National Institute on Aging

Annual Report of Intramural Research

October 1, 1988
to
September 30, 1989

ANNUAL REPORT OF THE OFFICE OF THE SCIENTIFIC DIRECTOR

NATIONAL INSTITUTE ON AGING

The Scientific Director, NIA, is responsible for the quality and direction of research conducted by the Intramural Research Program. In addition, the Office of the Scientific Director (OSD) includes selected central administrative and support functions essential to the program's efficient operation. The organizational units which comprise OSD are the immediate Office of the Director, Administrative Services (Administrative Office and Procurement), the Public Information Office, and the intramural Personnel Office.

Dr. Richard C. Greulich, the NIA Scientific Director since 1977, retired in 1988 and Dr. Gunther L. Eichhorn served as Acting Scientific Director while a search committee reviewed prospective candidates, prior to selecting Dr. George R. Martin as the new Scientific Director. Dr. Martin, former Chief, Laboratory of Developmental Biology and Anomalies, National Institute of Dental Research, officially joined the Institute in December 1988. He is a biochemist whose career at NIH began in 1958. He has a particular interest in the extracellular matrix and its involvement in development and disease.

The NIA Board of Scientific Counselors met in November 1988 to review the Laboratory of Molecular Genetics, in May 1989 for a review of the Laboratory of Clinical Physiology, and in September 1989 to review the Laboratory of Neurosciences. These represent in-depth reviews during which knowledgeable experts joined the scientific counselors to hear detailed reports on ongoing scientific projects, to advise on future directions, and to evaluate intramural scientific staff. These reviews represent the major external review of NIA intramural research and are invaluable in the operation of our program.

The NIA and the Tokyo Metropolitan Institute of Gerontology (TMIG) have signed agreements promoting cooperative activities and for the exchange of scientists. Most recently, Dr. Donald Ingram of the Laboratory of Cellular and Molecular Biology spent six weeks in Tokyo working at the TMIG. Also, a joint program was held with TMIG and Gerontology Research Center staff. During this program the Japanese and American scientists discussed the breadth of problems related to aging and called for the integration of efforts and coordination of programs. Another area for cooperative research is that of cross-cultural differences which may help to distinguish true age-related changes from those due to lifestyle.

Full details on research conducted by all Intramural Research Program components can be found on the following pages of this report. However, a few of the most interesting highlights follow.

o Pulmonary function has long been known to decline with age. Data from collaborative research by scientists from Johns Hopkins and the Longitudinal Studies Branch indicate that the pulmonary declines seen with aging are predictive for ischemic cardiac disease in men. In addition, the data shows that declines in pulmonary function are predictors of increased mortality in all cases for males over 60 years of age, but not for younger men.

o Investigators in the Behavioral Medicine Section, Laboratory of Behavioral Sciences completed an extensive cross-sectional study of pulmonary and cardiovascular function at rest and during a standardized breathing task. There were 120 subjects, stratified for sex, exercise, smoking, and age. Preliminary data analyses suggest that earlier reports of age-related declines in lung function volume (minute ventilation and tidal volume) are not present when the group is stratified for sex, smoking and exercise. Other analyses confirmed previous findings that cardiac stroke volume and cardiac index increase with age, but with no change in heart rate.

o Previous studies of thermoregulation in rodents have shown consistent declines in body temperature and in response to a cold challenge in aged mice. This year, studies of metabolic heat production showed that adult, C57BL/6J mice produce more heat in response to a cold challenge than do old animals. Since old animals can respond to mild cold (18^{o}C) but not to more severe cold (6^{o}C), it appears that old animals can detect cold as well as the adult animals, but cannot generate additional heat at the lower temperature.

o This year, the Laboratory of Personality and Cognition (LPC) began collaboration on a prospective study of the natural history of dementia in the Baltimore Longitudinal Study of Aging (BLSA). A sophisticated battery of neuropsychological tests are now being given BLSA participants over age 70. Archival data on cognitive performance and personality traits will be evaluated for use as long-term predictors of Alzheimer's disease in participants who subsequently develop this disease. One major finding, which has already come out of this study, is that in the absence of neurological evidence of impairment, memory complaints are not predictive of poorer neurological performance. Rather, such complaints appear to be related to psychological distress and neuroticism. This has important implications for research and clinical practice by suggesting that memory complaints themselves may not be useful in screening for early dementia.

o Another LPC finding this year was that subjects with symptoms of depression are not at increased risk for cancer. The investigators looked at 10-year follow-up data collected from 6400 men in the National Health Nutrition Examination Survey I (NHANES I) Epidemiologic Follow-up Study. The data analyzed showed that approximately 11 percent of depressed symptom subjects developed cancer, but so did 10 percent of non-depressed persons, a small and statistically insignificant difference between the two groups. These interesting findings shed considerable doubt on the purported relationship between depression and the etiology of cancer.

o Researchers in the Laboratory of Molecular Genetics (LMG) have isolated and characterized a gene which, when injected into cells, stops proliferation of these cells. The gene is expressed normally in cells that are not proliferating and in a wide variety of non-dividing tissues. This gene product, prohibitin, may play a role in cell senescence and aging although this has not yet been shown directly.

o The heat shock response is a universal response found in cells from bacteria to human cells. It involves expression of a specific set of genes apparently involved in protecting the cell against a variety of toxic and stressful situations. This year, LMG scientists have shown that the heat shock response is altered in old animals exposed to hyperthermic conditions. In collaboration with the Laboratory of Behavioral Sciences, investigators found that the defect in the ability of old animals to withstand cold stress is associated with the failure to express at least one member of this gene family.

