NINETEENTH ANNUAL MEETING

Wednesday-Saturday, October 4-7, 1989
Capital Hilton Hotel
Washington, D.C.

Annual Symposium — Neurosciences and Aging: A. "Neuroplasticity in the Aging CNS: Nerve Growth Factor and Other Factors"

Perez-Polo, R.: **Growth factors: An overview.**

Angelucci, L.: **Glucocorticoid and nerve growth factor receptors in the aged rat brain.**

Giacobini, E.: **Nerve growth factor, cholinergic system and Alzheimer's disease.**

Stromberg, I.: **NGF response of aged adrenal medulla grafted to the anterior eye chamber.**

Rapoport, S.: **Brain metabolism in aging: Stability of functional activity.**

Giuidotti, A.: **Pharmacology of the secondary neuronal damage following ischemias.**

B. "Receptors and Aging Revisited"

Dax, E.M.: **Adrenergic receptors in senescence.**

Bickford-Wimer, P.: **Age-related changes in noradrenergic and dopaminergic electrophysiology.**

Coffee

Blake, M.: **Expression of muscarinic receptor subtypes with age.**

Ingram, D.K.: **Cholinergic receptors and memory processes in aged rodents: Relationship or lack of it.**

Joseph, J.A.: **Striatal dopaminergic-cholinergic interactions in senescence and the relationship to second messengers.**

Plenary Lecture

Carol Fraser Fisk, Editor of *Aging Network News*, Former U.S. Commissioner on Aging: **Successful Life Extension: Effects on American Society.**

Minisymposium: "Molecular Biology and Aging."

Murasko, D.: **Lymphoproliferation: Lymphokines, phenotypes and heterogeneity with age.**

Goidl, E.: **Regulation of antibody repertoire expression in aging.**

Hart, R.: **Aging, caloric restriction, and DNA repair.**

Busbee, D.: **Possible interaction between caloric restriction, DNA polymerase function, immune function, and DNA repair.**

Roth, G.: **Age-related changes in the molecular biology of steroid hormone action.**

Minisymposium: "Genetic Analysis of Aging and Longevity"

Yunis, E.: **Possible genetic parameters of life span in mammals.**

Arking, R.: **Genetics of aging in *Drosophila:* Increased adult lifespan through selection.**

Phillips, J.P.: **Genetic analysis of Cu/Zn superoxide dismutase in *Drosophila:* Biological consequences of under and over expression.**

Bewley, G.: **Genetic analysis of catalase in *Drosophila:* Correlation of enzyme activity, life span and mutation rate.**

Munkres, K.: **The oxyregulation of *Neurospora* and yeast: Its role in free radical metabolism and longevity.**

Hutchinson, T.: **Genetic and molecular analysis of a longevity gene in *C. elegans*.**

CLINICAL GERONTOLOGY —Annual Symposium: "Expanding the Functional Life Span: Current Knowledge and Future Prospects"

Harman, D.: **Aging and disease.**
Executive Director, American Aging Association, Dept. of Medicine, Univ. of Nebr. College of Medicine, Omaha, NE

Katz, M.: **Prevention of age-related diseases of the retina.**
Dept. of Ophthalmology, Univ. of Missouri, Columbia, MO

Lipschitz, D.: **Inter-relationship between nutrition and aging.**
Director, GRECC, John L. McClellan VA Hospital, Little Rock, AR

Yansic, R.: **Cancer control for the aging population.**
Office of the Director, NIH, Bethesda, MD

Gordon, S.: **The role of dentistry in preserving functional life.**
Director, Geriatric Dentistry, VA Med. Center, West Roxbury and Brocton, MA

Engelberg, H.: **Atherosclerosis and aging.**
Arteriosclerosis Research Foundation, Beverly Hills, CA

Fillit, H.: **Immunology of aging.**
Dept. of Geriatrics and Adult Development, Mount Sinai Medical School, New York, NY

Lawlor, B.: **Serotonergic dysfunction and behavioral complications in Alzheimer's disease.**
Chief, Div. of Geropsychiatry, Mount Sinai Medical School, New York, NY

Harman, S.M.: **Hormonal therapy in aging: Present and potential.**
Chief, Endocrine Section, GRC, NIA, NIH, Baltimore, MD

Lowenthal, D.: **Can the elderly improve their functional capacity with exercise?**
Director, GRECC, VA Medical Center and Univ. of Florica, Gainesville, FL

Tsitouras, P.D.: **Sexual dysfunction in elderly man.**
Associate Chief of Staff, Bronx VA Medical Center and Dept. of Geriatrics, Mount Sinai Medical School, New York, NY

Luncheon (Friday)

Luncheon Speaker:
David Gershon, Ph.D.
"Perspectives on Biomedical Aging Research"

Annual Awards:

Research Award —
David Gershon, Ph.D.

"This award is presented to Dr. Gershon for significant contributions to biomedical aging research. These contributions include: 1) The identification of inactive enzymes in a variety of cell types and organisms. Dr. Gershon further showed that inactivation of the enzymes was caused by post-translational modifications and that their accumulation with age resulted from decreasing cellular capacity to dispose of altered proteins; 2) the introduction of the nematode as a model for aging research and demonstrating that many of the changes with age in nematodes corresponded to those in mammals, and 3) studies of erythrocytes which showed that those from older animals accumulated inactive enzymes and lipid peroxidation products at a faster rate than those of younger animals."

Clinical Research Award —
Reubin Andres, M.D.

"This award is presented to Dr. Andres for his significant contributions to clinical gerontology research. These contributions include: 1) development of the "glucose clamp" technique used for quantifying homeostatic mechanisms controlling blood glucose and insulin levels. These studies resulted in revision of the standards to judge normality in glucose tolerance tests; 2) serving as Clinical Director of the Baltimore Longitudinal Study of Aging. Research contributions from this study included work in the fields of nutrition, body composition, pharmacokinetics and alcohol metabolism; 3) development of new height-weight tables with built-in adjustments for age, and 4) significant contributions to the training of many individuals in gerontological research.

"We are also indebted to him for the book *Normal Human Aging: The Baltimore Longitudinal Study of Aging* which he wrote in collaboration with Dr. Nathan Shock and his colleagues in Baltimore, and for serving as a co-editor with Drs. E.L. Bierman and W.R. Hazzard of the textbook *Principles of Geriatric Medicine*. In addition, Dr. Andres has served as Clinical Director of the National Institute on Aging since its inception in 1975."

Distinguished Achievement Award —
President Ronald Reagan

"The Distinguished Achievement Award for 1989 is presented to President Ronald Reagan for demonstrating that age is no barrier to achievement. President Reagan's contributions to our country, while serving as the oldest President, included a clear enunciation of the values for which this country stands; positive constructive approaches to the problems of our times, including efforts to secure a peaceful world; and serving as an example of courage, decency and integrity.

"President Reagan serves as a role model for a growing number of people who continue to lead active productive lives long after the traditional retirement age."

President Reagan's Letter of Acceptance:
"Dear Friends:

"I am more than pleased to accept the American Aging Association's 1989 Distinguished Achievement Award. It is an honor for which I am truly grateful.

"I sincerely hope that your work will continue to lead to longer, healthier life spans and lessen the problems of the aged. Indeed, your efforts are of great benefit and value to all Americans. And so, to the men and women who lend their time and talents to the promotion of biomedical aging research, my hat's off to you for bringing this critical issue to the public's attention.

"Nancy joins me in wishing you every future success and reward.

Sincerely,
Ronald Reagan"

Submitted Papers
Oral Presentations

1. Enesco*, H.E., and McTavish, A.J.: **The calcium theory of aging tested on rotifers.**
2. Sternick*, S.M., and Massie, H.R.: **Dolichol and aging in *Drosophila*.**
3. Massie*, H.R., and Sternick, S.: **Elevated copper in bones from C57BL/6J mice with osteoporosis.**
4. Engelberg, H.: **The effect of heparin upon free oxygen radicals.**
5. Weiss*, A., Livne, E., and Silbermann, M.: **The *in vitro* effects of hormones and growth factors on the synthesis of DNA, protein and glycosaminoglycans in the articular cartilage of aging mice.**
6. McMahon*, T.F., Diliberto, J.J., and Birnbaum, L.S.: **Age-related changes in metabolism and disposition of salicylic acid (SAL) in male Fischer 344 rats.**
7. Saran, B., Pappolla, M., Fortunato*, L., Theodoropoulos, T., Benson, D., and Omar, R.: **Identification of ubiquitin in the CSF of young, old and Alzheimer's disease (AD) patients.**
8. Gertz, H.-J.: **Stability of cell size and nuclear size in tangle bearing neurons of the hippocampus in Alzheimer's disease.**
9. Mokrasch, L.C.: **Modulators of choline transport into fibroblasts of normals and Alzheimer's victims.**
10. Ball*, S.S., Schubarth, G., Strandburg, R., Brown, W.S., and Marsh, J.T.: **P300 changes in Alzheimer's disease: A 3-year longitudinal study.**
11. Ashadevi*, S., Kan, S., and Kawashima, S.: **Effect of culture age on lipofuscin and creatine phosphokinase in beating rat heart cells and its modification by tocopherol.**
12. Kitani*, K., Ohta, M., Ivy, G.O., and Kanai, S.: **Ceroid-lipofuscin in kidneys of young rats and mice induced by leupeptin is similar to age pigments.**

Poster Session I

13. Abbo, F.: **A computerized performance test battery for the early diagnosis of Alzheimer's disease.**
14. McClaran*, J., Forette, F., Golmard, J.L., Hervy, M.P., and Bouchacourt, P.: **Faller risk function for geriatric assessment unit patients.**
15. Perlin*, E., Mosee, S.J., Motley, Jr., T.E., Griffiths, M., and Bang, K.M.: **Falls among institutionalized elderly patients.**
16. Carnevale, K., and Steinberg*, J.J.: **Diseases in the elderly: An autopsy study of three decades of medical care.**
17. Fisman*, M., Bing, T., Kalow, W., Merskey, H., Rabheru, K., and Wong, C.: **Caffeine metabolism in aging, Alzheimer disease (AD), and schizophrenia (S).**
18. Ganguly*, R., Russell, D.W., and Cameron, D.J.: **Influenza vaccination status among health care professionals for prevention of nosocomial infection to hospitalized elderly patients.**
19. Lichtman*, S., Goldman, I., Budman, D., Hoexter, B., Labow, S., Moseson, M., Stiel, L., and McKinley, M.: **Flow cytometric (FCM) analysis of colon carcinoma: Correlation with age and clinicopathologic data.**
20. Gascho*, J.A., and Fanelli, C.: **Aging attenuates the venodilatory response to nitroglycerin.**
21. Koltover, V.: **The reliability theory approach to the problem of molecular markers of aging.**
22. Wallace*, D.R., and Dawson, Jr., R.: **Regional activity of phosphate-activated glutaminase from adult and aged male Fischer-344 rats.**

