membrane proteins were measured by means of fluorescence recovery after photobleaching (FRAP) in liver smears.

Leupeptin-treatment caused a linear increase of D and a decrease of FR with respect to the period of treatment in adult mice. After 14 days of treatment, FR tended to decline with age from 90% at the age of 2 months to 65% at 24 months, whereas the remaining mobile fraction displayed a large increase of D.

In conclusion, leupeptin appears to increase the immobile fraction of surface membrane proteins and this trend becomes enhanced as the age of animals advances. The increase in D could be interpreted as the compensatory mechanism of the surface membranes for the increasing immobile fraction.

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LOSS OF ANDROGEN RESPONSIVENESS OF RAT LIVER DURING AGING. *B. Chatterjee*, and A.K. Roy,* University of Texas Health Science Center, San Antonio, TX 78284.

The hepatic response to androgen in male rats changes sequentially from hormone insensitivity during prepuberty to androgen responsiveness in adult life, and subsequent gradual loss of the hormonal response during aging. We have demonstrated that the age-dependent differential androgen responsiveness is directly correlated to androgen receptor gene expression in parenchymal hepatocytes. The androgen receptor mRNA can be readily detected in the liver following the onset of puberty. However, receptor expression gradually declines with advancing age, and the corresponding mRNA is undetectable by 18- to 20-months of age. Loss of the tissue response to androgen during aging results in repression of the androgen-inducible α_{2u}globulin and derepression of the androgen-repressible SMP-2. Age-dependent reciprocal changes in the expression of these two androgen-regulated genes are due to loss of the hormone receptor itself, rather than to a decline in the circulating level of testosterone. Calorie restriction allows androgen receptor gene expression in the liver even in 27-month old rats, resulting in a sustained tissue response to androgen. Accordingly, transcription of the α_{2u}globulin gene continues in calorie-restricted old rats, whereas the SMP-2 gene continues to remain transcriptionally repressed. These studies indicate that dietary restriction is able to modulate important regulatory events which are likely to play crucial roles in the maintenance of cell functions and systemic homeostasis.

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AGING AND METABOLIC IMMUNODEPRESSION. *V. Dilman,* Endocrinology Lab., Inst. of Oncology, 189646 Leningrad, Pesochny-02, USSR

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USE OF ROTIFERS TO TEST THE RATE OF LIVING THEORY OF AGING. *H.E. Enesco*, V. Bozovic, A. McTavish, and R. Garberi,* Dept. of Biology, Concordia University, Montreal, Quebec, Canada, H3G 1M8.

The rate of living theory predicts that organisms with a greater energy expenditure should have a shorter lifespan. Energy is expended in reproduction, locomotion and metabolism. The first two of these parameters can readily be measure in rotifers. *Asplanchna brightwelli* (N = 24 per group) of known birth date were maintained in the single wells of tissue cluster dishes on a cerophyl medium containing *E. coli* and *Paramecium caudatum* as food source. Lifespan, number of offspring, and activity level were measured. Lifespan is strongly correlated with the length of the reproductive period (r = 0.70) and also with the number of offspring (r = .55). Lifespan and activity level were also correlated (r = .38) during the latter part of the lifespan. The results show that increased activity level and increased reproduction are positively correlated with a longer lifespan. Thus, the results do not support the rate of living theory of aging. There is evidently no "cost of reproduction" or "cost of movement" in rotifers leading to decreased survival.

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LIFESPAN EXTENSION PRODUCED BY REDUCED METHIONINE INGESTION MAY BE INDEPENDENT OF CALORIC INTAKE. *N.D. Orentreich, J.A. Zimmerman[1]*, and J.R. Matias,* Orentreich Foundation for the Advancement of Science, Cold Spring-on-Hudson, NY 10516, and [1]St. John's University, Jamaica, NY 11439.

Caloric restriction is a well-known technique for retarding development and extending lifespan. We have studied the potential life-extending actions of diets which, although isocaloric, contain reduced levels of the essential amino acid methionine. Twenty-five to 30 Fisher 344 male rats in each group were fed defined diets containing 0.86% (normal intake), 0.43% or 0.17% methionine beginning at 5-6 weeks of age. The diets were prepared with no cysteine, but sufficient choline. Consumption of 0.17% methionine produced a complete cessation of growth, and an extension in median lifespan from 105 weeks (.86% and .43% met) to 150 weeks (.17%). Measurements of food intake indicated that the low methionine-fed animals ingested nearly twice the food per gram body weight than did the animals offered eumethionine levels in the diet. Furthermore, feeding reduced methionine in diets which contained increased caloric density did not produce better weight gain than did reduced methionine in conjunction with normal caloric intake. Taken together these last experiments may indicate that lifespan extension can be accomplished by experimental means other than caloric restriction.

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ON THE MECHANISM OF LIFE-SPAN PROLONGATION BY ANTIOXIDANT BUTYLATED HYDROXYTOLUENE. *V. Koltover,* Inst. of Chemical Physics, USSR Acad. of Sciences, Chernogolovka, Moscow Region, 142432, USSR.

We examined the effects of butylated hydroxytoluene (BHT) on the functional activity of four subsystems of the endocrine regulation, namely: adenohypophysis, adrenal cortex, thyroid gland and blood. The effects of a single administration of BHT were studied in the experiments on adult (4-6 months) and old (24-26 months) male Wistar rats. Changes due to BHT took place in the intensity of electron spin resonance signals of transferrin and ceruloplasmin in the blood. These changes may indicate a shift in the redox potential of the blood plasma. It was shown by the spin label method that BHT was also capable of a direct interaction with transport proteins of blood. There were also significant BHT-induced changes in the plasma concentrations of ACTH, 11-OHCS, TSH and T_3 hormones. The amplitude and the direction of the changes depended upon the type of hormones, the time period that had elapsed after BHT injection, and the animal's age. Thus, the physiological effects of BHT seem to be mediated via the system of the organism's neurohumoral regulation. It can be suggested that with regular introduction into animal's food, BHT, as a mild stress factor, 'trains' the neurohumoral system and thus increases its reliability.

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INVESTIGATION ON TRACE METAL IN HAIR OF PATIENTS WITH CEREBRAL VASCULAR DISEASE. *A.-G. Lin, Y.-C. Yan, E.-A. Liu, and Q.-S. Dai,* Dept. of Neurosurgery, Harbin Medical University, Harbin, P.R.C. 150001.

25 kinds of trace metal in samples taken from occipital hair of 68 patients with cerebral hemorrhage and infarction were evaluated with Ion Coupled Plasma Spectroscope. The elements include V, Ba, Cr, Co, Mo, Cu, Zn, Mn, Sn, Ni, Ca, Mg, P, Fe, Pb, Y, W, Ce, Ti, Li, Na, Sb, Nb, Bi. Data were analyzed with Logress model (logic regression). The significance of the results shows in table below:

Hemorrhage Group

	Odds Ratios	95% Confidence Lower	Intervals Upper
CR	2.840	0.000	***
Sn	2.0886	0.000	***
Cd	>7	1.2262	***
Sb	3.9526	0.3537	44.1722
Li	>7	0.0001	***

Infarction Group

	Odds Ratios	95% Confidence Lowers	Intervals Upper
Ni	>7	0.000	***
Cr	>7	0.000	***
Ce	>7	0.000	***
Na	>7	0.000	***
Y	>7	0.000	***

Therefore, the elements included in table above might be related to cerebral vascular disease and there is significant difference of effecting elements between cerebral hemorrhage and infarction.