o Researchers in the Laboratory of Cellular and Molecular Biology recently started nuclear magnetic resonance (NMR) studies of aging utilizing BLSA participants. Thus far, no age-related effects have been identified due mainly to the fact that too few subjects over age 70 or greater have been tested. However, the investigators have observed an initial increase in pH level upon initiation of light (30 percent of maximum workload) exercise, followed by more intense acidosis as work continues. This effect has been observed previously elsewhere, but not consistently. The current long-term study should allow effective investigation of this and other transient phenomena.

o In one of the two exercise protocols used in the above study, the the subject must squeeze a hand dynamometer at 30, 40, 50, or 60 percent of his maximum workload for 30 seconds followed by a 60 second rest period between contractions. Typically, the PCr/Pi ratio declines during exercise and recovers toward the initial value during the resting portions of the testing. In many subjects the initial recovery period after the 30 percent contraction is interrupted by a drop in the PCr/Pi ratio. This study demonstrates that the isometric exercise method can be used successfuly to determine metabolic changes during exercise.

o Laboratory of Neurosciences studies using positron emission tomography (PET) have demonstrated disproportionate metabolic involvement of the frontal, parietal and temporal association neocortices in Alzheimer patients, with little involvement of primary and sensory motor regions. In addition, neurofibrillary tangles are selective to the association as compared to primary sensory and motor cortical regions, and Alzheimer neuropathology is found in non-neocortical brain regions which underwent rapid changes during recent hominid and higher primate evolution. These and other observations suggest the hypothesis that Alzheimer's disease is a phylogenetic disease which involves brain regions which underwent rapid expansion during evolution of higher primates.

o In other work by NIA neuroscientists, the rate of cerebrospinal fluid (CSF) production, measured with a draining method from lumbar CSF, was reduced by half in older as compared to younger healthy subjects, from 0.4 to 0.2 ml/min. As CSF spaces are larger in older persons, a lower production rate indicates that the turnover of CSF, which acts as a sink for washout of brain substances, is reduced in elderly individuals.

Information Office

This office completed a most productive year wrapping things up with the memorable N. W. Shock Laboratories dedication and extensive publicity coverage of the paper by Dr. Alan Zonderman, et al., Laboratory of Personality and Cognition, which appeared in the September 1 issue of JAMA. Over 200 family, friends, national figures in gerontology, and NIH employees attended the ceremony naming the Gerontology Research Center laboratories in honor of Dr. Shock. A videotape release on the Zonderman JAMA paper, dealing with the fact that depressive symptoms are not linked to increased cancer morbidity or mortality, stimulated local interest and stories over Cable News Network, WBAL-TV (CH. 11) Baltimore, and Washington stations, and in The Baltimore Sun, Washington Post, Los Angeles Times, and a host of other papers. An earlier JAMA video release attracted similar attention to the work of Dr. Reubin Andres concerning smoking cessation and effects on body fat deposition.

Another major project undertaken by the IO neared completion this year. The 30th Anniversary of the Baltimore Longitudinal Study of Aging (spread over a two-year subject visit cycle) saw completion of an orientation videotape for the Study, a research update information kit for participants, a new popular booklet on the BLSA scheduled for October publication, and a meeting display to recruit scientific collaborators being planned.

IO staff handled some 115 media contacts resulting in stories appearing on TV and radio as well as in a number of newspapers or journals. In addition to the media cited earlier, stories appeared in the N.Y. Daily News, Medical Week, USA Weekend Magazine, Science News, Geriatric Consultant, Health and You, Geriatric Nursing, Longevity Magazine, Mature Outlook, and papers served by Maturity News Service. TV and radio reports were aired over WJZ-TV (Baltimore), WHYY (PBS), CTN-TV (Canada), the "Discovery" series on national cable television, Physicians Radio Network, and the Mutual Broadcasting Corporation.

Staff prepared and placed articles on GRC scientists, research results, awards, and appointments in a number of newspapers, newsletters, or journals, including The Havre De Grace Record, Harford Aegis, Carroll County Times, MGA Newsletter, and, Human Factors Society Newsletter. An extensive article was prepared for SOMA, Engineering for the Human Body, three research highlights written for the 1988 Special Report on Aging, and half a dozen articles were printed in The NIH Record. Internal communication efforts included monthly preparation of NIA's staff newsletter, GERON-NEWS, and three issues of PAGES OF THE AGES, an information letter for participants in the Baltimore Longitudinal Study of Aging. The Communications Officer also is editor of the Maryland Gerontological Association's newsletter.

More than 350 individuals ranging from high school students to foreign scientists and administrators were briefed via tours of the Baltimore Center or during outside speaking engagements by staff. Thirty-two such events were handled this year.

The Information Office's two permanent staff served as members or in leadership roles on a number of NIA and other committees or boards--Intramural Research Program Awards Committee, NIH Handicapped Employees Committee, PHS Handicapped Employees Advisory Committee, Baltimore Federal Executive Board Committee for Individuals with Disabilities, Maryland Gerontological Association Board of Directors, and the NIH Recreation and Welfare Association Board of Directors.

Annual Report Of The Research Resources Branch
National Institute on Aging

Technical Development Section

The installation of a major revision of the VMS operating system, used in the central computer system, allowed us to extend our cluster to include two new workstations. These systems contain the equivalent of a VAX 780 CPU, but depend on the central system for system software and disk storage. Higher speed modems were installed on the central system's eight phone lines. By allowing out-going calls to be originated by our systems, these modems will give our users access to DCRT's BitNet. Two large disk drives are on order. Training was received on our networking software, that will allow us to better control the increasing usage. Several PC's now transfer data, collected in the laboratories, to the central system via our network.

Postcript printers were installed and linked to our graphics software. An in-house typesetting program was expanded to provide table generation, and allow the inclusion of illustrations and graphs from MacIntosh's and older VAX-based software.