Poster Session II

23. Scialla, S.: **Geriatric oncology — a process of care in a high risk elderly population.**
24. Martins*, C., Gambert, S.R., Gupta, K., O'Dell, C., and Pace, R.: **Effect of age and dementia on cardiovascular disease in the long-term care setting.**
25. Chodzko-Zajko*, W.J., and Schuler, P.B.: **Cardiovascular and pulmonary factors and memory loss in aging.**
26. Gelderloos, P., Ahlstrom, H.H.B., and Glaser*, J.L.: **Influence of a Maharishi Ayur-Vedic herbal preparation on age-related visual discrimination.**
27. Weinstein*, H.G., Greenberg, M., Nagraj, H., Jaroch, M., and List, N.D.: **Health care center planning for older veterans.**
28. Cushing, A.H.: **Health concerns of middle-aged women.**
29. Burris*, J.F., Weir, M.R., Oparil, S., Weber, M., and Cady, W.J.: **The antihypertensive effect of slow-release diltiazem in relation to age and race.**
30. Sharma, S.P., Reddy, B.N., James*, T.J., Gupta, S.K., and Patro, I.K.: **Lipofuscinolytic effect of ceflatone: An ayurvedic brain tonic.**
31. Koltover, V.: **Homeoviscosity adaptation and stabilization of membrane lipid fluidity in aging.**
32. Gupta*, S.K., Sharma, S.P., James, T.J., Reddy, B.N., and Patro, I.K.: **Lipofuscinolytic activity of centrophenoxine: A possible explanation.**
33. Nava*, P.B., and Mathewson, R.C.: **Effect of age on the structure of Meissner corpuscles in murine digital pads.**
34. Tatariunas, A.B.: **Pigment-protein complex existence in lipofuscin granules.**

Submitted Papers
Oral Presentations

35. Ball*, S.S., Wright, L., and Miller, P.: **Senex, a computer-based tool for organizing gerontologic information.**
36. Sorger, T.: **The effects of food restriction and steroidal inhibitors of glucose 6-phosphate dehydrogenase (G6PDH) on the composition and activity of the inner mitochondrial membrane.**
37. Lee*, D.W., Marler, C.G., and Yu, B.P.: **Food Restriction protects microsomal P-450 from free radical damage.**
38. Sastre*, J., Rodriguez, J., Pallardo, F.V., Gasco, E., and Vina, J.: **Effect of age on antioxidant defense related to glutathione in rat liver: Distribution of redox cycle of glutathione in the acinus.**
39. Sastre*, J., Pallardo, F.V., Estrela, J., Asensi, M., and Vina, J.: **Gluconeogenesis, ketogenesis and ureogenesis in isolated hepatocytes from aging rats.**
40. Ohta, M., Kitani*, K., and Zs.-Nagy, I.: **Decreased uptake of taurocholate by isolated hepatocytes in aged rats supports the regulatory role of membrane protein mobility in the hepatic uptake mechanism during aging.**
41. Ivy*, G.O., Racine, R.J., Nellis, P., Mendonca, A., and Milgram, N.W.: **(−)Deprenyl prolongs survival of aged rats.**
42. Livne, E., Brenmann, M., Reznick, A., Finkelbrand, S., Weiss*, A., and Silbermann, M.: **Age and exercise associated changes in the arterial wall concomitant with atrophic changes in musculoskeletal functional unit in mice.**
43. Giordano*, T., and Howard, B.H.: **Functional assays for the isolation of anti-proliferative cDNAs.**
44. Sakamoto, K., Fordis, C.M., Howard, T.H., Giordano, T., and Howard*, B.H.: **Negative regulation of cell growth: New gene transfer approaches and a possible role for the 7SL RNA/ALU gene family.**
45. Steinberg*, J.J., Kelly, B., Silverstein, T., Gleeson, J., and Brownlee, M.: **Two-dimensional (2D TLC autoradiography as a quantitative measure of DNA damage by non-enzymatic advanced glycosylation products (age).**
46. Ball, S.S., Neshat*, M.S., and Walford, R.L.: **DNA damage and repair in young and middle-aged mice.**
47. Albright*, J.W., and Albright, J.F.: **Decline of immunological resistance to trypanosomiasis in aging mice.**
48. Cizza, G., Calogero*, A.E., Gold, P.W., and Chrousos, G.P.: **Hypothalamic-pituitary-adrenal axis age-related changes in old make 344 Fischer rats.**

1

THE CALCIUM THEORY OF AGING TESTED ON ROTIFERS. *H.E. Enesco* and A.J. McTavish,* Dept. of Biology, Concordia Univ., Montreal, Quebec, Canada.

The calcium theory of aging suggests that neurons lose their ability to exclude or sequester calcium in the course of aging. We decided to try two new departures from this idea: 1) to test this theory at the whole animal level using rotifers and 2) to test the effect of a calcium channel blocker, which should act to prevent the age-associated buildup of intracellular calcium. We designed a series of experiments using the rotifer *Asplanchna brightwelli* to determine whether the calcium channel blocker nifedipine would influence calcium uptake and/or lifespan. Measurement of ^{45}Ca uptake showed that calcium uptake increases significantly in the course of rotifer aging, suggesting an age-associated loss of calcium homeostasis. Calcium uptake was significantly reduced in old animals by exposure to 1.0 μM nifedipine. Rotifers treated with 1.0 μM nifedipine had a lifespan of 6.28 + 0.12 days, which was significantly (23%) longer than that of control rotifers at 5.0 + 0.10 days. The results suggest that the calcium theory of aging is useful in interpreting data at the whole animal level. The results show that a calcium channel blocker can modulate the age-associated loss of calcium regulation and act to extend lifespan in the rotifer.

2

DOLICHOL AND AGING IN *DROSOPHILA*. *S.M. Sternick* and H.R. Massie,* Masonic Medical Research Lab., Utica, NY 13501.

The relationship between dolichol, a family of polyisoprenols found in membranes, and aging was studied in fruit flies (*Drosophila melanogaster*). The change in dolichol content with age and the effect of dietary supplementation on lifespan were measured.

Whole fly homogenates from flies of various ages were saponified in alkali with heat and the dolichols were isolated by hexane extraction. Analysis of the extract by high pressure liquid chromatography with UV detection at 210 nm showed that dolichol-15, -16 and -17 are the predominant homologs in fruit flies, with dolichol-16 being the largest component. The amount of total dolichols ranged from 5.9 to 18.8 ng per fly and from 9.6 to 33.0 μg per gram wet weight of flies. Both the dolichol content per fly and per gram wet weight declined with age but the correlations were not significant. These results are in contrast to reports of increases in dolichol content with aging in human and mouse tissues.

To study the effect of dolichol supplementation on lifespan, various concentrations of hog liver dolichol were added to the medium of fruit flies during larval and/or adult stages. There was no increase in the mean lifespan of the adult flies after dolichol supplementation.

3

ELEVATED COPPER IN BONES FROM C57BL/6J MICE WITH OSTEOPOROSIS. *H.R. Massie* and S. Sternick,* Masonic Medical Research Lab., Utica, NY 13501-1787.

In an effort to identify possible causative factors for osteoporosis, we used atomic absorption techniques to determine the changes with aging in various elements in bone.

Bone density was found to increase between 76 and 517 days of age and to decrease after 685 days of age. The boron content of femurs declined by 9% with aging but the decrease was not significant. Calcium increased between 76 and 198 days of age but declined by 36% between 200 and 1000 days of age. Copper declined between 76 and 198 days of age but increased by 61% between 200 and 1000 days of age. Bone collagen decreased 17.4% by 1000 days of age. Iron increased by 207% between 0 and 1000 days of age. The largest single change with aging was, therefore, in the iron content of bone.

Several correlations were found to be independent of the age of the animals. Bone density was correlated with both bone calcium and collagen. Iron was negatively correlated with both calcium and collagen. Calcium and collagent content were unrelated. Bone density and iron were also unrelated. Copper was negatively correlated with bone calcium, bone density and collagen content. Excess copper was, therefore, the single most important factor associated with decreasing bone size and density.

4

THE EFFECT OF HEPARIN UPON FREE OXYGEN RADICALS. *H. Engelberg*,* California Arteriosclerosis Research Foundation, Beverly Hills, CA 90210.

Heparin (H) has various actions which limit free oxygen radical (FR) effects. It decreases the release of myeloperoxidase and FR by stimulated neutrophils. H afforded significant (50%) protection of cultured porcine aortic endothelial cells (EC) against damage by FR. H *in vivo* decreased the shedding of EC into the bloodstream after the injection of hydrogen peroxide. Alteration of the endothelial glycocalyx heparin-like molecules by heparinase increased FR release by EC. H releases superoxide dismutase (SOD) from EC into the blood. H increased the FR quenching activity of SOD. H binds Cu^{2+}, which markedly enhances lipid peroxidation, with a strong affinity. H decreased the harmful effect of FR production following gamma irradiation.

5

THE *IN VITRO* EFFECTS OF HORMONES AND GROWTH FACTORS ON THE SYNTHESIS OF DNA, PROTEIN AND GLYCOSAMINOGLYCANS IN THE ARTICULAR CARTILAGE OF AGING MICE. *A. Weiss*, E. Livne and M. Silbermann,* Rappaport Inst. for Med. Research, Fac. of Medicine, Technion, Haifa, Israel.

An organ culture system of the mandibular condyles of male ICR mice aged 1 to 18 months was used to examine the age-related changes in the rate of synthesis of DNA, protein and glycosaminoglycans (GAG) by articular cartilage and the effect of various hormones and local factors upon these activities. Specimens were cultured for 48 h in BGJb medium supplemented with 10% FCS and 1-84 PTH (1 ug/ml), PGE_1 (10 ug/ml), dexamethasone (10^{-7}M) or TGFβ (1 ng/ml). ^{3}H-Thymidine (2 uCi/ml), ^{3}H-leucine (5 uCi/ml) or ^{35}S-sulfate (10 uCi/ml) were added for the last 24 h and the incorporation of radiolabeled compounds into trichloroacetic acid insoluble material was determined. Some specimens were processed for light microscopy and autoradiography. The results showed a marked age-dependent decrease in the synthesis of DNA, protein and GAGs from 1 to 6 months of age (-59, -50 and -66% respectively, $p<0.01$), followed by a more gradual decrease to -69, -67 and -83% respectively at 18 months, $p<0.01$. The addition of PTH and TGFβ into culture medium resulted in a significant increase in protein and GAGs synthesis up to 12 months of age with a maximum response at 3 months. Moreover, DNA synthesis could be stimulated by PTH and dexamethasone even in specimens from 18 month old animals (16-20%, $p<0.01$). The latter findings were further substantiated by autoradiography. Hence, it is concluded that chondrocytes from aged animals can be induced *in vitro* to resume their synthetic activity.