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HISTOMORPHOMETRY OF AGE-RELATED CHANGES IN THE PROXIMAL FEMUR OF FEMALE CW-1 MICE. *A. Weiss*, I. Arbell, and M. Silbermann,* Faculty of Medicine, Technion, Haifa, Israel.

Olympus Cue-2 image analysis system was used for quantitation of age-related changes in the proximal femur of CW-1 female mice, aging 3 to 32 months. An progressive thinning of bony trabecules in the femoral head, as well as appearance of cavities filled with bone marrow in cortical and subchondral bones were observed. As a result, the cortical and subchondral bones in senescent animals resembled trabecular bone. The trabecular, subchondral and cortical bones volume, as well as the thicknesses of cortical and subchondral bones showed a similar pattern: an initial increase, a peak at 12 months and a decline thereafter. Regression analysis of the data revealed that the pattern of changes with age for bone parameters fitted a quadratic model. Using this analysis, the age of maximal bone volume for cortical, trabecular and subchondral bone was estimated as 12.3, 14.8 and 18.0 months respectively. The highest rate of bone loss occurred in the trabecular bone (1.47% per month) so that by 32 months of age it was reduced by 58% as compared to that of 12 months ($p<0.001$). The volume of subchondral and cortical bones decreased at a slower rate of about 0.6-0.8% per month, and at the age of 32 months it was reduced by 18% in comparison to that of 12 months ($p<0.001$).

In conclusion, the study provides evidence that laboratory mouse might serve a model for studies related to age-associated bone loss.

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RATS EXHIBIT AGE-RELATED DEFICITS IN GENERALIZATION BUT NO IN ACQUISITION OF ACTIVE AVOIDANCE TEST. *A. Caprioli*, O. Ghirardi, A. Giuliani, M.T. Ramacci, and [1]L. Angelucci,* Institute for Research on Senescence, Sigma Tau S.p.A., 00040 Pomezia, Rome, and [1]Institute of Pharmacology II, "La Sapienza" University, 00100 Rome, Italy.

Rats of different ages were evaluated for their capacity of acquisition of active avoidance test and for their ability to generalize when the conditioned stimulus was modified. Fischer 344 rats aged 3 months (N=18) and 20 months (N=18) were subjected to 3 active avoidance tests in a Shuttle Box, using different conditioning stimuli (CS): a) acquisition of conditioned response, using light as CS (10 trials); b) generalization, replacing light with sound (6 trials). The unconditioned stimulus in both tests was electroshock; c) extinction as after test b). In a), both age groups showed a good acquisition (approx. 75% avoidances) with no significant differences between the two groups as for the cognitive parameters. The only one parameter possessing discriminative strength consisted in the measurement of intertrial crossings. In b), the multivariate analysis pointed out that results of the first trial (generalization) were independent of the successive learning process and of the results obtained in test a). The overall results of test b) pointed out that old rats exhibited a significantly lesser capacity for generalization than young rats. Moreover, differently from test a), performances of the old rats never reached a level that allowed comparison with those of the young rats. As regards extinction (c), the asymmetry of acquisition (b) between rats of different ages did not permit any comparison whatsoever between the two groups. Old rats showed no difficulty acquiring active avoidance test, whereas exhibited learning deficits when CS was modified.

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INFLUENCE OF PHYSICIANS' RECOMMENDATION ON INFLUENZA IMMUNIZATION ACCEPTANCE AMONG A GROUP OF INSTITUTIONALIZED ELDERLY. *R. Ganguly*, T.B. Webster, B.V. Yangco, J. Sinnott, and H. Chmel,* James A. Haley Veterans' Hospital, Tampa, FL 33612, and Bay Pines VA Medical Center, St. Petersburg, FL 33504.

Elderly VA nursing home care unit (NHCU) residents (≥65 years old) were surveyed by questionnaire to assess the contributing factors for their influenza vaccination behavior. The 201 male veterans studied had an average length of stay at the NHCU of 12 months and >70% suffered from chronic diseases with a past history of smoking. Physician's recommendation concerning immunization wase found to be the most significant factor for vaccine compliance. Over 50% of the residents immunized in the past could recall a physician personally giving a recommendation for vaccination. Among those not immunized during the past year and those not recalling a physician's recommendation for vaccination, cited reasons such as unawareness of vaccine need (22%), dislike or fear of side effects (20%) and general amotivation (14%) as factors for nonimmunization. These data suggest that physicians' intervention plays a strong role in the influenza vaccination behavior of hospitalized elderly veterans. Furthermore, physicians' intervention appears to be more effective than the usual standing NHCU practice of vaccine offering by the nursing staff. Data also suggest that the educational intervention measures may be beneficial, yet, not as effective as physicians' intervention.

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STIMULATION OF HAIR GROWTH BY PEPTIDE COPPER COMPLEXES. *L. Pickart, R.E. Trachy, and L.M. Patt*,* ProCyte Corporation, Kirkland, WA 98034-6900.

The loss of hair is a common symptom of advancing age. The most typical manifestation is progressive hair loss noted in male pattern baldness (androgenic alopecia). Some treatments of this condition are available in the form of antihypertensive compounds (Minoxidil) and certain anti-androgens. A peptide copper complex, Glycyl-L-Histidyl-L-Lysine: Copper (2:1) [code PC1020] has been found to possess multiple would healing properties. Certain analogs of PC1020 have been produced which stimulate hair growth in mice. The phases of active (anagen) and dormant (telogen) hair growth in mice necessitate precise timing of drug administration. Mice are clipped and examined to determine the hair growth cycle and injections are timed to coincide either with the anagen or telogen cycle.

The intradermal injection of analogs of PC1020 during the anagen phase results in prolongation of the anagen cycle while injection during the telogen phase results in the conversion of telogen follicles into active growing anagen follicles. Histological examination confirms the presence of anagen follicles during the normal telogen phase in both instances. These compounds represent a new class of hair growth pharmaceuticals with potent effects on hair follicle development.

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OVERVIEW OF MITOCHONDRIA AND AGING. *Organizer: R. Weindruch,* U. Wisconsin, Madison, WI 53706.

(Abstract appears on page 109)

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OXIDATIVE MITOCHONDRIAL DNA DAMAGE. *T.M. Hagen, and B.N. Ames*,* Division of Biochemistry and Molecular Biology, University of California-Berkeley, Berkeley, CA 94720.

DNA is constantly damaged by reactive oxygen species produced as a consequence of normal cellular metabolism. We have shown that oxidative DNA damage to mitochondrial DNA (mtDNA) is extensive. The steady-state levels of 8-hydroxy-2'-deoxyguanosine (oh^8dG), a marker of oxidative damage is 16-fold higher in mtDNA than in nuclear DNA, corresponding to approximately 1 in every 8000 bases that have been damaged. This large steady-state damage is presumably due to the proximity of mtDNA to sources of reactive species produced from electron transport and the lack of repair mechanisms in this organelle. We have isolated a subfraction of rat liver that contains 0.7 pmol oh^8dG/μg mtDNA, approximately double the steady-state concentration in the total mtDNA fraction. This subfraction corresponds to approximately 6% of the total mtDNA and appears to be associated with protein. Studies are presently under way to determine whether the damaged fraction corresponds to a certain subpopulation of mitochondria in the cell or whether this highly damaged subfraction of mtDNA increases with age.

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ROLE OF MITOCHONDRIA IN OXIDATIVE STRESS IN AGING. *R.S. Sohal,* Department of Biological Sciences, Southern Methodist University, Dallas, TX 75275.