The development of general purpose cards, for IBM micro-computers, has allowed us to begin replacing obsolete microprocessor-based equipment throughout the GRC. Recently completed were replacements for equipment used in reaction-time testing in the BLSA, and free-recall testing in the LPC. A system to collect rat maze data is currently being developed. An extensive effort was given to the development of a PC-based system to collect calcium data, at moderate rates, for the LCS.

Much of the interfacing hardware for the VAX-based, extremely high speed, data acquisition system in the LCS has been completed. Third-party hardware for this project has been received, and software development is beginning. Two small Vax's have been ordered for similar applications.

Photography and Arts Unit

In addition to the normal production of negatives, slides, prints, and poster materials, the computer graphics system was expanded to include the development of new software for use in the Unit. This new software enables the Unit to produce graphs which closely match almost any type of variation presented to the Unit. Plans are being made to make this software available to any VAX user with the proper hardware. In addition, new hardware has been ordered for the VAX machine room, for use by anyone in the building.

An increased demand for service this past year was matched by an increased capacity from the computer graphics system. A considerable amount of time was saved, not only because some of the work was done by others outside the Unit, but also because the time expended on the computer is far less than the time needed for conventional processes. The MacIntosh continues to help the Unit add to the computer graphic's capability.

Library Unit

In FY '89, major emphasis has been placed on solving the chronic problem of shelf overcrowding. About 2,700 volumes of journals, which were duplicated, discontinued, or out of the collection scopes, have been withdrawn. This amounts to a total of 135 journal titles, which have been weeded out since 1985. In addition, journal volumes, ranging between 1976 and 1980, have been successfully shifted to the basement storage area. Currently, only post - 1980 journals are kept in the main stacks. With a monthly influx of 400 issues of journals, we soon will run out of space again. Conversion of journal backfiles to microfilm format will inevitably be needed.

Updated inventory indicates that there are 14,900 bound journals and 7,800 books in our collection. From this collection, 12,000 volumes are placed in the main stacks and 10,000 are stored in the basement.

Since its installation in late FY '88, the compact disk version of Medline has been well received by the scientists. Its monthly update and the availability of abstracts have made current biomedical research information easily accessible to the Center's scientists. An average of five people per day have used this facility, ranging from 15 minutes to 1½ hours each session.

Increased productivity and services have been evidenced by the following statistics:

° Even with the end-user searching facility available, 318 online computerized literature searches have been filled by the librarian, compared to 225 in the previous year.

° 3,018 volumes of journals were bound in FY '89, compared to 1,874 in FY '88.

° 1,018 interlibrary loans were serviced in FY '89, compared to 850 in FY '88.

° 700 books were loaned out in FY '89, compared to 400 in FY '88.

The ongoing project of updating data for the automated serial control system will be continued throughout the years to follow.

Animal Resources Section

The Animal Resources Section has maintained full accreditation with the American Association for Accreditation of Laboratory Animal Care (AAALAC) since 1977. During this past year, the ARS underwent an onsite inspection by AAALAC and was confronted with a proposed revocation of accreditation. AAALAC based this proposal on new guidelines, which nearly doubled the floor space requirements for rats; therefore, the caging system utilized in the Aging Wistar Rat Colony was no longer in compliance with AAALAC recommendations. In an extremely short and rigid time frame, the ARS developed a plan that included structural renovations in the Colony, acquiring a multitude of used caging, and depopulating the aging rat colony in a way that would not impede ongoing research, but still come into compliance.

On May 26, 1989, full accreditation was restored to the ARS by AAALAC. New caging has been ordered, which will provide a uniform, efficient housing

system for the aging rats and will allow a significant growth in the population, resulting in increased numbers of aging rats available for research.

Care was provided for an average daily population of 11,900 rats, 10,800 mice, 37 dogs, 35 rabbits, 14 non-human primates, and 2 domestic pigs. In addition to these stock animals, approximately 1,617 rats, 6,779 mice, 162 rabbits, 14 dogs, 4 non-human primates, and 10 pigs were received, housed and cared for by the ARS.

Approximately 273 aging rats were supplied to other research institutes throughout the country.

The ARS was instrumental in developing a proposal for GRC employee counseling with the Francis Scott Key Medical Center's Chemical Dependency Department.

The ARS staff is collaborating on 5 research projects with both in-house and guest investigators.

250 hours were provided in support of 72 aseptic surgical procedures.

Six ARS employees received outstanding awards, and five ARS employees received excellent awards.

Instrument Design and Fabrication Section

In the past year, along with the many 30 minute to 2 hour construction and repair jobs, the section designed, fabricated and installed equipment, such as the Photomultiplier tube and multi-filter holder adapters for microscopes, copper constant-temperature chambers, cell culture devices, electrophoresis trays, radiation shields, a multi-section mouse maze - for use with a video tracker and uses water for motivation, and other longer term projects.

ANNUAL REPORT OF THE LONGITUDINAL STUDIES BRANCH

NATIONAL INSTITUTE ON AGING

The FY1989 Annual Report of the Longitudinal Studies Branch (LSB) has two parts. First, is a description of the research activities of LSB staff carried out in relation to long term studies of aging, in particular, The Baltimore Longitudinal Study of Aging (BLSA). The LSB research described is organized into three broad categories: sensation and perception in aging; health/disease relationships in aging; and, statistical methodology in the analysis of studies of aging. The second is a description of staff activities in the management and overall direction of the BLSA: management of the BLSA participants, management of the BLSA data bank; and, management and overall direction of the BLSA.