6

AGE-RELATED CHANGES IN METABOLISM AND DISPOSITION OF SALICYLIC ACID (SAL) IN MALE FISCHER 344 RATS. *T.F. McMahon, J.J. Diliberto, and L.S. Birnbaum,* NIEHS, Systemic Toxicology Branch, RTP, NC 27709.

It has been reported that older animals demonstrate increased susceptibility to SAL-induced acute nephrotoxicity. To examine age- and dose-related changes in disposition and metabolism, SAL was administered po at 5, 50, and 500 mg/kg to 3, 12, and 25 month old male Fischer 344 rats. At 5 mg ^{14}C SAL/kg, urinary excretion was complete by 24 hr in 3 and 25 mo rats, but not until 48 hr in 12 mo rats. No significant age-related differences were observed in the percentage of administered ^{14}C SAL excreted as unmetabolized SAL, oxidative metabolites, or salicyl ester glucuronide. 25 mo rats excreted significantly less of a total dose of ^{14}C SAL as the ether glucuronide, while a significant age-related increase was noted in the percentage excreted as the glycine conjugate salicyluric acid (SUA). At 50 mg ^{14}C SAL/kg, urinary elimination shifted towards zero-order kinetics and excretion was not complete until 48 hr in all age groups. The percentage of an administered dose of ^{14}C SAL found in urine as oxidative metabolites and SAL ester glucuronide increased significantly in all age groups, while the percentage excreted as SUA decreased. In addition, 12 and 25 mo rats excreted a significantly greater percentage of the total dose as 2,3- and 2,5-dihydroxybenzoic acid than 3 mo rats at this dose. The results of these studies

indicate that increased production of oxidative metabolites in older rats may be responsible in part for the age-related increase in susceptibility to acute nephrotoxicity of higher doses of SAL.

7

IDENTIFICATION OF UBIQUITIN IN THE CSF OF YOUNG, OLD AND ALZHEIMER'S DISEASE (AD) PATIENTS. *B. Saran, M. Pappolla, L. Fortunato*, T. Theodoropoulos, D. Benson, and R. Omar,* Depts. of Pathology and Medicine, VA Medical Center and New York Medical College, Valhalla, NY 10595.

The heat stock protein ubiquitin is present in the brain tissues of aged and AD patients at higher levels than in the young "normal" brain. In the present study, using the western blot method, we detected ubiquitin in the CSF of young, old and AD patients (n = 5). Although our current system does not allow quantitation, this is the first description of the existence of this protein in the CSF. Previous studies showed that ubiquitin-protein conjugates accumulate in the brain tissues of patients during aging, AD and other age-related neurological disorders. Studies are now under way using radioisotopic methods to quantitatively measure ubiquitin levels in the CSF of patients with a variety of neurological conditions. Our findings suggest that measurements of ubiquitin in CSF may have diagnostic applications.

8

STABILITY OF CELL SIZE AND NUCLEAR SIZE IN TANGLE BEARING NEURONS OF THE HIPPOCAMPUS IN ALZHEIMER'S DISEASE. *H.-J. Gertz,* Dept. of Geriatric Psychiatry, 1000 Berlin 19 FRG.

The diagnosis of dementia of Alzheimer type (DAT) is usually based on the demonstration of senile plaques (SP) and neurofibrillary tangles (NFT) in the cerebral cortex in significantly greater numbers than commonly encountered in non-demented persons of similar age. The precise relevance of NFT to the dementing process is not clear, as evidence relating the presence of these structures to other alterations in the affected nerve cells is lacking. Nucleolar size can serve as a valuable index of the amount of RNA and presumably the capacity of cells to synthesize proteins. Samples of 14 brains of autopsied patients suffering from DAT were examined. In Kongo red-hemalum stained 14 μm thick sections of the hippocampus 15 tangle bearing and 25-30 unaffected nerve cells of area CA 1 per case were measured for cell size and nucleolar size utilizing an interactive image processing unit. In affected cells tangle size was measured, too. There was no significant difference in neurone size and nucleolar size between affected and unaffected cells. In tangle bearing cells nucleolar size and cell size were not correlated with tangle size. Since nucleolar volume can serve as a parameter of RNA synthesis of a cell, tangles themselves seem not to disturb nerve cell metabolism.

9

MODULATORS OF CHOLINE TRANSPORT INTO FIBROBLASTS OF NORMALS AND ALZHEIMER'S VICTIMS. *L.C. Mokrasch*,* Dept. of Biochemistry, LSU Medical Center, New Orleans, LA 70119.

Previous studies have shown changes in the transport of choline and serine into fibroblasts of Alzheimer's victims; for both compounds, both the K_m and V_{max} are lower than those of normal cells. The transport of choline into fibroblasts has characteristics similar to those of neural cells. Six lines of normal fibroblasts and five from Alzheimer's victims were compared for the effect of modulatory compounds on choline transport. Hemicholinium-3 inhibits choline transports into normal and Alzheimer's cells with a K_i about 1 μM. Glutathione, insulin, dithiothreitol and thyroxine, which affect other transport processes, have no effect on choline transport into fibroblasts. Caffeine, theophylline, prednisolone, dexamethazone, dibutyryl c-AMP, and nicotine stimulate the transport of choline. This effect is generally greater in the normal cells. All of the stimulatory compounds exert their maximum effect within five minutes of exposure to the cells, suggesting a direct effect on the plasmalemma and not on a transport-protein synthetic mechanism. The K_ms for caffeine are about 0.1 μM and for dexamethazone, about 0.02 μM. Nicotine has a dual effect: Stimulatory to choline transport at concentrations below 10 μM and inhibitory at higher concentrations.

10

P300 CHANGES IN ALZHEIMER'S DISEASE: A 3 YEAR LONGITUDINAL STUDY. *S.S. Ball*, G. Schubarth, R. Strandburg, W.S. Brown, and J.T. Marsh,* Dept. of Psychiatry and Biobehavioral Science, UCLA School of Medicine, Los Angeles, CA 90024.

A longitudinal study of the changes in latency of the P300 (P3) wave of the auditory event-related brain potential was investigated in a group of 18 thoroughly screened and diagnosed possible and probable Alzheimer's disease (pAD) patients and 15 normal elderly controls. The 18 pAD patients were chosen from a group of 30 using the criteria of at least two identifiable P3s on two separate recording sessions at least one year apart. Twelve of thirty pAD patients, but none of the controls, were rejected because P3s observed on initial recording were no longer present after one year's progression of disease. Previous studies have found that after age 50, P3 amplitude diminishes and P3 latency increases by about 3 msec/year. On initial recording, P3 latency was significantly prolonged in the pAD group by more than 1.5 standard deviations beyond the normal group. Over the course of the next 3 years, the rate of increase in P3 latency was significantly greater for the patient group than for the controls. The P3 may provide a useful tool as a marker of neurobiologic processes in aging and dementia. The technique is non-invasive; it is suitable for longitudinal investigation; it objectively measures an aspect of cognitive function, most likely information processing and stimulus categorization, and it differentially reflects changes in normal and pathologic aging of the human central nervous system.

11

EFFECT OF CULTURE AGE ON LIPOFUSCIN AND CREATINE PHOSPHOKINASE IN BEATING RAT HEART CELLS AND ITS MODIFICATION BY TOCOPHEROL. *S. Ashadevi*, S. Kan and S. Kawashima,* Dept. of Zoology, Bangalore Univ., Bangalore 56, India and Zoological Inst., Faculty of Science, Univ. of Tokyo, Tokyo 113, Japan.

The relationship between creatine phosphokinase (CPK) activity and lipofuscin (LF) accumulation in rat heart cells in primary culture was studied. CPK activity (mU/ug protein) increased during culture from 0.12 (1 day) to 2.2 (21 days) with parallel increase in LF (as autofluorescence intensity, AFI/ug DNA) from 29.0 (1 day) to 120.0 (21 days). Cultures showed age-related decline in average beat rate and in beating/non-beating ratio of myocytes. Alpha-tocopherol (vit E) reduced the extent of changes seen in the control cultures. Cells treated with 5.0×10^{-3} IU/ml of vit E (Exp 1) for 6 or 12 days exhibited increased CPK activity. The extent of elevation in CPK was, however, less with a lesser concentration of vit E. In contrast, vit E reduced LF accumulation at a concentration of 5.0×10^{-4} IU/ml, at 6 and 12 days of treatment. The present work showed that the alterations in LF accumulation and CPK activity by vit E treatment was inversely related.

12

CEROID-LIPOFUSCIN IN KIDNEYS OF YOUNG RATS AND MICE INDUCED BY LEUPEPTIN IS SIMILAR TO AGE PIGMENTS. *K. Kitani*[1], M. Ohta[1], G.O. Ivy[2], and S. Kanai[1],* [1]1st Lab. Clin. Physiol., Tokyo Metropol. Inst. Gerontol., Tokyo 173, Japan, and [2]Life Sci. Div., Univ. Toronto at Scarborough, Toronto, Canada.

The "Protease inhibitor model of aging" has been proposed based on the observation that young rat brains exposed to a protease inhibitor, leupeptin, accumulate ceroid-lipofuscin (C-L) which is similar to age pigment (Ivy *et al.*, 1984). In order to validate this hypothesis in more general terms, the present study attempted to induce C-L in kidney cells of young animals. Male F-344 rats and C-57 BL mice (4-5 wks) were continuously infused (i.p.) with various doses of leupeptin (1-50 mg/100g/day) for 2 wks. Control animals received isovolumetric saline solution. Animals were sacrificed after treatment and subjected to histological examinations. In kidneys of leupeptin treated rats and mice, generally round-shaped PAS positive particles were clearly observed, which were dominantly distributed in proximal convoluted tubules. With increasing doses, particles tended to become bigger. Fluorescence micrographs revealed that these particles give off a yellowish-green fluorescence similar to that of age

pigments in old animals. Emission profiles of fluorescence also resembled that of age pigments with a dominant emission peak between 500 and 550 nm in wavelength. The dominant accumulation of C-L in cells of the proximal convoluted tubules also resembles age pigments reported for old rats. The results, therefore, strongly support the "Protease inhibitor model of aging" and provide an experimental tool for probing the cellular mechanisms of aging.

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A COMPUTERIZED PERFORMANCE TEST BATTERY FOR THE EARLY DIAGNOSIS OF ALZHEIMER'S DISEASE. *F. Abbo,* La Jolla, CA.

Purpose: To develop a computerized battery of performance tests useful in the early diagnosis and follow-up of Alzheimer's disease.

Methods: A battery of tests commonly used in the diagnosis of Alzheimer's disease were adapted to a microcomputer, and designed to be easily learned by the operator and easily understood by the patient.

Results: The test has been used in more than 150 subjects and found to satisfy the above criteria. It makes available, for the first time, an instrument that is economical, standardized and clinically useful in the management of patients with Alzheimer's disease.