The *in vivo* level of oxidative stress, i.e., ratio of pro-oxidants/anti-oxidants, increases *in vivo* during aging in insects and mammals as indicated by age-associated increase in the exhalation of alkanes, which are products of lipid peroxidation. Increased oxidative stress appears to be due to enhanced rates of oxygen radical production by mitochondria. Rates of O_2^- and H_2O_2 from flight muscles of houseflies were up to 2-fold higher in old than in young flies. Rate of O_2^- production in the liver, heart and brain submitochondrial particles was higher in the 16-month than 4-month old rats. Rates of O_2^- and H_2O_2 production by liver mitochondria were inversely related to maximum life span potential of six mammalian species, namely mouse, rat guinea pig, rabbit, pig and cow.

Activities of respiratory complexes such as NADH-cytochrome c reductase, succinate-ubiquinone reductase and succinate-cytochrome c reductase were two-fold higher in mitochondria of old than young flies suggesting an increase in the speed of electron flow in the respiratory chain. Lipid peroxidation levels and state 4 respiration rates were higher in older flies. Experimental damage to mitochondria and inter-molecular cross-linking were found to enhance the rate of O_2^- and H_2O_2 production. It is proposed that generation of O_2^- and H_2O_2 by mitochondria leads to mitochondrial membrane damage, which in turn further enhances the rate of pro-oxidant production. This model can explain the age-related increase in the level of oxidative stress. Mitochondria could thus represent an epigenetic factor influencing the aging process.

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ROLE OF MITOCHONDRIA IN *DROSOPHILA* AGING. *J.E. Fleming,* Linus Pauling Institute of Science and Medicine, Palo Alto, CA 94306.

We previously postulated that the mitochondria of differentiated cells may be the site of primary senescent damage to multicellular organisms. This was based on the idea that, during normal metabolism, the mitochondria release toxic oxygen metabolites that induce irreversible damage to cellular components. That mitochondria experience age related functional loss is supported by a wealth of fine structural, biochemical and physiological data. However, it is not known whether this decrease in function is related to oxidative processes. In order to understand the *in vivo* relationship between efficient dismutation of 0_2 radicals, we generated transgenic strains of *Drosophila melanogaster* overproducing CuZn superoxide dismutase (SOD), an enzyme that catalyzes the dismutation of the superoxide radical to the less toxic hydrogen peroxide. This was achieved by microinjecting *Drosophila* embryos with p-elements containing bovine CuZn SOD cDNA under the control of the actin 5C gene promoter. Adult flies of the resulting transformed lines, which express both mammalian and *Drosophila* SOD were then used as a novel model to examine the role of oxygen radicals in aging and other degenerative processes. Our data show that expression of active enzyme in adults confers resistance to paraquat, an O_2^- generating compound. This is consistent with our data on adult mortality, because there is a slight but significant increase in the mean lifespan of several of the transgenic lines. The highest level of expression of the active enzyme in adults was 1.60 times that observed in controls. Higher levels may have led to the formation of toxic levels of H_2O_2 during development, since transgenic flies that died during the process of eclosion showed an unusual accumulation of lipofuscin (age pigment) in some of their cells.

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DEVIATION OF LINEAR ELECTRON FLOW IN MITOCHONDRIA AS ULTIMATE CAUSE OF AGE-DEPENDENT OXIDATIVE STRESS. *H.Nohl,* Institute for Pharmacology and Toxicology, Vet. Univ. of Vienna, Linke Bahngasse 11, A-1030 Vienna.

The biological process of aging is unequivocally accepted to be associated with an imbalance of oxygen homeostasis in favor to prooxidant events. Although, parts of the antioxidant defense system become less efficient the main cause of "oxidative stress" results from an increased formation of potent oxidants. The initial step to this situation is supposed to mainly occur in mitochondria. One reason for that is the fact that mitochondrial respiration accounts for more than 90% of total cellular oxygen. Second, mitochondria reduce 0_2 to H_20 by consecutive single electron transfer which necessarily involves the existence of 0_2-radical intermediates. Thus, a rigid control of electron transfer steps and of the interaction of 0_2 with mitochondrial electron carriers is a prerequisite to prevent the formation of deleterious oxygen intermediates on the way to H_20. A loss of control of linear electron transfer would not only initiate the existence of dangerous oxygen metabolites but will also decrease the efficiency of energy conservation. We have evidence from our *in vitro* experiments that for many "internal and external" reasons mitochondria lose their capacity to efficiently control redox steps of energy-linked respiration as the animal ages.

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REGULATION OF BIOENERGETICS DURING AGING IN RATS. *E. Shrago,* University of Wisconsin Medical School, Dept. of Medicine, Div. of Nutritional Science, Madison, WI 53706.

(Abstract not available)

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MODIFICATION OF MITOCHONDRIAL AGING BY CALORIE RESTRICTION. *B.P. Yu*, and J.J. Chen,* Dept. of Physiol. Univ. of Texas Health Science Center, San Antonio, TX 78284-7756.

Several hypotheses on aging implicated mitochondrial aging as the basis of cellular aging of organisms. These hypotheses were premised that altered mitochondrial genomes, deterioration of membrane, and eventual dysfunction are the underlying mechanisms. Works with rat liver from our laboratory provided evidence supporting the notion. The first evidence of mitochondrial impairment was the reduced yield of mitochondrial protein from old rats. Changes in membrane fatty acid composition and increased lipid hydroperoxide were observed in old rats, making the membranes more peroxidizable. Calorie restriction counteracted these alterations. Mn-superoxide dismutase shows no age-related decrease, but calorie restriction maintained it at higher levels throughout 24 mos. Investigations leading to the age-related changes on the physical property of membranes with fluorescent probe clearly showed the loss of membrane fluidity in old animals as indicated by both increased anisotrophy and transition temperature. Evidence indicate that the loss of membrane fluidity may be due to the increased cholesterol/phospholipid ration and membrane lipid peroxidizability which are modulated by calorie restriction. Experiments on malondialdehyde oxidation indicate a progressive loss of the oxidation capacity with age, which was prevented by dietary restriction. However, succinate-supported mitochondrial 02 consumption, P/O ratio, state 3 and 4, and respiratory control index show little evidence of the age or dietary effects.

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ASCORBIC ACID IS SYNTHESIZED BY *DROSOPHILA.* *S. Sternick*, H. Massie, M. Shumway, and W. Whitney,* Masonic Medical Research Laboratory, Utica, NY 13501.

Ascorbic acid (AA) is synthesized by *Drosophila melanogaster.* Whole adult flies were homogenized in HEPES buffer with 10^{-4}M DTPA (diethylenetriaminepentaacetic acid). The AA content of Oregon R *Drosophila* varied with age and with the medium on which the flies were grown. On cornmeal medium AA was synthesized at all stages of adult life, showing a slight decrease with age. The range was from 0.0719 µg/fly at 3 d to 0.0299 µg/fly at 51 d of age. When the flies were maintained on instant medium, the amount of AA per fly was high in early imagos but decreased and then increased again at later stages. The range on instant medium was from 0.0479 µg/fly at 1 d to 0.1324 µg/fly at 47 d of age. The age related changes in Swedish C strain *Drosophila* were found to be different from those in Oregon R. In addition, various precursors of AA were added to the cornmeal medium; only one, gulonolactone, resulted in an increase in the amount of AA per fly. We conclude that the presence of AA in *Drosophila* may have been previously undetected because of the instability of AA. This confirms the initial observations of Fleming *et al.* 1988 and demonstrates a method of AA detection which may be useful in other insect species as well.

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CORRELATION OF FRUCTOSAMINE AND HbAlc IN OLDER DIABETIC PATIENTS. *C. Johnson*, B. Gerson, S. Podolsky,* VA Outpatient Clinic, Boston, MA 02130.