Research within the LSB. Historically, the organization and function of the LSB was dictated by a staff-perceived need to establish an overall plan and set of operating principles for a major multidisciplinary study of human aging, the Baltimore Longitudinal Study of Aging (BLSA). Accordingly, a major task undertaken in the LSB is to establish overall scientific objectives for the BLSA that transcend the specific interest of the many scientists who work with the BLSA. Moreover, lack of central planning during the 30 year history of the Study had resulted in a number of projects continuing with little or no direct scientific supervision; many of these were left as a legacy to the LSB when it was created in FY1986. For each of these projects, aggressive efforts are underway to accomplish the following: bring the quality of the activity up to acceptable scientific standards; get the longitudinal story of the research told; reevaluate the scientific value of the project; and plan and implement new directions for the research in question. Current examples of such projects include clinical evaluation, hearing, distribution and amount of physical activity, pulmonary function, and reaction time and vision. During FY1989, LSB staff developed three research themes to organize and guide scientific activities within the LSB: sensation and perception and aging; health/disease relationships in aging; and, statistical methodology in research. In various combinations, the three research themes complement BLSA-related research conducted by scientists in other GRC laboratories.

Some research activities in the LSB are designed to promote and facilitate the work of many investigators who use the BLSA. Examples include studies on the morbidity and mortality of participants, diagnoses and medications used, and demographic information. In addition, new applications of statistics and methodology for longitudinal studies are developed which benefit many investigators.

The LSB has been in the process of evolution since its inception in Fiscal Year 1986. Over the first two years of operation, our primary goal was to establish a strong and reliable scientific base for the operation of the BLSA. This goal was set and progress toward it is described in this Annual Report. Perhaps most prominent, the major change developed for the BLSA physical examination program involved using the nurse practitioners and physician assistants for performing all the examinations starting in FY1989.

At the same time, staring in Fiscal Year 1986, ground work was being laid to create a foundation for research within the Branch. No specific research goals for the Branch were established prior to its creation except the general mandate to identify, evaluate and analyze underutilized longitudinal data.

During FY1989, the primary research goals of the LSB have been established; they reflect the principal goals of the BLSA, i.e. to describe scientifically the aging processes in man, and where possible, to explore and understand the underlying mechanisms that lead to aging. At present, the major research yield from the BLSA in the LSB and other laboratories is at the descriptive level. Our goal for the BLSA as a whole and for research in the LSB, in particular, is to explore more directly mechanisms of aging.

The research in the LSB falls into three main areas. First are studies of sensory and perceptual processes in relation to aging. Longitudinal changes in hearing and vision based on the BLSA have been reported. Cross-sectional differences in taste, smell, and other oral senses have been reported and studies of age changes will be initiated in FY1989. The major accomplishments in FY1989, in addition to the descriptive studies, include the preparation of scholarly reviews of the scientific literature in vision, hearing and the chemical senses, and preparation of a review paper dealing with practical interventions for problems of age losses in sensory and perceptual function is underway. Planning for initiation of research that will move us toward a better understanding of the mechanisms behind age changes in sensory function. The description of these research activities are in the FY1989 Annual Report, "Sensation and Perception in Relation to Aging."

The second focus for LSB research concerns the associations among health, disease and aging. Such associations are relevant to the Federal Government's consideration of health policy and the cost of health care. Our population is aging, and the elderly currently have a greater need for health care than younger individuals. How much will secular changes in longevity and the greater number of elderly affect health costs? This in part will be dependent on overall health, the amount of disease, and resulting morbidity.

We believe that the detailed medical and physiological information that is collected longitudinally in the BLSA offers a unique opportunity to examine how relationships among health, disease and age change over time. Central to our thinking are three concepts. First, development of and adaptation to chronic and acute disease are integral parts of the normal aging process. Second, the roles of disease in health and functioning at different points in the life cycle are not the same. Third, significant secular trends are occurring in health disease relationships. With these ideas in mind, we have initiated several studies to characterize the presence and extent of disease in BLSA participants. Results to date indicate that while individuals of all ages in the BLSA consider themselves to be healthy, they have a prevalence of diagnosed diseases that increases steadily with age. Mortality studies of the BLSA male participants show that they live an average of 8 years longer than the general white U.S. male population. Thus, BLSA participants include a long-lived group of men

who consider themselves to be healthy, but who have a significant prevalence of disease including heart disease, stroke and cancer. An understanding of the factors associated with longer life is of great scientific interest. To answer this question, risk factor analysis has been applied to the BLSA to investigate the effects of age-specific risk on all cause and specific cause mortality. Another reason that the BLSA is an interesting population for such studies is that it is well educated and responds to dictums for health improvement. Thus, the participants represent a natural study of the effects of improvement of health by changes in correctable environmental and social factors related to disease, e.g., hypertension, cholesterol, and fiber intake.

The major intellectual legacy of BLSA-related research is the demonstration that physiological changes occur in all organ systems with aging. These changes may have consequences for health, morbidity and mortality that are poorly understood. Moreover, as is well documented in BLSA research, it is difficult to separate age and disease processes as they affect physiology. To the extent that morbidity and mortality change over time, cross comparisons of changes in the physiological processes with changes in morbidity and mortality should provide an additional method for the estimation of physiological changes with age that are independent of disease.

Since BLSA participants have not been selected based on the presence or absence of specific disease processes, this allows us to study the natural history of development of many specific disease, as well as the physiological changes that occur with aging. The FY1989 Annual Report documents some LSB efforts to explore the association of pulmonary disease with physiology. Pulmonary function has long been known to decline with age. During the past year, this change has been shown to be predictive for ischemic cardiac disease in men. Likewise, declines in pulmonary function have been shown to be a predictor of increased mortality in all cases in males over 60 years of age, but not in younger men.

In summary, the description of health and disease relationships in the BLSA will help understand the effects of age specific risks and the effects of some classes of intervention in a select, educated population. At a more basic level, we believe results from our studies will aid in exploring age changes in host defenses in the future. Thus, a clearer description of the health-disease relationship in the BLSA will allow for more refined questions addressing the role of specific physiological, and molecular systems on long-term outcomes of mortality and morbidity. Results of the specific studies relating to these general statements are contained in the report on "Health-Disease Relationships in the BLSA."