Conclusions: The Abbo Brain Function Test, a computerized battery of performance tests, provides for screening patients for early Alzheimer's disease and following their progress.

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FALLER RISK FUNCTION FOR GERIATRIC ASSESSMENT UNIT PATIENTS. *J. McClaran*, F. Forette, J.L. Golmard, M.P. Hervy, and P. Bouchachort,* Broca Geriatric Hospital, Paris, France.

This study was done in order to determine which potential faller risk factors could distinguish fallers from non-fallers. Fifty patients in a geriatric assessment unit were systematically assessed for: age, gender, symptoms of dizziness, symptoms of urinary urgency, abnormal gait, and self-selected gait speed. Bivariate analysis revealed that only age, abnormal gait, and self-selected gait speed were associated with fallers. From logistic regression analysis, two best models were found for identifying those at risk to be fallers: age plus gait speed, and age plus abnormal gait. These two risk models differ only by the gait measure that each incorporates. Gait speed is measured as a continuous quantitative variable with no known limit of normal. Abnormal gait is measured as a qualitative variable. Since abnormal gait is defined by clear clinical criteria, the predictive model which depends on age plus abnormal gait is more suitable for general clinical use. This cross sectional study is a pre-test for a longitudinal prospective study.

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FALLS AMONG INSTITUTIONALIZED ELDERLY PATIENTS. *E. Perlin*, S.J. Mosee, T.E. Motley, Jr., M. Griffiths, and K.M. Bang,* Howard Univ. Hosp., Washington, D.C. 20060.

Falls among the elderly can be due to accidents or medical reasons. To study falls among the elderly at a long-term care facility, we collected data from incident reports and medical records relative to 74 residents who had experienced a total of 120 falls between October, 1987 and May, 1988. These residents represented 28% of the resident population (180 males and 80 females). The average age of the residents who fell was 79 years. All of the residents who fell suffered from at least one medical illness; a neurologic diagnosis was next most common (92%). Females fell more frequently than males (59% vs. 41%). However, a greater percentage of the male resident population fell compared to the female population (38% vs. 24%). 41% of the females who fell experienced multiple falls, while only 30% of the males did so. Most falls occurred from 7:00 a.m. to 11:00 p.m. 55% of them occurred in patients' rooms, 22% in dayrooms, and 15% in the bathrooms. Most of the falls resulted in no injury (69%), but 28% were associated with mild to moderate injury (bruises, abrasions, etc.), and 3% resulted in severe injury (hip fractures). Three of the four latter residents died in relationship to the injuries. At the time of the falls, most residents were taking a variety of medications, most commonly psychotropic agents. These data suggest the following strategies to help prevent falls in the institutionalized elderly: (1) careful assessment of risk of falling at time of admission; (2) removal of environmental hazards; (3) elimination of unnecessary medication; and (4) maintenance of staff alertness for falling potential.

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DISEASES IN THE ELDERLY: AN AUTOPSY STUDY OF THREE DECADES OF MEDICAL CARE. *K. Carnevale and J.J. Steinberg*,* Dept. of Pathology, Albert Einstein Coll. of Med., Bronx, NY 10461.

To assess current care and disease presentation in an elderly (mean age 79, n = 212, range 70 to 101) urban population, we examined autopsy findings of hospitalized patients from years 1989-1985, 1979, and 1969. Females comprised 56%; males were 44%; Whites 61%; Blacks 24%; Hispanics 14%; Orientals 1%. Hospitalized days averaged 17 (range of less than 1 to 310), but varied from decade to decade (*1980s = 15; 1970s = 24;* and 1960s = 17). Age related stay was 15 days for patients in their 70s, 18 days for patients in their 80s, and 16 days for patients in their 90s. The shortest hospital stay was for white males with cardiovascular disease (8 days). Sex variation in hospitalization was also present with an average 19 days for females and 15 days for males. This variation was constant through the decades. Variation of hospital stay were: Whites 15 days, Blacks 19 days, and Hispanics 24 days. Average stay on the medical services was 13 days vs. surgical services' average of 37 days. Diseases common to the population included cardiovascular disease (61%, average stay of 17 days), hypertension (27%, average stay of 12 days), diabetes mellitus (19%, average stay of 18 days), chronic obstructive pulmonary disease (19%, average stay of 14 days). Bronchopneumonia was a cause of death in 29% of patients (22 day stay), and sepsis comprised 17% (26 days). Tuberculosis was present in 3%. Significant gastrointestinal diseases included: Ulcer, 21%; cholelithiasis, 13%; diverticulosis, 23%, and colonic polyps, 14%. Fractures, osteoporosis, and decubitii represented less than 16% of the overall population, but accounted for a slightly longer hospital stay (23 days). Central nervous disease was evident in 18% with stroke, and 11% with dementia or Alzheimer's disease. Pulmonary emboli were present in 11% of cases, with a 22 day stay. Few tumors existed in this population. This data supports the significant component of common treatable diseases in the elderly, with significant sex and race variations for length of hospital stay through the decades. It is possible that public policy and personal choice decision of hospitalization can be enhanced with this data.

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CAFFEINE METABOLISM IN AGING, ALZHEIMER DISEASE (AD), AND SCHIZOPHRENIA (S). *M. Fisman*, T. Bing, W. Kalow, H. Merskey, K. Rabheru, and C. Wong,* Univ. of Western Ontario, N6A 588 and Univ. of Toronto, Dept. of Pharmacology, Toronto, Ontario, M5S 1A8.

Elderly patients as a group are known to be sensitive to the development of side effects from medications. AD patients respond poorly and have a high incidence of side effects from medications used in behavioral control, and older schizophrenics treated with phenothiazines are sensitive to the development of tardive dyskinesia. The purpose of this study using caffeine as a probe is to determine whether there is any difference in drug metabolizing capacity of AD and S patients as compared to age and sex matched controls.

It has been established that urinary metabolite ratios of caffeine are indices of three drug metabolizing enzymes in the liver, i.e., the polymorphic n-acetyl transferase (NAT), xanthine oxidase (XO) and aromatic hydrocarbon hydroxylase (AHH).

Patients AD (n = 16) and S (n = 9) were age and sex matched and met DSM III inclusion criteria and specific exclusion criteria. The community controls (n = 15) were age and sex matched healthy subjects living in the community. Data from a population of young healthy subjects (mean age 25 years) was available from a previous study. Subjects were each given 100 mg. caffeine at midday followed by collection of the first morning

specimen of urine. Urinary levels of caffeine metabolites were determined by HPLC.

No significant differences between groups were found for NAT and AHH activity, although the highest AHH values were found in the AD group. The main finding was a significant increase in XO activity ($p<.001$) in the old compared to the young group which is in agreement with the reported increase of XO with age. As XO is a major generator of free radicals, we speculate that these findings of elevated XO activity in the elderly may be of relevance to the free radical theory of aging.

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INFLUENZA VACCINATION STATUS AMONG HEALTH CARE PROFESSIONALS FOR PREVENTION OF NOSOCOMIAL INFECTION TO HOSPITALIZED ELDERLY PATIENTS. *R. Ganguly*, D.W. Russell, and D.J. Cameron,* James A. Haley Veterans' Hospital and Univ. of South Florida, Coll. of Med., Tampa, FL 33612.

Health care professionals (HCP) in close contact with hospitalized high-risk patients, including the elderly, are recommended for influenza immunization, but their acceptance of the vaccine remains alarmingly low. A cohort of 63 HCP were randomly chosen and surveyed by questionnaire at the James A. Haley Veterans' Hospital to determine their influenza vaccination status and some of the reasons affecting their compliance. Subjects studied consisted of 18 physicians, 17 nurses, 15 clinical laboratory personnel and 12 other support personnel. The overall vaccination rate during the last year for this study population was 19% while 43% never received influenza vaccine; 13 of these were physicians, 9 nurses, 2 clinical laboratory and 3 other support personnel. Sixty-three percent of the HCP indicated that they had close contact with patients (higher percentage among physicians and nurses). The primary reason for nonimmunization was that the HCP did not want the vaccine. This amotivation was predominantly due to fear of side effects and lack of time and knowledge about easy availability of the vaccine at the VA clinic free of charge. When the physicians and nurses were asked if they recommended influenza vaccination for their high risk patients, more physicians said they did (82%) than did the nurses (69%). These data indicate that the HCP intellectually accept the influenza vaccine, but they do not practice what they teach.

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FLOW CYTOMETRIC (FCM) ANALYSIS OF COLON CARCINOMA: CORRELATION WITH AGE AND CLINICOPATHOLOGIC DATA. *S. Lichtman*, I. Goldman, D. Budman, B. Hoexter, S. Labow, M. Moseson, L. Stiel, and M. McKinley,* Don Moni Div. of Oncology and Div. of Gastroenterology, Depts. of Med. and Surgery, North Shore Univ. Hosp., Manhasset, NY 11030 and Cornell Univ. Med. Coll., New York, NY 10021.

A prospective analysis of colon carcinoma (1987-89) using FCM was performed in order to correlate DNA aneuploidy with age, stage of disease and tumor differentiation. Surgical specimens from 74 consecutive patients were analyzed using the DNA fluorochrome, DAPI. The specimens were fresh, unfixed and processed immediately after resection. The mean age was 68.4 ± 10.8 years with a range of 44-92. 39 patients were male. 38 patients (51.3%) were age $\geq$70 yrs. including 9 (12.2%) $\geq$80 yrs. The distribution of Dukes stage were: A-1; B-41; C-26; D-4; unknown-2. The degree of tumor differentiation was: well-9, moderate-50; poor-12. FCM showed 46 (62.2%) were aneuploid and 28 (37.8%) were diploid. There was no statistical difference ($p>.05$) in mean age between the aneuploid (67.0 ± 10.7 yrs.) or diploid (70.7 ± 10.7 yrs.) groups even when age was stratified by decade of presentation. There was also no correlation of age distribution to degree of tumor differentiation and stage of presentation. In this study no correlation between age, DNA aneuploidy and other clinicopathologic parameters of colon carcinoma was noted. A long-term follow-up study is under way.

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AGING ATTENUATES THE VENODILATORY RESPONSE TO NITROGLYCERIN. *J.A. Gascho* and C. Fanelli,* Penn State Univ. Coll. of Med., Hershey, PA 17033.

Although aging alters arterial impedance, little is known about the effects of aging on venous tone. We therefore measured venous distensibility, using the equilibration technique, before (CON) and after 0.8 mg nitroglycerin (TNG) spray in 50 healthy volunteers age 21-78 years. The increase in forearm volume induced by cuff inflation to 30 mmHg above cuff zero (VV [30], cc/100 cc arm) and the increase in volume occurring after TNG were measured by mercury-in-silastic plethysmography. Subjects were divided into those <60 yrs ($n=28$) and those >60 ($n=22$).