HbAlc is widely used to assess diabetic control over the preceding 6-8 weeks, but is expensive and difficult to perform. We compared fructosamine to HbAlc in 100 older diabetics for monitoring glycemic control. HbAlc was determined by Biorad microcolumn chromatography (Hercules, CA) and fructosamine on the Roche COBAS Mira S using RoTAG reagent (Nutley, NJ).

Patients were 63±1.4 yrs (mean±SEM); average serum glucose 200±8.7 mg/dl. Mean HbAlc was 6.4±0.2% (normal=3.2-5.7%); mean fructosamine was 3.2±0.07 mmol/L (normal=2.0-2.7 mmol/L). Both assays resulted in normal values in 34% of patients tested. In 66% one or both of the assays were abnormal. Of these, in 47 both were abnormal, in 17 the HbAlc was normal while the fructosamine was elevated, and in 2 the fructosamine was normal while the HbAlc was elevated.

Fructosamine correlated well with the accepted HbAlc assay when used to evaluate long term diabetic control. Also, changes in average glycemia were reflected earlier using fructosamine than with HbAlc. It appears that fructosamine assays may provide valuable clinical information in addition to being more cost effective than HbAlc tests.

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EVALUATION OF OSTEOCALCIN AS A SERUM MARKER FOR OSTEOPOROSIS. *J.H. Healey*, M. Nuby, C. Gundberg, J. Godbold, and M. Bansal,* The Hospital for Special Surgery, New York, NY 10021.

Osteocalcin, the most prevalent non-collagenous protein of bone, has been advocated as a serum marker of bone metabolism and a useful adjunct for evaluation of osteoporosis and other bone disease. We studied the correlations of serum osteocalcin to 20 standard parameters of bone metabolism and bone mass via univariate and multi-variate analysis by linear regression technique. Specifically tested was the hypothesis that serum osteocalcin could predict the results of bone formation rates and other histomorphometric parameters. If it were able to do this, iliac bone biopsy could be eliminated from the work up of osteoporosis patients.

METHODS: Osteocalcin was measured by radioimmunoassay in triplicate on morning fasting blood samples. 80 patients were evaluated during a comprehensive work up for metabolic bone disease, including iliac bone biopsy. Undecalcified bone histomorphometry was performed on double-tetracycline labelled iliac samples. Al but 3 patients had idiopathic osteoporosis, and 85% were female with a mean age of 61 years. Statistical analysis was by multi- and uni-variate linear regression methodology.

RESULTS: Substantial differences are found between the univariate and multi-variate analyses. Alkaline phosphatase, radial apparent density, trabecular osteoid volume, and trabecular osteoid surface were clearly related to osteocalcin. Purported correlates such as age, renal function, vitamin D status and bone formation rates correlated poorly. Using all combinations of the measured parameters, only 42% of the osteocalcin could be accounted for.

CONCLUSION: 1) Serum osteocalcin doesn't predict bone formation rate and poorly correlates with dynamic parameters measured by histomorphometry. 2) It correlates best to osteoid surface and volume measurements. 3) Iliac biopsy still provides the best information and should be retained as part of the metabolic bone disease work up.

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RELIABILITY OF BIOLOGICAL SYSTEMS AT DIFFERENT ORGANIZATION LEVELS AND THE PROBLEM OF MOLECULAR MECHANISMS OF AGING. *V. Koltover,* Inst. of Chemical Physics, USSR Acad. of Sciences. Chernogolovka, Moscow Region, 142432, USSR.

The reliability theory approach unites the deterministic and stochastic principles. That is why this approach provides the opportunity to explain Gompertz's law of mortality and other empirical demographic and comparative correlations. There are the sets of reliability parameters at all levels of biosystems organization. The values of such parameters are stabilized at the invariant levels. Aging of animals is characterized by stabilization of fluidity of membrane lipids at physiological temperatures. Similar results have been obtained in experiments with Acholeplasma laidlawii cells. Aging of the cell culture in the stationary phase takes place without any significant change in lipid fluidity at the growth temperature. The values of intracellular contents of oxygen free radicals may be considered as other examples of such invariants. The searching for molecular mechanisms of aging is a question of the reliability analysis of biosystems during adaptation processes to low levels of ionizing radiation or other small changes in environmental conditions.

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LYMPHOCYTIC HYPOPHYSITIS: A RARE AUTOIMMUNE DISORDER IN THE ELDERLY. *P.G. Rosario*, M. Greenberg, and S. L. Weitz,* Dept. of Surgery, Bronx Lebanon Hospital; Dept. of Neurosurgery, Montefiore Med. Center, Bronx, NY 10468.

A 71-yr old female had two syncopal episodes not associated with headaches, convulsions or any visual disturbance. Her neurological exam was normal; the visual fields were intact. An enhancing sellar mass was however detected on both CT Scan with contrast and MRI. An endocrinology profile showed panhypopituitarism with no evidence of diabetes incipitus. Stimulation tests using TRH revealed a modest rise in both TSH and Prolactin. The patient underwent transphenoidal resection of the suspected adenoma. Histopathology revealed the anterior pituitary was densely infiltrated by mature small lymphocytes.

Lymphocytic infiltration of the pituitary resulting in end organ failure is an extremely rare occurrence. Most previously reported cases have been related to the immediate postpartum period when fetal suppressor cells are believed to cross react with maternal antigens. In the elderly however only one similar case has been reported previously. This clinicopathologic entity may therefore represent a distinct new autoimmune disorder.

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PHARMACOLOGICAL MANIPULATIONS OF NEURONAL AGING. *K. Nandy,* Dept. of Anatomy, Boston Univ. School of Medicine, Boston, MA 02118.

One of the most consistent cytological changes in the neurons of aging mammals is the deposition of lipofuscin pigment. The pigment appears to develop in two stages with different properties. A number of experimental manipulations of neuronal aging have been studied in our and other laboratories and these include nutritional alterations and pharmacological agents. The drug known as centrophenoxine has been shown to reduce lipofuscin in the neurons of hippocampus and frontal cortex in aging mice and this was associated with changes in the learning and memories of the animal. When mice were treated with the drug for 6 months followed by no treatment for another 6 months, the neurons of the frontal cortex hippocampus showed an increase in the pigment compared to the animals on centrophenoxine alone for 12 months. In another experiment, animals treated with centrophenoxine and vitamin E deficient diet simultaneously for 12 months exhibited less pigment in the neurons than the mice fed on vitamin E deficient diet alone for 12 months. It appears that lipofuscin pigment is a reliable marker of neuronal aging and this can be utilized in the study of experimental manipulations of the mammalian aging process.

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METABOLIC ACTIVATION OF 3,4-BENZO(A)PYRENE BY HEPATIC NUCLEI ISOLATED FROM YOUNG AND OLD C57BL/6J MALE MICE. *M.B. Baird*, and J. L. Hough,* Masonic Med. Research Laboratory, Utica, NY 13501.

Aging is accompanied by an alteration in the rate of metabolism of xenobiotics, including various chemical carcinogens. The manifestation of these alterations in intact animals has been related *in vitro* to changes in microsomal membrane metabolism. The activation of chemical carcinogens presents a special case, however, in that highly reactive, short-lived electrophiles are generated which interact with genomic DNA to initiate cancer. Thus, it appears likely that the intracellular membrane site of greatest importance as regards carcinogen activation may be the nuclear envelope. The present studies were initiated to examine this suggestion.

Hepatic nuclei were isolated from young and old (105 and 784 days of age respectively) male C57BL/6J male mice by sucrose gradient centrifugation. Washed nuclei were incubated with tritiated benzo(a)pyrene (BP) in the present of NADPH. Following incubation, nuclear DNA was isolated and purified (O.D. 260/280 > 1.8) by column chromatography, solubilized, and counted for radioactivity.