The third area of research in the LSB concerns statistical methodology, and cuts across the two described above. The overall goal of this research is to improve our ability to describe aging processes at many levels and to develop and apply the mathematical theory and tools required to do so. In FY1989, significant contributions were made in the areas of age specific risk factors: development of a two component hierarchical model to describe between and within subject variance from longitudinal observations of individuals representing several cohorts; estimation of mortality rates in the BLSA; applications in biomedical applications of tests for more linear relationships; and, application of mathematical mixture models to help

identify subpopulations clusters within complex frequency distributions. The details are contained in the FY1989 Annual Report "Development of Statistical Methodology for the Analysis of Studies of Aging."

Management and Overall Direction of the BLSA. In tandum with its research activities, the LSB manages and operates the BLSA. When the Branch was created in FY1986, the duties of all personnel except for the Chief and the mathematical statistician were assigned to this activity. Currently, the duties of all LSB staff include both a research and service component. The staff directs operations related to participant management, data management, and perform a variety of duties to support the Associate Scientific Director, for the BLSA to provide overall leadership and direction to the study.

The major recommendations resulting from every scientific peer review of the BLSA including the most recent one in 1986, stress repeatedly the need to provide improved overall scientific direction to the BLSA, and to establish clear overall objectives and goals for the Study. These recommendations have their basis in two observations about the BLSA: the first is that both the subjects in the study and the scientists who use the study represent an open panel, inasmuch as the composition of both groups is changing over time; and, the second is that the important research questions posed in both longitudinal and cross-sectional research studies necessarily vary over time both for questions asked retrospectively as well as prospectively. A turnover in research volunteers and scientists over a very long period is a fact of life for this or any other longitudinal study. Thus, the overall direction and management of the study should center around managing the changes. The vitality of any scientific enterprise depends in part on the ability to ask new questions as knowledge advances, so a conscious effort should be made to preserve and nurture this quality of the scientific activity in the BLSA. Accordingly, the overall direction of the research involves balancing the interests of the scientists working with the BLSA to assure continuity of research, while at the same time incorporating new ideas and techniques into the study.

The special characteristics of the BLSA mentioned above--changes over time in scientists, research volunteers, and questions--dictate the management goals with respect to participants, data and research activities.

Participant Management. The specific requirements for participant management include development and implementation of a plan governing the duration of service and the number of active subjects in longitudinal studies. This plan must also allow us to obtain information about potential inactive and deceased participants. Accordingly, staff activities range from recruitment of new participants and management of the activities of the Study to obtaining and analyzing information about deceased BLSA participants. Goals for the size and composition of the sample consistent with BLSA objectives have been established, and all ongoing recruitment and retention activities are organized around those objectives. A pilot project to ascertain the health status of approximately 1000 applicants to the BLSA was initiated in FY1989. Its purpose is to increase the likelihood that new recruits will be able to fully participate in the BLSA. A process for obtaining and analyzing information from inactive participants was implemented in FY1989. Two systems for determining the underlying cause of

death of deceased participants are now in place. Procedures have been initiated that markedly reduce the level of the uncertainty of information about participants who die. An autopsy program has been established and all participants are invited to allow their bodies to be autopsied following their death. Aggressive efforts have been instituted to develop specialized protocols for the postmortem study of the cardiovascular, visual and auditory systems.

Data and Research Management. For data management, the most salient goal is to assure the availability and assessibility of data and information so that research questions may be addressed that span time and the interests of many scientists, including those not associated with the original studies. The management goals for the research activity include planning and implementing studies that transcend, as well as complement the interests of other scientists with the BLSA, e.g. studies of overall health and disease patterns of BLSA participants, and cause of death; managing the diverse and often conflicting goals and needs of the various scientists who work with the study; and, doing the overall long range planning for the BLSA, in a way that involves the active participation of the many scientists with the BLSA.

Work relevant to both goals has been carried out this year. For example, a major effort has been undertaken to review the overall use and quality of the data collected in the BLSA. Senior investigators from sister laboratories who use the BLSA have been asked to identify data sets which they believe will be of greatest use by themselves and to future investigators. The purpose of these activities is: to further develop overall goals and direction for the BLSA; to maximize the use of all data being collected; and, to identify ways of bringing new resources and talent to bear on the unmet needs of the BLSA. In addition, rapid developments in molecular biology are creating new opportunities for genetic and cellular studies using samples of stored materials, including sera, urine, and tissue from skin biopsies. We have initiated steps to develop research in these areas.

Administrative Highlights. The first IRTA fellow Dr. Jay Pearson joined the LSB staff in July 1989. The Medical Officer, Dr. E. Jeffrey Metter, was appointed to the faculty of Medicine, and both he and Dr. Larry Brant were appointed to the faculty of the School of Hygiene and Public Health at the Johns Hopkins University. A satisfactory resolution of the assignment and use of space on the third floor of the "B" Building of the Francis Scott Key Medical Center was achieved. At the same time a collaborative research project in pulmonary research was started with the hospital's General Clinical Research Center. Several collaborative arrangements were established or initiated. Within GRC, the sponsorship of the research on age differences in physical activity was transferred from the Applied Physiology Section of Laboratory of Clinical Physiology to the Longitudinal Studies Branch. The sponsorship of the Study of Risk Factors in Dementia was transferred from the Longitudinal Studies Branch to the Laboratory of Personality and Cognition.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00015-31 LSB

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

The Baltimore Longitudinal Study of Aging

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.)* *(Name, title, laboratory, and institute affiliation)*

J. L. Fozard	Chief, LSB & Asso. Scientific Director	BLSA, OSD, NIA
L. J. Brant	Mathematical Statistician	LSB, NIA
E. J. Metter	Medical Officer	LSB, NIA
N. W. Shock	Scientist Emeritus	NIA
C. Morrell	IPA, Loyola College, Baltimore, Statistics	
J. Pearson	IRTA Fellow	LSB, NIA
M. Tockman	IPA, School of Hygiene	JHU

Other Investigators: See next page

COOPERATING UNITS *(if any)*

Francis Scott Key Medical Center (FSKMC); National Institute of Dental Research (NIDR); Johns Hopkins University (JHU), University of Calgary (C), Oakland University (O), University of Maryland (UM).