RESULTS:	HR (b/min)	BP (mmHg)	VV [30]
< 60 CON	58 ± 9	82 ± 7	3.22 ± 1.37
TNG	66 ± 11	81 ± 7	3.70 ± 1.50*
> 60 CON	65 ± 10 +	97 ± 11 +	2.01 ± 0.67 +
TNG	72 ± 10* +	94 ± 9* +	2.24 ± 0.79* +

$\bar{x} \pm$ SD; * $p<0.05$ vs CON; + $p<0.05$ vs <60

When all 50 subjects were grouped together, there was a significant inverse relation between age and baseline venous distensibility (CON VV[30] = 4.31 − .033 [age], $r=0.51$, $p<0.001$) and between age and the change (Δ) in venous distensibility after TNG (Δ VV[30] = 0.71 − 0.0068 [age], $r=0.55$, $p<0.001$). Although BP was higher in those >60, multiple regression analysis showed that age, not BP, correlated with the response to TNG.

These results suggest that aging reduces venous distensibility and that the venodilatory effect of TNG is attenuated in older patients.

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THE RELIABILITY THEORY APPROACH TO THE PROBLEM OF MOLECULAR MARKERS OF AGING. *V. Koltover,* Inst. of Chemical Physics, USSR Acad. of Sciences, Chernogolovka, Moscow Region, 142432, USSR.

The maximum lifespan of an individual or a species is determined by the specific gene program which establishes the design and the reliability of the molecular machines functioning in cells. Among such machines are the enzymes of electron transport, of defense against oxygen-free radicals, etc. However, the realization of the program is of stochastic nature because it proceeds at the molecular level. The reliability theory approach unites the deterministic and stochastic principles. That is why this approach provides the opportunity to explain easily and adequately Gompterz' law of mortality and other empirical demographic and comparative correlations as well as to estimate the maximum lifespan limits of species. The searching for biomarkers of aging is a question of the reliability analysis of defense systems at all levels of organization. This approach has been illustrated by the analysis of age changes in reliability parameters of the antioxidant defense in rats and Acholeplasma laidlawii cells. Biological age of an individual may also be indicated by changes in noise characteristics of biochemical processes.

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REGIONAL ACTIVITY OF PHOSPHATE-ACTIVATED GLUTAMINASE FROM ADULT AND AGED MALE FISCHER-344 RATS. *D.R. Wallace* and R. Dawson, Jr.,* Coll. of Pharmacy, Univ. of Florida, Gainesville, FL 32610.

The aim of these studies was to examine the possible age-related alterations in either regional activity, or subcellular location of PAG, phosphate-activated glutaminase (PAG: EC 3.5.1.2, L-glutamine amidohydrolase). Enzyme assays were carried out by the addition of 500uM glutamine to 20-25ug protein in the appropriate buffer containing 20mM HEPES, and either 10mM or 100mM monobasic sodium phosphate, pH = 7.4. The product of the PAG hydrolysis of glutamine, glutamate, was quantitated by HPLC with electrochemical detection after pre-column derivatization with o-phthalaldehyde. Adult (6 month) and aged (28 month old) Fischer-344 male rats were used, and discrete brain regions were examined. In the P-2, synaptosomal fraction, from the temporal cortex, PAG activity was significantly reduced in

aged rats by 35% compared to adults. Activity in both the striatum and hippocampus were unchanged by age, although there were regional differences between the striatum, cortex and hippocampus. There appeared to be glutamate formation in the S-2, but this was not due to PAG activity as indicated by the lack of phosphate activation at 100mM phosphate. This decrease in PAG activity found in the temporal cortex correlates with our earlier finding of cortical reductions in glutamate content in 26 month old Fischer-344 rats. The regional variations in PAG activity found in the present study may reflect changes found in both content and release, and may be used as a marker for changes in neuronal activity associated with aging.

23

GERIATRIC ONCOLOGY — A PROCESS OF CARE IN A HIGH RISK ELDERLY POPULATION. *S. Scialla,* Hematology & Oncology Assoc. of N.E. PA and Wainright Cancer Program, Moses Taylor Hosp., Scranton, PA 18510.

The management of cancer has been based on research and treatment of the young. Such factors as eligibility criteria for research protocols, side effects of chemotherapy, psychologic and physiologic adaptation to cancer and treatment, and end points (outcome) of successful management have not been addressed in the elderly. Based on a stable elderly population in Lackawanna County, PA and a hospital with unique programs to care for the elderly, our group has established a process of geriatric oncology based on principles of geriatric medicine. A pilot study of 31 patients over 60 years old has been conducted with a geriatric assessment questionnaire. This profile identified the baseline state and follow-up quality of life index of geriatric cancer patients. Utilizing clinimetrics and identifying high risk areas in each patient, we are able to institute programs of cancer rehabilitation. Quantification of successful treatment in geriatric oncology is more complex than survival data and response rate. A quality of life index based on complete individual assessment can better identify risk versus benefit of specific treatment plans.

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EFFECT OF AGE AND DEMENTIA ON CARDIOVASCULAR DISEASE IN THE LONG-TERM CARE SETTING. *C. Martins*, S.R. Gambert, K. Gupta, C. O'Dell, and R. Pace,* Ctr. for Aging, New York Med. Coll. and Westchester Med. Ctr., Valhalla, NY 10595 and Heliopolis Hosp., Sao Paulo, Brazil 04523.

While persons with Alzheimer's disease (AD) have been reported to have low rates of coexisting illness, those with multi-infarct dementia (MID) have been noted to have a higher rate of cardiovascular disease (CVD). Little is known regarding the prevalence of CVD in AD compared to those with MID and non-demented controls. We reviewed 275 medical records from residents of a long-term care facility and selected consecutive cases with AD (20), MID (21), and non-demented, age-matched controls (18). Data were analyzed and compared using student t-test or chi-square as appropriate. Persons with mixed AD and MID were excluded from analysis.

Both the AD and MID groups had statistically more myocardial infarcts, ASCVD, LBBB, and atrial fibrillation than the control group. In addition, the MID group had significantly more RBBB and LVH compared to the AD and control groups. No differences were found between groups in cholesterol, A-V block, VPCs, APCs, valvular disease, CHF, diabetes, or hypertension.

We report a higher rate of CVD in institutionalized persons with either MID or AD as compared to non-demented controls.

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CARDIOVASCULAR AND PULMONARY FACTORS AND MEMORY LOSS IN AGING. *W.J. Chodzko-Zajko* and P.B. Schuler,* Dept. of Human Performance, Box 870312, Univ. of Alabama, Tuscaloosa, AL 35487.

Extensive efforts have been directed to understanding the variability with which memory performance declines with advancing age. Our own research has concentrated on the evaluation of the influence of general health status on various aspects of the aging process. In this experiment, we focus on the influence of physiological status on age-related declines in human memory. In a cross-sectional design, 48 volunteers were divided into young (n = 13, 18-27 yrs.), middle-aged (n = 20, 50-65 yrs.), and old (n = 13, 66-89 yrs.) groups and evaluated on a series of cardiovascular, pulmonary, hemodynamic, and biochemical tests in order to determine overall health status. In addition, memorial function was evaluated by an extensive battery of memory tasks distributed along an effortful-to-automatic processing continuum. Traditional chronological analyses revealed expected declines in memory performance with advancing age. However, further analyses revealed that the magnitude of these declines varied as a function of cardiovascular and pulmonary status. In particular, elderly individuals in good cardiovascular and pulmonary health exhibited markedly less memory loss than less healthy age-matched peers. Our data suggest that declines in memory function which are most often attributed to chronological age factors may be at least partially explained by physiological changes which accompany the passage of time. In order to increase our understanding of the variability with which performance declines in advancing age, future research should supplement traditional measures of chronology with appropriate physiological indices of senescence.

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INFLUENCE OF A MAHARISHI AYUR-VEDIC HERBAL PREPARATION ON AGE-RELATED VISUAL DISCRIMINATION. *P. Gelderloos, H.H.B. Ahlstrom, and J.L. Glaser*,* MIU Inst. for Maharishi Ayur-Ved, Maharishi Internat. Univ., Fairfield, IA 52556.

Capacity of attention has been found to decline in older subjects. An ancient system of natural medicine — Maharishi Ayur-Ved — prescribes certain herbal formulas to enhance cognitive functioning, prevent illness and alleviate the detrimental effects of the aging process. A double-blind study was conducted to test the effect of a Maharishi Ayur-Ved herbal preparation, Maharishi Amrit Kalash (MAK), on an age-related alertness task. Forty-eight men over 35 years of age were randomly assigned to receive MAK tablets or a closely-matched placebo twice daily for six weeks. A visual discrimination task consisted of identification of the exact location of a stimulus "V" within an array of "x" symbols during 350 msec tachistoscopic presentations. Repeated measures analysis of covariance revealed that the MAK group improved significantly more in their performance of this task after three and six weeks of treatment relative to the placebo group. Performance was highly significantly correlated with age ($p < 0.004$). Because successful performance apparently requires an unrestricted flow of homogeneous attention over the entire effective visual field as well as focalized concentration, it is concluded that MAK may enhance attentional capacity or alertness, and thus appears to have an effect which is opposite to the detrimental cognitive effects of aging.

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HEALTH CARE CENTER PLANNING FOR OLDER VETERANS: A PLAN. *H.G. Weinstein*, M. Greenberg, H. Nagraj, M. Jaroch, and N.D. List,* Geriatrics/Extended Care Serv., VAMC, North Chicago, IL 60064.

A prototype plan for a regional Health Care Center for Older Veterans (HCCOV) has been developed. Nationwide, such centers could serve ca. 8.4 million older veterans. The prototype differs from that of the Department of Veteran Affairs-Geriatric, Research, Education, and Clinical Centers in that it focuses on maximizing long-term care and related clinical research, rather than being a disease specific program. By expanding the epidemiologic and research data base we shall enhance our ability to care for the older veteran and improve the quality of his life.

The multidisciplinary nature of this meeting provides an ideal forum for discussing this plan.

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HEALTH CONCERNS OF MIDDLE-AGED WOMEN. *A.H. Cushing,* Wellness Ctr., Univ. of New Mexico School of Med., Albuquerque, NM 87131.

Perimenopausal women (n = 81) enrolled in a health seminar (Nifty Fifty) completed questionnaires about health concerns and behaviors.

Major health concerns were: weight in 30%, heart disease in 20%, skeletal disease in 10% and cancer in 8%. Twenty percent had no health concerns and took the class for information only.

Of women whose major concern was weight, 64% exercised regularly, 55% had dieted within one year and 20% knew how to estimate caloric needs or knew caloric content of foods they regularly ate.

Of those concerned about heart disease, 85% had had an EKG, 85% knew their blood pressure and 57% knew their serum cholesterol level.

Of those concerned about the skeleton, 100% exercised regularly, 80% took supplemental calcium and 60% took replacement hormones.