Isolated whole nuclei readily metabolized BP to forms which bind covalently to the nuclear DNA. There was a 30% decline in radioactivity bound to DNA in nuclei obtained from senescent mice, a decline in extent of BP metabolism similar in magnitude to that observed for other membrane sources in aging rodents. These results show that ER is not required to activate BP to forms which bind covalently to nuclear DNA. Furthermore, the magnitude of change in carcinogen-activating activity in the nuclear envelope is similar, if not identical to that observed for cytoplasmic ER.

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DIFFUSE IDIOPATHIC SKELETAL HYPEROSTOSIS (DISH) AND ARTHRITIS IN AN EARLY 20TH CENTURY GERIATRIC POPULATION. *B.M. Rothschild*, and R.J. Wood,* Arthritis Center of Northeast Ohio, Northeastern Ohio Universities College of Medicine, Youngstown, OH 44512 and Ohio State University, Columbus, OH 43210.

The Todd Collection comprises the autopsied, defleshed skeletons of 2906 individuals who died in Northeast Ohio between 1913 and 1933. Previous studies of osteoporosis and rheumatoid arthritis have documented no significant variance from contemporary populations. Bone and joint alterations were characterized in 498 individuals age 64+ from this representative population.

Diffuse idiopathic skeletal hyperostosis, rare in young individuals, was found in 25% of men over age 65, compared with only 4% of women (Chi square = 21.1, $p<0.0005$), independent of race. Osteo-

arthritis was present in 42% of Blacks but only 24% of Caucasians (Chi square = 11.3, $p < 0.001$), independent of sex. Rheumatoid arthritis was present in 4.4% of women and 0.7% of men (Chi square = 7.32, $p < 0.008$), independent of race. This 6.3:1 ratio contrasted with the 2.7:1 ratio among individuals <65. Infectious arthritis (0-1.6%) and spondyloarthropathy (3.7-7.3%) were equally represented in all groups. Calcium pyrophosphate deposition disease, equally represented (22-27%) by race and sex, increased logarithmically with age. This unique population survey provides new insights to rheumatologic impact on aging and should facilitate health care planning.

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IS TUBERCULOSIS IN AGING RETIRED COAL MINERS A THREAT TO ERADICATION? *R.C. Young, Jr.*, and R.E. Rachal,* College of Pharmacy, Xavier University of Louisiana, New Orleans, LA 70125.

Tuberculosis (TB) is more prevalent among coal miners than in the community. We studied 122 ex-miners, of which 89 had coalworkers' pneumoconiosis (CWP). Mean age of ex-miners was 59.9 years. Forty-six were White and 76 were Black. West Virginia, in central Appalachia, was the most frequently mined state. Mean dust exposure was 18 years. Tuberculin skin tests (PPD) were reactive in 39% of ex-miners. Four percent of miners still needed testing. Inactive TB was present in 29%, while active TB was present in 2.5, as confirmed by chest radiograph. Only one miner had complicated CWP and active TB. High risk variables which indicated preventive therapy were: advanced age, medical problems, diabetes mellitus, CWP, inactive TB on X-ray not previously treated, the post-gastrectomy state, and leukemia. Eradication of TB may be enhanced by awareness that ex-coal miners constitute a reservoir for potential spread of TB. We urge aggressive administration of PPD to all ex-coal miners with preventive anti-TB therapy to reactors, and a high index of suspicion for active disease.

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ICONAUTHOR/INTERACTIVE VIDEODISC COMPUTER PROGRAMMING FOR BIOGERONTOLOGY AND GERODONTOLOGY. *E.A. Tonna,* Dept. of Histology and Cell Biology, N.Y.U. Dental Center, New York, NY 10010.

Computer based information delivery technology has been initiated at the dental center to meet the changing educational needs of the dental undergraduate, graduate and post-graduate programs in support of teaching of biogerontology and gerodontology. Currently, computer assisted instructions (CAIs) are being developed using icon authoring software to supplement the teaching of general and oral histology covering the area of aging dental tissues. An image library is also being developed using an interactive video (IV) optical laserdisc recorder/player system. A database having a capacity of 24,000 analog images per 8 inch laser disc is generated from a variety of inputs, including microscope and 35 mm slides, graphic and textural materials, etc. These images, both still and motion, are coupled to CAI templates creating interactive programs. Initially, our focus is to instruction and testing for remediation of academically weak students.

Composite IV/CAIs are conducive to small group learning at any time available and provide, for the first time, integrated basic and clinical science relevancy. Software feedback generates a motivating student participation environment which allows movement to supporting subjects at different levels of complexity by hypertexting. Student program reruns are encouraged to increase knowledge, comprehension and response time. Grading, timing, user record keeping, and student performance evaluation is automatic. The interactive computer system provides a path to the future electronic curriculum.

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MODIFICATION OF COLLAGEN AGING. *H. Niedermüller*, G. Hofecker, and M. Skalicky,* Institut für Physiologie, Veterinärmedizinische Universität Wien, A-1030 Wien, Austria.

Several models of collagen aging were established to describe and to explain aging processes of the skin, the tendon and the aorta of male Sprague Dawley rats (strain OFA 17) and to investigate into their modification. We used the models of collagen solubility, isometric chemical contraction-relaxation of the tail tendon and the rheology of the skin by simultaneous determination of biochemical parameters. The following modification influences were tested: oxidation and glycosylation of the tendon, UV irradiation of the skin, the influences of juvenile collagens and proteoglycans, and that of cytoskeleton preparations on the skin, and the influence of whole matrix extracts on the tendon. UV irradiation, oxidation and glycosylation accelerated, the other influences delayed the rate of aging. Furthermore it was possible to understand better the change of structure and function with aging (biomorphosis) by mutual interpretation of the results. The explanation of the mechanisms of these influences gives us, in return, a chance to understand other functions of collagen and also holds an instrumental value.

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CELL-RECEPTOR MEDIATED INTERACTION OF GLUCOSE-MODIFIED PROTEINS AND THE VASCULAR WALL: ROLE IN VASCULOPATHY OF AGING AND DIABETES. *M. Kirstein*+, J. Brett‡, S. Radoff+, S. Ogawa‡, D. Stern‡, and H. Vlassara+,* +Laboratory of Medical Biochemistry, The Rockefeller University, New York, NY 10021, ‡Dept. of Physiology, Columbia University, College of Physicians and Surgeons, New York, NY 10032.

Atherosclerosis and arteriosclerosis are prevalent in normal aging and diabetes. Such complications have been thought to be due in part to tissue damage resulting from the steady accumulation of irreversible crosslinking glucose-protein adducts known as Advanced Glycosylation Endproducts (AGEs). Human macrophages/monocytes the body's scavenging cells normally recognize and internalize AGE-modified proteins via a specific AGE-receptor, while they simultaneously produce growth promoting cytokines (TNF, IL-I,IGF-I), thus possibly coordinating tissue remodeling. Significant chemotactic activity is now shown to be exhibited in both *in vitro* and *in vivo* glucose-modified proteins, including soluble human albumin, and lipoproteins, as well as structural proteins such as myelin obtained form aged and diabetic individuals. Human monocytes are shown to move directionally through an intact endothelial monolayer toward AGE-modified subendothelial matrix, where they phagocytose gold-linked AGE-protein. Along with ingesting AGE-matrix, monocytes are shown to respond by synthesizing growth promoting PDGF mRNA *in situ.* It is therefore possible that AGEs present in vascular tissues mediate monocyte migration normally recruited for tissue repair. However, in aging and diabetes, excessive AGE formation within vessel wall proteins followed by enhanced monocyte chemotaxis and multiple growth factor induction, may generate the substrate for proliferative events typical of atherogenesis.