LAB/BRANCH

Gerontology Research Center, Longitudinal Studies Branch

SECTION

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
14.95	5.0	9.95

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The Baltimore Longitudinal Study of Aging (BLSA), the NIA's major research program on human aging, has been conducted at the Gerontology Research Center since 1958. The overall scientific goals of the BLSA are:

To identify differences among individuals of different ages and changes that occur in the serial observations of these individuals with the passage of time; to determine the relative contribution of aging, disease processes, cohort effects and secular effects in producing observed differences and changes; and to establish the degree of interrelation and/or interaction among these factors.

To expand scientific understanding about predictors and risk factors for specific diseases and for other end points related to successes and failures of adaptation to aging processes.

Scientists working with BLSA are assigned to 11 sections of 7 laboratories in addition to the LSB. The Chief, LSB is the Director of the BLSA and LSB staff administer and manage the BLSA as well as conduct research with it.

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00621-01 LSB

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Sensation and Perception in Aging

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

J. L. Fozard	Chief	LSB, NIA
S. K. West	Guest Researcher, Wilmer Eye Institute	JHU
S. D. McLeod	Guest Researcher, Wilmer Eye Institute	JHU
F. Schieber	Guest Researcher, Dept. Psychology, Oakland U.,	MI
D. W. Kline	Guest Researcher, Dept. Psychology, U. of Calgary	
S. Gordon-Salant	Guest Researcher, Dept. Hearing & Speech Sci.	UM
J.R. Weiffenbach	Guest Researcher, Clinical Research Branch	NIDR

Other Investigators: See next page.

COOPERATING UNITS *(if any)*

Francis Scott Key Medical Center, Johns Hopkins University, Oakland University, University of Calgary.

LAB/BRANCH

Gerontology Research Center, Longitudinal Studies Branch

SECTION

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
8	3	5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Many individuals as they age lose some of their ability to interact with their environments. A major cause of this difficulty are with changes in primary sensory functions including vision, hearing, taste and smell, all of which are investigated in the BLSA. BLSA research resulted in the most comprehensive longitudinal studies demonstrating the individual changes in vision and hearing using standard techniques. It also resulted in landmark studies of age differences in judgments of taste thresholds and quality, and starting in FY1989 it will initiate the first studies of age changes in taste.

Starting in FY1989, the LSB began measuring the relationships between levels of sensory and perceptual functioning and self reports of functioning related to vision and hearing. To better understand underlying and coincidental components of the observed changes, the LSB is developing plans to investigate the physiological, anatomical and pathological changes that lead to age related declines in sensation and perception, thereby facilitating development of methods for treatment. The report contains summaries of five projects in vision, two in hearing, and one in taste.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00622-01 LSB

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Health/Disease Relationships in Aging

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	J. L. Fozard	Chief	LSB, NIA
	E. J. Metter	Medical Officer, BLSA	LSB, NIA
	L. J. Brant	Mathematical Statistician	LSB, NIA
	L. Fried	Guest Researcher, Physical Activity	JHU
	M. Tockman	IPA, School of Hygiene	JHU
	R. G. Bennett	Dept. of Medicine, School of Medicine	JHU
	B. J. Baum	Guest Researcher, Oral Physiology	NIDR

Other Investigators: See next page.

COOPERATING UNITS *(if any)*

Francis Scott Key Medical Center, Johns Hopkins University, NIDR

LAB/BRANCH

Gerontology Research Center, Longitudinal Studies Branch

SECTION

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
12	4	8

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

A number of projects from the Baltimore Longitudinal Study of Aging (BLSA) examine the changing health status of an aging individual in order to understand how disease interacts with normal aging to affect an individual's health and longevity. In such analyses is it necessary to define appropriate end points that can act as the dependent variable in research studies. For some purposes, the presence or absence of medically defined disease is the appropriate endpoint, particularly when examining the natural course of a pathological process or when examining the risk associated with certain factors (e.g. weight, blood pressure, or cholesterol) or mortality. The presence or absence of one or more diseases at various ages has different meanings. At another level, the outcome is health. Independent of age, health is so broadly defined that a variety of measures are needed examine different aspects of it. Disease can reflect health, but the presence of a disease process may not imply poor health. The presence of colonic cancer may be an index of poor health, but if a person were to be treated 10 years before and was considered "cured," it no longer would imply poor health in this individual. Similar observations can be made for other major diseases including heart disease and stroke. Contemporary concepts of health include functional ability and self reports of well being; thus, health is a multifactorial process.