All women who were concerned about cancer had had Pap smears, fecal blood tests and mammograms. Only 58% of the total group had had a mammogram.

Health concerns perceived by the women differed in rank order from those which epidemiologic studies predict will determine their mortality — cancer and heart disease — though weight may be linked to either of these. Moreover they lacked basic information which would enable them to cope with their concerns. Compliance with recommended procedures such as mammography fell far short of ideal in this cohort of health-conscious women with ready access to health care.

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THE ANTIHYPERTENSIVE EFFECT OF SLOW-RELEASE DILTIAZEM IN RELATION TO AGE AND RACE. *J.F. Burris*, M.R. Weir, S. Oparil, M. Weber, and W.J. Cady,* Georgetown Univ., Washington, DC 20007.

The hypotensive effect of a slow-release formulation of diltiazem (DSR) relative to age and race was assessed in 297 participants in a multi-center randomized multifactorial trial of DSR alone and in combination with hydrochlorothiazide (HCTZ) for treatment of hypertension (baseline supine diastolic BP 95-110 mmHg, age range 18-70 years, mean age 52.1, 76 black, 221 non-black, baseline BP 152/99). After placebo run-in, 13-17 patients per group were randomized to placebo, 1 of 4 doses of DSR (60, 90, 120, 180 mg bid), 1 of 3 doses of HCTZ (6.25, 12.5, 25 mg bid), or 1 of the 12 possible combinations of DSR and HCTZ doses. Surface response techniques and analysis of variance demonstrated dose-related reductions in systolic and diastolic BP with each drug alone and in combination. Treatment by demographic variable interaction testing no significant interactions:

Demographic Variable	*Response Variable*	*P-Value*
Age	Systolic BP	0.6896
	Diastolic BP	0.4612
Race	Systolic BP	0.9032
	Diastolic BP	0.3625

DSR and HCTZ were clearly shown to have additive antihypertensive effects. In contrast to reports suggesting calcium antagonists are more effective in older patients and blacks, in this study DSR was equally effective in younger, older, black and non-black patients.

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LIPOFUSCINOLYTIC EFFECT OF CEFLATONE: AN AYURVEDIC BRAIN TONIC. *S.P. Sharma, B.N. Reddy, T.J. James*, S.K. Gupta and I.K. Patro,* Dept. of Zoology, Kurukshetra Univ., Kurukshetra-132 119, India.

Ceflatone (CT), an indigenous Ayurvedic neurotropic drug preparation based on time-tested Rasayana principles, has been used to register its effects on lipofuscin in aging rats. A total of 72 male Wistar rats (young and adult) were used. CT was administered to both the groups, i.e., young (YCT) and adult (ACT) rats, orally (60 mg/kg body weight/day blended with cane sugar in 1:1 ratio) for periods of 1, 3 and 6 months. Rats were killed at the end of each said treatment period and the cerebella were processed for histochemical, fluorescent and micrometric analysis of lipofuscin. While a progressive accumulation of lipofuscin was found in the Purkinje cells of controls, the pigment significantly got reduced in the treated ones depending on the period of treatment with CT. For example, while pigment depletion was 46.97% after 6 months of CT treatment, it was only 19.89% after 1 month of treatment of adult animals. Thus, CT is found to be an effective lipofuscinolytic agent.

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HOMEOVISCOSITY ADAPTATION AND STABILIZATION OF MEMBRANE LIPID FLUIDITY IN AGING. *V. Koltover,* Inst. of Chemical Physics, USSR Acad. of Sciences, Chernogolovka, Moscow Region, 142432, USSR.

Liver endoplasmic and heart sarcoplasmic membranes, brain synaptosomes and heart plasma membranes from rats of different ages were studied by spin and fluorescent probe techniques. It was shown that aging is characterized by stabilization of microviscosity (fluidity) of the 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. Such factors as membrane lipoprotein network, cholesterol, lipid peroxides, lysophosphatidylcholine appear to play important roles in the stabilization of lipid fluidity. The limited reliability of the regulatory adaptation mechanisms makes it possible to observe the age differences in lipid fluidity at low temperatures as well as at other deviations from normal physiological conditions.

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LIPOFUSCINOLYTIC ACTIVITY OF CENTROPHENOXINE: A POSSIBLE EXPLANATION. *S.K. Gupta*, S.P. Sharma, T.J. James, B.N. Reddy, and I.K. Patro,* Dept. of Zoology, Kurukshetra Univ., Kurukshetra-132 119, India.

Protein malnourished Wistar rats were used as model to trace out the mechanism of lipofuscinolytic effect of Centrophenoxine (CPH). A total of 96 3-month-old animals were divided into three experimental groups; one group was maintained on low protein (LP; 4%), another on LP along with CPH. The third group consisted of 6-months' malnourished animals fed CPH for the next 6 months. Age-matched controls were maintained on high protein diet (HP; 20%). Spinal cords were removed and processed for histochemical, fluorescent and biochemical studies. It was found that lipofuscinolysis by CPH was accompanied by an increase in the tissue RNA and protein contents. Lipid peroxidation product, malonaldehyde, registered a decline after CPH treatment. Moreover, histochemical analysis revealed hyperactive nucleoli as well as regeneration of Nissl substance consequent upon CPH treatment. Thus, the lipofuscinolytic action of CPH may be due partly to revitalization of protein synthesizing machinery and partly to its free radical scavenging action which can be attributed to dimethylaminoethanol, a chemical moiety of CPH.

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EFFECT OF AGE ON THE STRUCTURE OF MEISSNER CORPUSCLES IN MURINE DIGITAL PADS. *P.B. Nava* and R.C. Mathewson, Dept. of* Anatomy, Loma Linda Univ. School of Med., Loma Linda, CA 92350.

A light and electron microscopic study was performed to determine age changes in Meissner corpuscles. In forepaw digital pads of mice aged to their maximum life expectancy, corpuscles were found to increase in size and complexity until middle age, and then to become smaller, disorganized and lobulated with more advanced age. Nerve terminals at more advanced ages became attenuated with a loss of axonal processes, increased density of the axoplasm, and disordered arrangement of the organelles. Degeneration of axonal mitochondria accelerated with age. Lamellar cell processes investing the axons often became dense and attenuated with fewer plasmalemma-associated vesicles. Basal laminae remained where lamellar processes had disintegrated. Lipofuscin was seen in the lamellar cells only at extremely old age. Extracellular material composed of fine basal lamina substance and collagen fibrils increased remarkably with age.

Increased growth and complexity of corpuscles until middle age perhaps compensated for age-associated loss of corpuscles and primary sensory neurons. Changes predominating at older ages are attributed to distal axonopathy and atrophy of the sensory neurons. The probable effect of these age changes on cutaneous sensitivity is considered in relation to current theory of mechano-electric transduction.

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PIGMENT-PROTEIN COMPLEX EXISTENCE IN LIPOFUSCIN GRANULES. *A.G. Tatariūnas,* Lab. of Neuron Physiology, Kaunas Med. Inst., Kaunas 233000, Lithuania.

Assumption of a starting viewpoint that lipofuscin granules (LG) are cell organelles with their specific functional-ultrastructural significance led us to make definite progress in settling the question on genesis of LG in cells; LG are products of endoplasmic reticulum as was shown earlier by us (*Bull. Exp. Biol. Med. [USSR],* 107:363-7, 1989). However, the question of the nature of autofluorescenting chromophore in LG still remains open.

The microspectrofluorimetric measurements showed that the main band in the visible region of LG fluorescence spectrum *in situ* undergoing changes in intensity under exciting ultraviolet irradiation ($\lambda_{ex} = 365$ nm) lies within 530-560 nm and has several submaxima. In the case of tryptophan fluorescence excitation ($\lambda_{ex} = 280$ nm), the protein fluorescence maximum of LG isolated from bovine myocardium is at 325 nm. However, the second maximum in the visible region (ca 580 nm) of fluorescence spectrum on tryptophanyls excitation in proteins was stated. This indicates the existence of chromophore-protein complex in natural LG. Chromophore/protein ratio approximately calculated from the absorption spectrum of such a complex of isolated LG in visible and ultraviolet regions must be nearly equal to one suggesting the polyisoprenoid (retinoid) nature of chromophore.

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SENEX, A COMPUTER-BASED TOOL FOR ORGANIZING GERONTOLOGIC INFORMATION. *S.S. Ball*, L. Wright, and P. Miller,* Med. Informatics Program, Yale Univ. School of Med., 333 Cedar St., P.O. Box 3333, New Haven, CT 06510.

We are currently developing a computer-based tool (SENEX) for coping with the explosion of new information in the biomedical domain. SENEX is being developed using the Common Lisp Object System (CLOS), an object-oriented extension of the Common Lisp programming language. Object-oriented programming is useful in representing the complex and diverse field of biomedical knowledge. The structure and interactions of biomedical entities, as well as retrieval of (possibly remote, electronically accessed) references to them, can be defined in a uniform way at the top level of the system, and then extended and redefined as needed within specialized modules dealing with particular areas of knowledge. The benefits of data abstraction and modular development are particularly important where a large system needs to be developed, maintained and extended, possibly by many people. SENEX is currently implemented in prototype form with a limited set of knowledge, which includes salient information from approximately 250 journal articles in addition to a significant amount of basic information about the domain. Other features, such as CLOS's flexible scheme for inheritance of properties within the class hierarchies, is also useful. We are exploring ways in which such knowledge representation can be used in an interactive system for purposes of education and for designing basic research experiments in the domain of neurodegeneration and aging.

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THE EFFECTS OF FOOD RESTRICTION AND STEROIDAL INHIBITORS OF GLUCOSE 6-PHOSPHATE DEHYDROGENASE (G6PDH) ON THE COMPOSITION AND ACTIVITY OF THE INNER MITOCHONDRIAL MEMBRANE. *T. Sorger,* The Wistar Inst. of Anatomy and Biology, Philadelphia, PA 19140.

Administration of the glucose 6-phosphate dehydrogenase (G6PDH) inhibitor dehydroepiandrosterone (DHEA) in the diet causes weight loss in certain strains of mouse and rat independent of any change in food intake. We examined the effects of DHEA on the cytochrome content and electron transport activity of the hepatic mitochondria of C57BL/6J mice. Treatment with DHEA (0.4% in the diet) was compared with: (a) *ad libitum* feeding of a control diet; (b) 60% food restriction (control diet); dietary administration of (c) pregnenolone, another inhibitor of G6PDH and (d) etiocholanolone, a major end-product of DHEA metabolism. Over a two-week period, food restriction and DHEA caused similar losses of weight. DHEA alone caused a decrease in the level of cytochrome aa_3 per mg mitochondrial protein and a significant reduction in the maximal (uncoupled) rate of electron transport (-45%; $p<0.01$ compared to the *ad libitum* fed group). In contrast, resting (State 4) oxygen consumption was markedly stimulated following treatment with DHEA, an effect which was eliminated following incubation of the mitochondria with the ATP synthetase inhibitor oligomycin. These data indicate that DHEA exerts specific effects on the mitochondrial inner membrane which are not secondary to weight loss, the inhibition of G6PDH or steroid metabolism.