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ALTERED T CELL REPERTOIRE IN AGING. *C. Russo*, E.P. Cherniack, A. Wali, R. Schwab, and M. Weksler,* Cornell University Medical College, New York, NY 10021.

The thymus is the central organ where maturation and establishment of the T cell repertoire occur. In the thymus antigen-specific T cells acquire knowledge of self (positive selection) and autoreactive T cells are deleted (negative selection). We studied whether the age-associated changes in T cell function are the result of thymic involution. The ability of T cells from young and old C57BL/6 mice to respond to influenza antigens presented by syngeneic and C3H, CBA and BALB/c allogeneic antigen presenting cells (APCs) was analyzed. T cells from old immunized mice responded to influenza antigen presented by syngeneic and allogeneic APCs, while T cells from young mice responded only when presented with influenza on syngeneic APCs. Young euthymic BALB/c mice normally delete anti-self Mls 2a and anti-self-I-E reactive T cells (bearing T cell receptor Vbeta 3 and Vbeta 11 respectively). A four fold increase in peripheral CD4 and CD8 T cells bearing Vbeta 3 and Vbeta 11 TCRs was observed in old compared to young BALB/c mice. Conversely, no difference in the number of normally non-deleted Vbeta 6 and 8 T cells was observed in young and old BALB/c mice. The Vbeta 3 and 11 T cells present in old mice are functionally competent since they responded when stimulated with staphylococcus enterotoxin-E. These findings suggest that thymic involution affects both positive and negative selection events and results in the altered T cell function observed in aging.

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THE SERUM LEVEL OF LIPID PEROXIDES AS A AGING SUBSTANCE IN CHINESE ADULTS. *E.-Z. Liu, Y.-C. Yan, T.-J. Zhao, and F.-P. Han,* Dept. of Neurosurgery, Harbin Medical University, Harbin, P.R.C. 150001.

The serum levels of lipid peroxides (LPD) were evaluated with the fluorescent method in 107 Chinese adults. The mean level of LPD is 2.32 ± 1.01nmol/ml (m+SD). The level of LPD in each age group is

seen in the table below, in which the level of LPD increases with aging and there is a significance between each group of 20 years ($p<0.05$).

Therefore, the serum level of LPD may be considered as an aging substance.

LPD Level of Chinese Adults

Age Group	Mean Age	n	m+SD (nmol/ml serum)
21-30	26.2+3.1	25	1.87+0.88
31-40	35.8+3.2	21	2.04+0.84
41-50	44.2+2.7	27	2.29+1.05
51-60	56.3+3.8	14	2.61+0.61
61-70	64.9+2.9	12	2.86+1.26
>70	73.6+1.7	8	3.29+0.94

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AGE-RELATED CHANGES IN THE MORPHOLOGY OF PANCREATIC BETA-CELLS. *M. Masini, Z. Gori, P. Masiello, M. Pollera, A.D. Roso, and E. Bergamini*,* Instituto di Patologia Generale, II Cattedra, University of Pisa, Italy.

Crinophagy has been regarded as mechanism for the degradation of unsecreted insulin. In view of the well known age-related alteration in insulin secretion, in this study we explored lysosome morphology in the β-cells of C57BL/6J and of the beige (bg/bg) mice, a spontaneous mutant of the black strain with altered lysosome morphology and function.

Islets were isolated from 6- or 24-month-old mice by a modified collagenase digestion method and processed by standard techniques and sections examined at the electron microscope.

In the younger age-groups, no crinophagic bodies were observed in β-cells with the black mouse, and enlarged secondary lysosomes and vacuoles resembling the residual bodies of the secretary granules were observed in the mutant counterpart.

In the older age-group, crinophagic bodies were observed with both strains. In the bg/bg mouse, these inclusions were different in size, number and morphology with respect to the younger age-group.

It is concluded that the process of crinophagy of β-cell secretary granules changes through adult life in mice, and that differences may be magnified in animals with a Chediak-Higashi like genetic lysosome disease.

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BAND 3 PROTEIN DEGRADATION BY CALPAIN IS ENHANCED IN ERYTHROCYTES OF OLD INDIVIDUALS. *T. Glaser, N. Schwarz-Benmeir, and N.S. Kosower*,* Dept. of Human Genetics, Sackler School of Medicine, Tel Aviv University, Israel.

Aging of erythrocytes (RBC) has been studied extensively. Little is known about RBC in relation to aging of the whole organism. Band 3 protein is a major RBC transmembrane glycoprotein responsible for anion-exchange (HCO_3^- for Cl^-). We discovered that degradation of band 3 protein by calpain I (cytoplasmic, μM Ca^{2+}-requiring thiol protease) was enhanced in RBC membranes of old individuals (>70 years old) as compared to that of young ones (20-30 years old). Degradation was inhibited by the calpain inhibitor, calpastatin, and by EDTA. DIDS (which binds to Band 3 protein and inhibits anion transport) enhanced Band 3 degradation by calpain. The difference between young and old was retained in membrane vesicles (membranes stripped of peripheral proteins by NaOH) and in chymotrypsin-generated 60kDa(CH-60). The 17kDa membrane domain of the CH-60 and the trypsin-generated C-terminal, membrane spanning 55kDa were not degraded by calpain in the young nor in the old. The isolated N-terminal, cytoplasmic 43kDa fragment was degraded by calpain both in old and young. We found more calpain and less calpastatin to be associated with old membranes. The observed age-related enhanced sensitivity to calpain is consistent with changes in band 3 protein, and/or altered association with membrane components and with the calpain-calpastatin system. Band 3 protein has several important functions, with modifications in the protein having implications for altered cell behavior in the old individual.

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COLD TOLERANCE AND METABOLIC HEAT PRODUCTION IN ADULT AND AGED C57BL/6J MICE AT DIFFERENT LEVELS OF COLD STRESS. *H. Tatelman*, and M. Talan,* Gerontology Research Center, National Institute on Aging, NIH, Baltimore, MD 20224.

Previously we have shown that during cold stress at 6°C, aged mice have a worse cold tolerance (CT) and a reduced metabolic heat production (MHP) compared to adults. To examine the hypothesis whether aged mice have a reduced responsiveness to cold, or whether age differences in MHP resulted from a lower capacity of aged mice for thermogenesis, separate groups of adult (9 mo) and aged (30 mo) C57BL/6J mice were tested at either 24°C, 18°C, 12°C, or 6°C. The change in colonic temperature (°C/hr) was our measure of CT. MHP (kcal/kg body weight to the 2/3 power/hr) was calculated from body mass, oxygen consumption and carbon dioxide production. With reduction in ambient temperature, CT of aged mice was diminished while CT in adults was not changed. MHP in adults increased with decreased ambient temperature. In aged mice, MHP at 18°C, 12°C, and 6°C was similar and always greater than MHP at 24°C. The thermogenic response of aged mice to 18°C was similar to adults, indicating that the ability of mice to respond to cold by increasing heat production does not diminish with age. However, more severe ambient temperature revealed the low capacity for thermogenesis in aged mice.

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CHANGES IN THE LIVER IN ALZHEIMER'S DISEASE (AD): AN INVESTIGATION OF HEPATIC ZINC, COPPER, AND METALLOTHIONEIN. *E. Lui, M. Fisman*, C. Wong, and F. Diaz,* Victoria Hospital, London, Ontario, N6A 5G5, Canada.