In FY1989, progress was made on a number of studies leading to a more complete multidimensional functional definition of health in relation to disease and age. We report a number of studies of the distribution of diagnoses of disease and their relationships to aging and the reliability of its findings. We report a study of age changes in risk factors for mortality. We report on age changes in several physiological systems including pulmonary and oral physiology, and the relationship of changes in these systems to disease.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

PROJECT NUMBER

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00623-01 LSB

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Development of Statistical Methodology for the Analysis of Studies of Aging

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.)* *(Name, title, laboratory, and institute affiliation)*

P.I.:	Larry J. Brant	Mathematical Statistician	LSB, NIA
Others:	Christopher H. Morrell	IPA	LSB, NIA
	Jay D. Pearson	IRTA Fellow	LSB, NIA

COOPERATING UNITS *(if any)*

LAB/BRANCH

Gerontology Research Center, Longitudinal Studies Branch

SECTION

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.3	1.0	0.3

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The applied and theoretical development of statistical methodology is progressing in the areas of biological and epidemiological models, mixture models for describing age changes in distributions of biological markers of morbidity and mortality, multiple comparisons, survival analysis, and the design of experiments, each of which is applicable to longitudinal studies and other studies of aging. The research utilizes various types of statistical models - regression models for studying risk factors' association with outcomes observed in prospective studies, and mixed effects models for longitudinal data which consider both within- and between-subject variation in analyzing the repeated measurements for all individuals in the study population. Other techniques used include Bayesian, maximum likelihood and numerical computing methods. The methodology created provides original contributions to experimental testing associated with longitudinal studies, simultaneous comparison of various specified experimental effects, epidemiological study of disease states, survival or failure analyses of longitudinal observations representing growth, physical and mental disability, and other biological and behavioral changes in humans and animals. A major emphasis of this research project is on the development of methods which yield cogent yet easily understood results when applied to data.

ANNUAL REPORT OF THE LABORATORY OF BEHAVIORAL SCIENCES

NATIONAL INSTITUTE ON AGING

Significant Administrative Events

On April 30, 1989, two of our major research programs were forced to stop. The following paragraphs describe the chain of events which led to this avoidable outcome.

In 1986, in anticipation of restrictions on our nonhuman primate research, we initiated plans to modify our facilities to comply with projected changes in NIH regulations governing such research. After a thorough review of the commercially available equipment needed to implement our research, we identified the one vendor who was manufacturing a suitable recording system, and submitted a purchase order in February 1987, for a single, prototypic system. It was our plan to test this system, to modify it to suit our needs, and in collaboration with the vendor to develop a product that would be useful for our research needs. This purchase order lingered in the NIH (Bethesda) procurement system until May when it went to HHS for "authorization to make a contract award to an organization owned or controlled by a government employee." In June, this was returned by HHS for further "testing in the marketplace." By the end of July, our original research was confirmed, the vendor we had specified was the only person manufacturing a system adequate for our needs. However, NIH procurement never forwarded this information to HHS because the procurement agent "does not have time to write memos due to the end-of-the-year workload." Thus, our effort to maintain an orderly operation of our research program was thwarted.

In October 1987, we resubmitted our purchase order, and in November we were informed that the (same) purchasing agent "will get to it when she has time. It is on her desk with everything else." By February 1988, NIH procurement had reconfirmed its original finding, the vendor we had specified was the only available manufacturer. Finally, in March 1988, the purchase request was sent to HHS. In May 1988, our purchase request was finally approved and in the ensuing four months, we tested the prototype; identified specific changes that needed to be made; and in October 1988, submitted a purchase order for five recording systems that would satisfy our research needs.

Once again, our purchase request languished in NIH procurement until February 1989, when it went out for open bidding. By March 1989, five months after we had submitted our purchase order, we were advised that the purchase request might "have to be advertised for 45 days competitively" since the agent "had only advertised as sole source for 15 days and no companies [had] responded." However, in April, HHS agreed to accept the purchase order for consideration. The order is still "under consideration." We have been advised that the reason for this latest review is that the vendor is under investigation to determine whether any of the work on the system was done while he was on official duty. It is not clear why this investigation was not carried out when we ordered our prototype, nor is it clear why we were allowed to invest the time and effort in developing an improved system when this potential cloud could be lowered over our order for a useful system. In any case, not only do we not have a functional system, but also, since the end of the fiscal year is approaching, it is possible

that all of our efforts throughout this year will need to be repeated during the next fiscal year.

In the interim other events, in this case political, have intervened. In April 1988, we were advised by the Chairman of the GRC Animal Care and Use Committee (ACUC) that there was:

> . . . "virtual unanimous feeling by the Committee of your lack of good faith efforts to look for and implement in a timely manner, alternatives to the long-term chairing of non-human primates. As an aside, Committee members view the scientific rationale of the experiment highly favorably, even though this was not an important factor in our latest deliberations on your proposals."

Three days later we received a letter of apology from the Chairman, ACUC, for impugning our integrity; however, no reference was made to the observation that the quality or importance of our research was not an important factor in their deliberations.

Also, in April 1988, at my request, the Acting Scientific Director, NIA, sought a legal opinion from the NIH counsel regarding the GRC practice of requiring the GRC contract veterinarians to approve our purchase requests for animals. (It should be noted here that GRC does not have its own veterinarian; instead it uses veterinarians contracted from Johns Hopkins University to provide these services.) However, by delegating approval authority to these contractors, GRC is giving nonfederal employees authority to control federal research programs. The legal opinion on my request was subsequently received by the Acting Scientific Director and affirmed my judgement that it is inappropriate to delegate this authority to contractors. Nevertheless, it should be noted that this policy is still in effect. Thus, even though the NIH counsel has advised the Scientific Director that it is inappropriate to allow nonfederal contractors to judge intramural research, these agents still are authorized to disallow purchase orders for animals.

A second set of political events has occurred which is relevant to our research.

In July 1988, GRC was advised by the American Association of Accreditation of Laboratory Animal Care (AALAC) that GRC was not in compliance with AALAC's requirements for animal care and was in danger of losing its accreditation. AALAC is a private organization with no federal affiliation (despite the implications of its title), and with no legal status as a certification authority. In response to this threat, and in response to additional pressure for the Director, OACU, to comply with AALAC, the Scientific Director required us to terminate our scientific research activities in our nonhuman primate laboratory effective April 30, 1989. We have done so and are in compliance with this directive. However, it should be clear that the NIH counsel's opinion raises a serious legal question about the validity of requiring a federal laboratory to comply with regulations of a private agency, particularly since these regulations are not statutory. Thus, we wish to emphasize the following points:

1. LBS has made considerable effort to comply with anticipated federal regulations, even though these have not yet been implemented.