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FOOD RESTRICTION PROTECTS MICROSOMAL P-450 FROM FREE RADICAL DAMAGE. *D.W. Lee*, C.G. Marler, and B.P. Yu,* Dept. of Physiol., Univ. of Texas Health Sciences Ctr., San Antonio, TX 78284.

The aging processes are accompanied by an increase in the incidence of diseases and by changes in many biological functions including degenerated xenobiotics metabolism. Previous data indicated that lipid peroxidation and free radical reactions are responsible for destabilizing the microsomal membrane and for deactivating the microsomal mixed function oxidase system; however, food restriction recently has been shown to attenuate these alterations. We investigated the effects of age and food restriction on the 1) changes in microsomal P-450 and the activity of its related enzymes, 2) resistance of P-450 against peroxidative stress, and 3) cytosolic protective activity against P-450 degradation. Fischer 344 rats were used with the food restricted rats receiving 60% of the *ad libitum* rats' mean intake. To test membrane stability and P-450 degradation, *in vitro* peroxidation was carried out by addition of either NADPH/ADP-Fe^{++} or cumene hydroperoxide. In our experiments, the content of P-450 and its related enzyme activities showed no age or dietary effect with exception of NADH ferricyanide reductase. The age-related changes in P-450 degradation were modulated effectively by food restriction. Also, the cytosolic protective capacity against P-450 destruction was enhanced with food restriction. Therefore, we concluded that food restriction enhances the stability of the microsomal membranes against lipid peroxidation and free radical damage and provides an optimal structural environment for microsomal mixed function oxidase activity.

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EFFECT OF AGE ON ANTIOXIDANT DEFENSE RELATED TO GLUTATHIONE IN RAT LIVER: DISTRIBUTION OF REDOX CYCLE OF GLUTATHIONE IN THE ACINUS. *J. Sastre*, J. Rodriguez, F.V. Pallardo, E. Gasco, and J. Viña,* Depto. de Fisiologia, Univ. de Valencia, 46010 Valencia, Spain.

Free radicals may play a central role in cellular aging. Reduced glutathione (GSH) levels decrease in many tissues with age. There is no available data on the effect of age on the acinar distribution of GSH. Periportal (PP) hepatocytes are exposed to a higher oxygen pressure than perivenous (PV) cells. This O_2 gradient apparently does not change with age. We studied the effect of age on the distribution of components of the glutathione system in the liver acinus. We used 3- and 22-month-old Wistar rats using double-plus digitonin perfusion technique. Plasma levels of GSH were significantly ($P<0.05$) lower in old rats than in young rats (0.46 ± 0.04 vs. 52 ± 0.02 moles/ml). However, hepatic GSH levels and the rate of GSH synthesis in isolated hepatocytes did not change with age. Glutathione peroxidase, glutathione reductase and glucose 6-phosphate dehydrogenase activities in old rats were respectively 500%, 150% and 267% of the values found in young rats. PP/PV ratio for GSH was higher in young rats (1.7 ± 0.3) than in old ones (1.3 ± 0.3). No change with age was found in the PP/PV ratio for glutathione reductase. In summary, the activities of the enzymatic antioxidant system

related to glutathione increased with age in rat liver. Differenes in GSH antioxidant system observed between PP and PV hepatocytes in young rats were found to be diminished with age.

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GLUCONEOGENESIS, KETOGENESIS AND UREOGENESIS IN ISOLATED HEPATOCYTES FROM AGING RATS. *J. Sastre*, F.V. Pallardo, J. Estrela, M. Asensi, and J. Viña,* Depto. Fisiologia, Univ. de Valencia, Valencia 46010, Spain.

Gluconeogenesis, ketogenesis and ureogenesis are characteristic pathways of liver, particularly in fasting. Isolated hepatocytes from 48 h-starved Wistar rats (3 and 22 months old) were used to investigate the effect of age on gluconeogenesis, ketogenesis and ureogenesis. The rate of gluconeogenesis from lactate (10mM) plus pyruvate (1mM) was significantly ($P<0.05$) lower in hepatocytes from old rats (0.60 ± 0.07 moles/min.g wet wt.) than in those of young rats (0.98 ± 0.09 moles/min/g wet wt.); gluconeogenesis from fructose did not change. We have also found that malate levels in hepatocytes incubated with lactate (10mM) and pyruvate (1mM) were significantly ($P<0.05$) higher in old rats than in young rats (0.77 ± 0.08 vs. 0.56 ± 0.05 moles/g wet wt.). These results indicate that probably the step catalyzed by phosphoenolpyruvate carboxyquinase is responsible for the decreased rate observed in gluconeogenesis. We have also studied the distribution of ATP and ADP between cytosolic and mitochondrial compartments by digitonin fractionation technique. [ATP]/[ADP] ratios in the cytosolic and mitochondrial fractions of hepatocytes incubated with lactate plus pyruvate did not change with age. The rate of ketogenesis from oleate was significantly lower ($P<0.05$) in hepatocytes from old rats (0.91 ± 0.05 moles/min.g wet wt.) than in those from young rats ($1.57 + 0.13$ moles/min.g wet wt.). On the other hand, the rate of ureogenesis from $ClNH_4$ (10mM) plus ornithine (2mM) and lactate (10mM) did not change with age.

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DECREASED UPTAKE OF TAUROCHOLATE BY ISOLATED HEPATOCYTES IN AGED RATS SUPPORTS THE REGULATORY ROLE OF MEMBRANE PROTEIN MOBILITY IN THE HEPATIC UPTAKE MECHANISM DURING AGING. *M. Ohta*, K. Kitani, and I. Zs.-Nagy,* 1st Lab. Clin. Physiol., Tokyo Metropol. Inst. Gerontol., Tokyo 173, Japan.

Our previous studies on ouabain uptake by rat hepatocytes (*Biochem. Pharmacol.* 37:935-942, 1988) as well as fluorescence recovery after photobleaching (FRAP) (*Arch. Gerontol. Geriatr.* 5: 131-146, 1986) suggested that the decrease with age in protein mobility in plasma membranes is at least partially responsible for the age-dependent decrease in the hepatic uptake of ouabain. In order to examine whether this hypothesis is more generally valid, the hepatic uptake of taurocholic acid (TC) was examined using isolated hepatocyte preparations obtained from rats of different ages.

The Vmax (nmol/mg protein/min, mean ± SE) for young rats (4-5 months; $n=6$) was 2.15 ± 0.11, while in old rats (24-29 months); $n=4$) the value was 50% lower (1.16 ± 0.11, $P<0.005$). In contrast, Km (μM) values were not significantly different between young (25.88 ± 1.90) and old (30.34 ± 4.96) rats ($P>0.05$). When the uptake velocity (Y) at 1μ M TC concentration was correlated with rat age in months (X), a significant linear relationship ($Y = 77.1\text{-}1.595X$, $n=14$, $r=-0.79$; $P<0.005$) was obtained, suggesting a steady and almost linear decrease of TC uptake velocity with age. The decrease in rate with age (2.1%/month) was quite similar to that previously observed for ouabain uptake (2.4%/month).

The results support our previous proposal that protein mobility of the hepatocyte surface membrane may play at least a partial regulatory role in carrier mediated hepatocyte uptake functions for various materials.

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(−) DEPRENYL PROLONGS SURVIVAL OF AGED RATS. *G.O. Ivy*, R.J. Racine, P. Nellis, A. Mendonca and N.W. Milgram,* Life Sciences, Univ. of Toronto, Scarborough, Ontario, M1C 1A4 Canada.

Maintenance of laboratory rats on low doses of (−) deprenyl, an inhibitor of MAO B which is widely used to treat symptoms of Parkinsonism, has been previously reported to increase both mean and maximum lifespan in male rats of a Logan-Wistar hybrid strain when treatment is begun at 24 months of age (Knoll *et al., Mech. Aging Dev.* 46:237, 1988). The present study was designed to replicate these findings in the Fischer 344 rat, as this strain is the one most commonly used in aging studies.

Male Fischer 344 rats 24 months of age were housed in individual cages and were both weighed and injected with physiological saline ($n=31$) or (−) deprenyl ($n=31$) every other day until time of natural death. Clear differences emerged only after 3½ months of treatment, when the deprenyl treated animals were significantly heavier than the controls, reflecting a slowing of the loss of body mass which is known to occur during aging. After 7 months of treatment, at 31 months of age, there were 9 surviving rats in the deprenyl group and 1 control rat. The median survival interval for the control animals was 116 days, while the median was 147 days for the (−) deprenyl treated rats. Further, the maximum lifespan of the deprenyl treated rats will be over 31 months, as compared to the 27-29 months previously reported for this strain. Our results thus indicate that (−) deprenyl can prolong the survival of laboratory rats even when treatment is begun at a late age.

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AGE AND EXERCISE ASSOCIATED CHANGES IN THE ARTERIAL WALL CONCOMITANT WITH ATROPHIC CHANGES IN MUSCULOSKELETAL FUNCTIONAL UNIT IN MICE. *E. Livne, M. Brenmann, A. Reznick, S. Finkelbrand, A. Weiss* and M. Silbermann,* Rappaport Inst., Faculty of Med., Technion, Haifa, Israel.

Recent studies in our laboratory indicated that various tissues of the musculoskeletal complex undergo profound atrophy in aging female C57Bl/6 mice. Moreover, physical exercise, which was a potent stimulant for musculoskeletal tissues in young animals, failed to increase muscles and bone mass in aged animals. Tissue metabolism highly depends on blood supply. The aim of this study was to evaluate the effect of age and controlled physical training on the structure of arterial walls. Young (6 month old) and old (27 month old) female C57Bl/6 mice were exercised in treadmill 30 min/day, 3.5 m/min for a period of 10 weeks. The hind legs were fixed, processed for light microscopy and sections from mid-shaft were examined. The thickness of the femoral artery's wall was found to increase with age (7.9%, $p<0.05$). This was due to enlargement of fibrous tissue within the tunica media along with a significant decrease in the number of smooth muscle and elastic fibers. This trend was even more profound in trained animals. Young animals responded to training with a significant hypertrophy of the quadriceps femoris muscle (29% increase in both number and diameter of muscle fibers, $p<0.01$) and by an increase in bone mass (10%). No significant changes in the number and diameter of muscle fibers in old trained animals were observed. Moreover, many fibers showed numerous lipid and lipofuscin granules. Thus the present findings indicate that the response to physical training varies with the age of the animal. The lack of adaptation in old animals could possibly be due, at least in part, to the atrophy of arterial walls and the tissues supplied by them.