Significant alterations of tissue metal levels have been reported in AD. Because the liver is intimately involved in metabolism and storage of metals it may provide a useful model for study of these metals in AD. The purpose of this study is to compare in AD and controls hepatic concentrations of zinc, copper, cadmium and metallothionein, a metal binding protein important in regulation metal metabolism. Liver tissue was obtained from 17 patients with AD and 17 age and sex matched controls within 12 hours of death and stored at -70oC. Neuropathological confirmation of diagnosis was available in all cases. Liver homogenates (20%) were used for metal analysis by atomic absorption spectroscopy following wet digestion. Cytosolic metallothionein levels were quantitated by the cadmium or silver saturation method. A marked decline in body and liver weight was found in AD, with no significant change in liver protein or DNA concentration. Hepatic cadmium ($p<.001$) and zinc ($p<.030$) concentrations were significantly elevated in AD. The Sephadex G75 chromatographic profile was altered in AD with reduction in zinc bound to metallothionein fractions and increased binding to high molecular weight fractions. These data suggest that metabolism of cadmium and zinc are altered in AD.

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CEREBELLAR NORADRENERGIC FUNCTION AND MOTOR LEARNING IMPAIRMENTS IN AGED F344 RATS. *P. Bickford-Wimer* and C. Heron,* Veterans Administration Medical Center, Denver, CO 80220.

Age-related declines in motor function are well documented in the literature for both humans and animals. In humans there is a decline in mirror tracking proficiency with advanced age suggesting that motor learning is altered. We investigated age-related alterations in the ability of F344 rats to learn novel motor tasks. Performance on this task has been demonstrated to be dependent on cerebellar NE in young rats. Our previous work has identified alterations in noradrenergic receptor function with age in the cerebellum. Therefore, it was our hypothesis that age-related decrements in motor learning abilities would be correlated with the deficits in cerebellar NE function. Three groups of rats were tested for motor learning performance: young rats; young rats treated with 6-hydroxydopamine; and 20 month old rats. Both the young group without NE and the old rats had performance deficits on the motor learning task. Subsequent to behavioral testing, rats were prepared for electrophysiological recording under urethane anesthesia. The modulatory actions of isoproterenol to augment GABA responses was chosen as the index of NE function. There was a significant correlation between behavioral performance and electrophysiology ($r=.78$; $p<0.05$). This supports our hypothesis for a role of cerebellar noradrenergic function in motor learning deficits in aged rats.

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AGE-DEPENDENT CHANGES IN THE POTASSIUM-EVOKED RELEASE OF DOPAMINE IN THE STRIATUM AND NUCLEUS ACCUMBENS OF THE FISCHER 344 RAT: AN *IN VIVO* ELECTROCHEMICAL STUDY. *M. Friedemann* and G.A. Gerhardt,* Departments of Pharmacology and Psychiatry, University of Colorado Health Sciences Center, Denver, CO 80262.

The aging process produces a continual decline in the number of dopamine (DA) neurons in the nigrostriatal and mesolimbic systems. In order to investigate the effects of this degeneration on the function of remaining DA neurons, we have studied potassium-evoked DA release in the striatum and nucleus accumbens of young and aged male Fischer 344 rats. High-speed (5 Hz) *in vivo* electrochemical measurements of potassium evoked DA overflow were recorded in groups of 6, 18, 24, and 30 month old urethane anesthetized rats using Nafion-coated multiple carbon fiber electrodes. The 18, 24 and 30 month age groups showed age-dependent declines in average response amplitudes compared to the 6 month old control group. Response amplitudes were more significantly decreased in the ventral striatum and nucleus accumbens than in the dorsal striatum of aged rats. While the amplitudes were decreased in aged rats, the average time courses of the DA signals were either increased or unchanged in the older rats. These results indicate that there are regional age-dependent changes in presynaptic DA elements that may be more pronounced in mesolimbic DA projections.

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EFFECT OF N-METHYL-D-ASPARTATE (NMDA) RECEPTOR BLOCKADE AND AGE ON ACQUISITION (AQ) OF A 14-UNIT T-MAZE IN THE RAT. *E.L. Spangler*, P. Garofalo, and D.K. Ingram,* Gerontology Research Center, NIA, Baltimore, MD 21224.

MK-801 (Dizilpine), a noncompetitive NMDA antagonist, disrupted AQ performance of young (Y) rats in a dose-dependent fashion in a previous study. In the present study Y and aged (A) rats were given MK-801 to determine if an age by drug interaction (AxD) would emerge in AQ performance in the 14-unit T-maze. Nineteen 3-mo old (Y) and twenty-one 24-mo old (A) F-344 rats were trained in one-way active avoidance (0.8 mA; 2 min ITI) to a criterion of 13 successful avoidances/15 trials (maximum = 30 trials) 24 hr prior to maze testing. On the following day Y and A rats were assigned to one of three groups that received either saline (SAL) or MK-801 (0.02 or 0.04 mg/kg; injection volume = 0.5 cc/kg) s.c. 20 min prior to maze testing. In this maze task the rat had to negotiate an initial segment within 10 sec to successfully avoid foot shock (0.8 mA). After the rat entered the second segment, a door was closed. The contingency was reset 4 times as the rat moved through the maze to a goal box. Each rat received 15 trials in the maze (2 min ITI). Measures of maze performance included errors, alternation errors, run time, shock frequency and duration. A 2 (age) x 3 (drug) x 5 (blocks of 3 trials) factorial analysis of variance (ANOVA) was performed for each dependent measure. The ANOVA for errors revealed main effects of Age ($F(1,34)=40.93$, $p<.0001$), Drug ($F(2,34)=5.82$, $p<.007$) and Blocks ($F(4,31)=73.99$, $p<.0001$). Significant Age x Drug $F(2,34)=3.82$, $p<.03$) and Age x Block ($F(4,31)=3.87$, $p<.01$) were observed to indicate that A rats receiving MK-801 were more impaired (i.e., made more errors) than their Y counterparts and A learned more slowly than Y rats. Similar effects were observed in the other measures of maze performance. NMDA receptors are thus implicated in age-related impairments in learning and memory previously observed in this task, and the appearance of an A x D interaction suggests a decline in concentration of NMDA receptors in A F-344 rats.

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RHEUMATOLOGIC DISORDERS IN THE ELDERLY. *Barney Spivack*,* Dept. of Medicine, New Britain Memorial Hosp., New Britain, CT 06053.

Joint disorders are second only to cardiovascular disease in producing severe chronic disability in the elderly. Alterations in joints with aging include cellular and biochemical changes in collagen, elastin, and cartilege. The relationship of aging to the development of osteoarthritis will be explored. General considerations and the approach to the diagnosis of musculoskeletal disorders frequently encountered in the elderly will be reviewed. The epidemiology, clinical features, and etiopathogenesis of osteoarthritis will be reviewed. Crystal arthropathies, the low back pain syndrome, polymyalgia rheumatica, and selected other common disorders in the elderly will be discussed. Treatment considerations and principles of therapy in the elderly will be reviewed.

2

HORMONAL ASPECTS OF AGING. *S.R. Gambert*,* Center for the Study of Aging and Health Promotion and Dept. of Med., New York Med. Coll., Valhalla, NY 10595.

Aging is associated with numerous physiological changes affecting every cell, organ, and tissue in the body. The endocrine system provides an excellent example of normal age-related change, age-prevalent illness, and the atypical and/or nonspecific manner in which many diseases may be present.

This presentation will focus primarily on normal and disease-related change involving thyroid hormone, insulin, and sex steroids.

3

ALPHA-2 AGONISTS AND SPASTICITY IN PARALYZED MAN. *J. Tuckman, A. Fischer and P.D. Tsitouras,* Depts. of Geriat. and Rehab. Med., Bronx VA Med. Ctr., Bronx, NY 10468, Mt. Sinai School of Med., New York, NY 10029.

Alpha-2 receptors are in close anatomical approximation with the dorsal and ventral horns of the spinal cord. The administration of clonidine, an alpha-2 agonist, to animals with spinal cord transections reduces spasticity and allows the beasts to walk in a normal manner. Tuckman *et al.* reported in 1982 that the drug might have a beneficial effect in quadriplegic patients. Preliminary results from a dose-response study of the antispastic effects of clonidine tablets (0.1-0.6 mg) and patches (1XTTS#1-2XTTS#3) indicate that increasing doses of the drug dramatically reduce or eliminate abnormal EMG activity and gross spasms.

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URINARY INCONTINENCE: BASIC AND CLINICAL ASPECTS. *Perry Starer,* Jewish Home and Hosp. for Aged, New York, NY 10025. City Hosp. Ctr. at Elmhurst, Queens, NY 11373.

Urinary incontinence contributes to the isolation, embarrassment, and institutionalization of the elderly patient. Although urinary incontinence is a problem for many elderly patients, it may not always be appropriately addressed by the physician. The successful treatment of incontinence can provide an improved quality of life. In order to select an effective treatment for incontinence, its etiology needs to be determined. Detrusor instability is a frequent urodynamic finding in incontinent patients. Management strategies include scheduled toileting, treatment of impaired mobility, and the use of accessible toilet facilities. In certain cases, medications may be used to treat incontinence. Adult diapers should not be used prematurely.

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NUTRITIONAL REGULATION OF IMMUNITY AND ILLNESS IN OLD AGE. *Ranjit K. Chandra*,* Health Sciences Ctr., St. John's, Newfoundland, Canada, A1B 3V6.

Aging is associated with a number of physiological changes. This includes the immune system as well. The average immune response of the elderly declines progressively from young adult life onwards. At the same time, there are well recognized changes in nutrient intake, body composition and nutritional status. We have suggested that there is a causal relationship between nutrition and immunity in old age. This is based on several observations. Firstly, although the mean immune response is lower in the elderly, there is a wider range of values, so that there are some elderly individuals whose immunocompetence is as vigorous as that in younger subjects. Secondly, elderly with intact immune responses tend to be in a better nutritional status. Thirdly, other observations in younger age groups have proven the critical role of nutrition in maintenance of the immune system and those who are undernourished have reduced immune responses. This applies also to selected deficiencies of individual nutrients, such as zinc, iron, vitamin A, vitamin B_6, and vitamin E. Finally, in several studies using the double-blind design, we have observed an improvement in immune response of elderly when they were provided with nutritional counselling and supplements to correct nutritional deficiencies.

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CYTOSKELETAL PROTEIN PATHOLOGY IN AGING AND ALZHEIMER DISEASE. *K. Iqbal* and I. Grundke-Iqbal,* Inst. for Basic Research in Develop. Disabil., Staten Island, NY 10314.

One of the most characteristic cellular and molecular changes in Alzheimer disease (AD) is the accumulation of aberrant filaments, the paired helical filaments (PHF) in the affected neurons. There is growing evidence from a number of laboratories that dementia correlates better with the accumulation of PHF than that of the extracellular amyloid, the second major lesion of AD. PHF are both morphologically and biochemically unlike any of the normal neurofibrils. Microtubule associated protein tau is a major component of PHF. Tau in PHF is phosphorylated differently from tau in microtubules. This abnormal phosphorylation of tau in PHF occurs at more than one site. The accumulation of abnormally phosphorylated tau in the affected neurons in AD brain precedes both its incorporation and ubiquitination in the neurofibrillary tangles. In AD brain tubulin is assembly competent but the *in vitro* assembly of microtubules is not observed. *In vitro* the phosphate groups in PHF are less accessible than those of tau to alkaline phosphatase. These studies suggest that a defect in the protein phosphorylation/dephosphorylation system is one of the early events in the cytoskeletal pathology in AD. Phosphorylation and polymerization of tau into PHF is postulated to lead to a microtubule assembly defect and consequently to a compromise in axoplasmic flow and neuronal function.

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MOLECULAR MARKERS OF INTERCELLULAR SIGNALLING IN NORMALLY AGING BRAIN AND IN ALZHEIMER'S DISEASE. *P. Coleman* and K. Rogers,* Dept. of Neurobiol. & Anat., Univ. of Rochester Med. Ctr., Rochester, NY 14642.

Previous quantitative Golgi-Cox studies of dendritic extent of single neurons from our laboratories have shown an age-related increase in dendritic extent in some, but not all, regions of normally aging brains, and absence of this age-related dendritic proliferation in the Alzheimer's disease (AD) brain. We have interpreted these findings as suggesting a compensatory, plastic dendritic proliferation of surviving neurons in response to the death of their neighbors. In AD there appears to be a loss of this plastic capacity of surviving neurons.

On the basis of these and other data, we have proposed a model intercellular signal cascade by which surviving neurons know of the death of their neighbors and are able to mount compensatory responses. In AD there may be a failure in this signal cascade. We are studying both known intercellular signalling molecules (e.g. IL-1B) as well as starting to define new peptides that may be serving as intercellular signal molecules. Findings to date indicate that IL-1B message levels increase with increasing age in normal aging. This is not the case in AD. We have also found peptides whose release into the microenvironment is altered by manipulations designed to produce neuron death. Some of these peptides have been shown to influence the proliferation of astrocytes.

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AGING AND METABOLIC IMMUNODEPRESSION. *V. Dilman,* Endocrinology Lab., Inst. of Oncology, 189646 Leningrad, Pesochny-2, USSR.

The efficiency of cell-mediated immunity decreases with advancing age. There are many arguments suggesting the functional nature of age-related immunodepression.

In particular, the age-associated decrease of glucose tolerance and postprandial hyperinsulinemia are the key pathogenetic factors of immunodepression. In order to check the mechanism of age-linked immunodepression we have administered the antidiabetic drug phenformin to middle-aged persons. This drug improves the metabolic pattern in nearly 60% of these persons and correspondingly decreases the concentration of cholesterol in the T-lymphocytes, and improves such indices of immune function as phytohaemagglutinin-induced blasttransformation of lymphocytes, phagocytic activity of monocyte-derived macrophages and the sensitivity to skin recall antigens. Therefore, by definition, metabolic immunodepression (MID) is a decrease of cellular immunity and phagocytic function of macrophages caused by regular age-associated disturbances of carbohydrate and lipid metabolism. MID arises in the course of normal aging as a regular disease. In those cases when MID results from environmental factors, example, excessive food consumption or increased cholesterol content in the diet, we deal with the syndrome of metabolic immunodepression. In particular, diets enriched by cholesterol and sugar or by saturated fat and sugar produce the decrease of mitogen-induced blastogenic reaction of T-lymphocytes and the decrease of thymus gland weight in young rabbits and mice, correspondingly. Hormonal-metabolic pattern inherent to MID exerts immunosuppressive action via the decrease of sensitivity of neuroendocrinė system to regulatory signals, also. Meanwhile, MID is a reversible phenomenon.

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OVERVIEW OF MITOCHONDRIA AND AGING. Organizer: *R. Weindruch,* U. of Wisconsin, Madison, WI 53706.

The role of mitochondria in aging processes has been the subject of several studies; however, these investigations have not yielded widespread agreement. Mitochondria may be involved in aging processes via age-related lesions or losses of the organelle caused by free radical production. Also, mitochondrial generation of free radicals could inflict damage in other key sites. In this symposium, studies on mitochondria and aging are presented by six investigators.