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FUNCTIONAL ASSAYS FOR THE ISOLATION OF ANTIPROLIFERATIVE cDNAs. *T. Giordano* and B. Howard,* Lab of Molecular Biology, NIH, NCI, Bethesda, MD 20892.

Attempts to identify the mechanisms involved in cellular senescence have been frustrated by the lack of a functional assay. We have developed two assays for the study of antiproliferative genes in which the cell surface marker, pRSV-IL2R, is co-transfected with the gene of interest and then growth inhibition in the transfected subpopulation is assayed by magnetic affinity cell sorting (MACS) or fluorescent antibody cell sorting (FACS). These assays will be utilized to isolate a cDNA(s) involved in growth cessation. To identify potentially rare antiproliferative mRNAs, a high quality cDNA library must be constructed, enriched for full length cDNAs inserted in the proper reading frame

and orientation. Directional cloning into the eukaryotic expression vector, pSV2, is accomplished by synthesizing a poly d(T) primer with a partial *Bam*HI restriction site. A synthetic linker is then utilized which completes the *Bam*HI site at the 3' end, and contains an internal *Hind*III site, such that when the cDNA is double digested after linkering, the 5' end will contain a *Hind*III and the 3' end a *Bam*HI site (*Hind*III and *Bam*HI sites in the cDNA insert are protected by DNA methylases). Thus, the system is designed so that only those cDNAs with intact 3' poly(A)tails will be cloned. To enrich for cDNAs complete at the 5' end, we are utilizing a monoclonal antibody (mAb) to the 5'methyl cap of mRNA. Following first strand synthesis, mRNA/cDNA hybrids are incubated with the mAb attached to a solid matrix, washed and eluted to enrich for cDNAs reverse transcribed from intact mRNA for the library construction. The library will be transfected into cells along with the selectable marker pRSV-IL2R, sorted and assayed for growth inhibition. To identify the clones of interest, the fraction of the library demonstrating inhibition can be further fractionated or alternatively, the slow growing cultures can be passaged. In separate experiments we have obtained evidence that pRSV-IL2R can be used to develop a stable line carrying a cotransfected gene. This technique can also be used to select stable clones which allow normal fibroblasts to escape senescence.

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NEGATIVE REGULATION OF CELL GROWTH: NEW GENE TRANSFER APPROACHES AND A POSSIBLE ROLE FOR THE 7SL RNA/ALU GENE FAMILY. *K. Sakamoto, C.M. Fordis, T.H. Howard, T. Giordano, and B.H. Howard.* Lab. of Molecular Biology, National Cancer Inst., Bethesda, MD 20892.

We are exploring the hypothesis that interspersed repetitive gene families which are transcribed by RNA polymerase III, in particular the 7SL RNA/Alu family, may play a role in cellular senescence. There are a variety of mechanisms by which such interspersed repeat families may normally serve to regulate gene transcription and/or DNA replication. The accumulation of stochastic "activation" events (e.g., resulting in loss of appropriate control) at interspersed repeat loci during the life span of a cell strain could cause loss of proliferative potential. To test this hypothesis, we have utilized two gene transfer assays to examine the capacity of 7SL RNA and Alu gene sequences to regulate HeLa cell growth. These gene transfer assays are based on cotransfection of putative growth control genes with a cell surface marker plasmid: transiently transfected cells that display the plasmid-encoded surface marker are analyzed with respect to growth either by BrdUrd labelling/fluorescence activated cell sorting or ^{3}H-thymidine labelling/magnetic affinity cell sorting. In such experiments, DEAE-dextran-mediated transfection with 7SL RNA or Alu gene sequences causes suppression of ^{3}H-thymidine incorporation in recipient cells. Inhibitory activity is dependent on the presence of two sequence motifs: the B block RNA polymerase III promoter signal and an undecanucleotide, GAGGCNGAGGC, which is homologous to the T antigen binding region in the SV40 DNA replication origin. $CaPO_4$-mediated transfection with these sequences results in growth suppression that is also dependent on the presence of the B block pol III promoter signal. These results represent the first direct evidence that 7SL RNA and Alu elements have the potential to regulate cellular DNA synthesis and that specific sequence motifs at which DNA- or RNA-binding factors interact are responsible for such regulatory activity.

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TWO-DIMENSIONAL (2D) TLC AUTORADIOGRAPHY AS A QUANTITATIVE MEASURE OF DNA DAMAGE BY NON-ENZYMATIC ADVANCED GLYCOSYLATION PRODUCTS (AGE). *J.J. Steinberg*, B. Kelly, T. Silverstein, J. Gleeson, and M. Brownlee,* Depts. of Pathol. and Med., Albert Einstein Coll. of Med., Bronx, NY 10461.

Advanced products of nonenzymatic glycosylation play a critical role in the evolution of diabetic complications because of their characteristic chemical properties. These slowly-formed glucose derived compounds are chemically irreversible, and thus accumulate continuously with time. To better quantify the amount of AGE DNA-adduct formation, we have developed a 2D-TLC autoradiographic technique employing a highly reactive fragmentation product of glucose-amines, glycolaldehyde, After co-incubation with calf-thymus DNA for 45 minutes at room temperature, 32P was incorporated into DNA constituent mononucleotides by [32P]-alpha-dTTP (thymine as a non-amino nucleic acid) via nick-translation and subsequent digest by spleen phosphodiesterase and micrococcal nuclease. The monophosphate separation was carried out by two dimensional PEI-cellulose TLC employing acetic acid, 1.3 M, pH 3.5, in the first dimension, and 4 M ammonium sulfate, 70 mM EDTA, pH 3.5, in the second dimension. This was then followed by autoradiography. Alteration of DNA nucleotides was shown by comparison with known markers overlying 32P counts on autoradiographic developed film. Results indicate that at 0.5 mM glycolaldehyde, at least five new adduct spots were generated with altered 2-D migration coordinates which reflect glycation modified bases. In addition, an increased percentage of undigested polynucleotides were present at the origin. At 50.0 mM glycolaldehyde, an additional four new adduct spots were present with altered 2-D migration coordinates, including undigested polynucleotides, and nucleotide ring-open products. Since these AGE DNA adduct products can participate in the critical process of glucose-derived cross-link formation, this accumulation may ultimately result in altered function of genetic elements.

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DNA DAMAGE AND REPAIR IN YOUNG AND MIDDLE-AGED MICE. *S.S. Ball, M.S. Neshat*, and R.L. Walford,* Dept. of Pathol., UCLA Med. Ctr., Los Angeles, CA 90024.

Female C57BL/10 mice two and 14 months of age were injected with 0.4 mg of benzo(a)pyrene-trans-7,8-diol in the peritoneal cavity. Mice were sacrificed at 3, 6, 9, 12, 18 and 24 hours and DNA was isolated from liver and kidney of each animal individually. The amount of carcinogen bound to DNA was determined as benzo(a)pyrene, 7,8,9,10-tetrol liberated upon acid hydrolysis of the DNA. The benzo(a)pyrene-7,8,9,10-tetrol was determined by synchronous scanning fluorometry and compared to the amount of hydrolyzed DNA present in the sample. Considerable variability was observed in the amount of carcinogen bound to DNA in liver and kidney of both young and middle-aged animals. Despite this variability, evidence for repair of DNA-bound carcinogen from both liver and kidney of young animals was obtained. A subset of older animals failed to sustain appreciable damage upon injection of the carcinogen. The results of our experiments suggest a greater variability in response to carcinogen injection in the middle-aged animals.

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DECLINE OF IMMUNOLOGICAL RESISTANCE TO TRYPANOSOMIASIS IN AGING MICE. *J.W. Albright* and J.F. Albright,* Dept. of Microbiol., George Washington Univ. Med. Ctr., Washington, DC 20037.

Immunological cure of *Trypanosoma musculi* infections in mice is a reflection of Kupffer cell (KC) destruction of the parasites facilited by IgG2a antibodies and possibly C3 fragments. The infections are much more severe, and frequently fatal, in aged animals. We have produced several lines of evidence which indicate that the age-associated decline in immunological resistance results from: (a) retarded generation of antibodies against the trypanosomes in aged compared to young mice; (b) quantitative deficiency in the generation of IgG2a antibodies in aged mice; and (c) the production of blocking substances, especially in aged mice, that interfere with KC uptake of the trypanosomes. On the other hand, it appears that the efficiency of KC with respect to ingestion of trypanosomes is about the same in young and aged mice. This investigation is among the first to demonstrate the increased susceptibility of the aged to parasitic infections. Furthermore, the investigation has revealed the utility of the trypanosomes as live, natural immunogens for analyses of the age-associated deterioration of the immune system.

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HYPOTHALAMIC-PITUITARY-ADRENAL AXIS AGE-RELATED CHANGES IN OLD MALE 344 FISCHER RATS. *G. Cizza,[1,2] A.E. Calogero*,[1,2] P.W. Gold[2] and G.P. Chrousos[1]*, Develop. Endocrinol. Branch, NICHD[1] and Clin. Neuroendocrinol. Branch, NIMH[2], Bethesda, MD 20892.

The hypothalamic-pituitary-adrenal (HPA) axis plays a major role in sustaining homeostasis at both the basal and stress states. The process of aging, on the other hand, is associated with decreased capacity of an individual to attain homeostasis. To examin the possible relationships between aging and the function of the HPA axis, we studied male 344 Fischer rats at 2, 18, and 22 months (mo) of age. We measured hypothalamic (H) and pituitary (P) content of immunoreactive (ir) CRH and ACTH, respectively. We also studied the ability of the hypothalamus to release ir-CRH in response to KCl *in vitro* and assessed the plasma concentrations of ir-ACTH and ir-corticosterone (B). The results ($\bar{X} \pm SEM$) are shown in the Table.

Age (mo)	H-CRH content (pg/H)	H-CRH secretion (• of basal)	Pituitary ACTH (ng/anterior P)	Plasma ACTH (pg/ml)	Plasma B (ng/ml)
2	1841±125(15)*	896±172(14)	61±7(35)	178±18(24)	221±20(51)
18	1384±190(6)	NT	79±8(6)[a]	NT	137±18(15)[a]
22	1247±113(5)	379±109(13)[b]	100±17(23)[a]	126±11(23)[b]	104±13(38)[a]

*Animal number in parentheses; a: $p<0.05$ vs 2 mo; b: $p<0.02$ vs 2 mo

We found slightly decreased hypothalamic CRH content and significantly compromised hypothalamic *in vitro* release of ir-CRH in the older rats. These rats had elevated content of pituitary ir-ACTH and decreased concentrations of plasma ir-ACTH and B. These findings are consistent with deteriorating HPA axis function with age, possibly contributing to the increasing inability of aged individuals to sustain homeostasis. The increase of pituitary ir-ACTH content may be a result of decreasing glucocorticoid negative feedback with aging.