2. Our efforts have been largely thwarted by a number of delays in procuring needed equipment.

3. Our scientific program has been terminated in response to political pressures, even though there is some question about the legality of the requirements that have been imposed on us.

4. As was noted by the GRC/ACUC, and has been confirmed by the actions of the Scientific Director, NIA, and the Director, OACU, ". . . the scientific rationale [of our research] was not an important factor in [the] deliberations on [our] proposals."

During this year we were fortunate to have Professor George Adam, Chairman of the Department of Comparative Physiology, Budapest University, as a Visiting Scientist in LBS. Professor Adam also is Chairman of the Hungarian Association for the Dissemination of Science, an organization which is equivalent to our American Association for the Advancement of Science. During his tenure here, Professor Adam consulted with a number of scientists in LBS and NIH, and with university scientists at Johns Hopkins University School of Medicine and the Pennsylvania State College of Medicine. He also collaborated in studies which are still continuing in LBS. In addition, he also took advantage of our library facilities to develop material for a book he is writing. As a result of his visit here, we are maintaining an active, collaborative research program with his faculty.

Scientific Accomplishments

Behavioral Medicine Section (BMS)

There are two major program areas in BMS: the first includes a broad range of studies designed to better understand the role of behavioral factors in pulmonary function, and the interaction between pulmonary function and cardiovascular function; and the second is the completion of a major program on the effectiveness of behavioral treatments of incontinence in the long-term care setting.

An extensive, cross-sectional study of pulmonary and cardiovascular function at rest and during a standardized breathing task has been completed. This study included 120 people, stratified for sex, exercise, smoking and age. Although data analyses are not complete, preliminary analyses have shown that earlier reports of age-related declines in lung volume (minute ventilation and tidal volume) are not present when the group is stratified for sex, smoking and exercise. Other analyses have confirmed earlier findings that cardiac stroke volume and cardiac index increase with age with no change in heart rate.

Considerable progress has been made in the development of an ambulatory monitor which records breathing rate and tidal volume in man. This development is of potential clinical importance since there are no data on respiratory function in natural settings, yet the treatment of various respiratory disorders is based

on the assumption that laboratory studies of pulmonary function accurately reflect in vivo performance; we know from considerable research over the last 25 years that cardiac and blood pressure performances in vivo differ considerably from those obtained during laboratory studies. This year we developed a microprocessor that records breathing rate and tidal volume in ambulatory people. We have studied 20 subjects ranging in age from 21 to 62 years: each subject was studied for 24 to 48 hours while carrying out his normal activities. Findings from these subjects indicated that minute ventilation is consistently higher during daytime activities than during nighttime sleep: these differences are primarily mediated by diurnal changes in tidal volume since breathing rate does not show consistent day/night differences. On the other hand, the coefficient of variation in breathing rate is higher during the day than at night, whereas there is no consistent diurnal pattern in variability of tidal volume.

Last year we completed data collection from a three-year study of behavioral treatment of urinary incontinence in long-term care patients. We found that behavioral treatment of urinary incontinence was effective in reducing the frequency of incontinent epidsodes. Since incontinence among nursing home residents is, in part, related to the inability of these people to toilet themselves, a major portion of any effective treatment program is maintenance. However, it should be clear that maintenance in this case means changing staff behaviors so that the patients will be toileted. Therefore, a major portion of our research effort was to develop and implement a staff management program which enabled us to show that it was possible to organize nursing staff behaviors so that the residents were consistently and reliably toileted. Some of the major findings from our program are: (a) following treatment for urinary incontinence, the subjects were about 10% dryer than during baseline; (b) this improvement was maintained throughout the follow-up period so that at three months post-discharge the subjects continued to be 10% drier than during baseline; (c) the staff management program was effective in maintaining nursing performance since about 80% of the scheduled toiletings were completed; (d) there was a significant reduction in decubitus ulcers in a group of subjects with severe motor impairments who need lifts to transfer from a bed to another location. Since decubiti are not only clinically significant problems, but also major cost factors in long-term care, this improvement is highly significant; and (e) we were able to show that a relatively inexpensive fiber diet could improve stool quality and stool production in a group of residents selected because they had significant bowel disfunctions. Since this project was jointly funded by NIA and HCFA, a complete report based on our findings will be submitted to HCFA soon.

Behavioral Physiology Section (BPS)

This section supports three major research programs:

1. Age differences in thermoregulation

2. Mechanisms underlying the central neural regulation of the cardiovascular adjustments to exercise

3. Diurnal hemodynamic patterns

We have been studying age differences in thermoregulation in the rodent for a number of years, and have reported consistent declines in body temperature as well as in response to a cold challenge (thermoregulation) in aged mice. Studies this year have been directed at determining the mechanism for this age-related decline. Studies of metabolic heat production have shown that adult, C57BL/6J mice produce more heat in response to a cold challenge than do old animals; since old animals can respond to mild/cold (18°C) but not to more severe cold (6°C), it is clear that the old animal can detect cold as well as the adult animal, but it cannot generate additional heat at the lower temperature.

Preliminary data suggest that at room temperature, the brown adipose tissue of adult and aged mice contain similar amounts of HSP70 mRNA (one of a class of proteins known as "heat shock" protein); however, after cold exposure, adults show a large amount of induced HSP70 mRNA while aged animals show only trace amounts. Not only are there age differences in induced HSP70 mRNA in brown adipose tissue, but also there are differences in brain and liver tissues: thus, it is not yet clear whether the differences noted here are specific to thermoregulation or whether these are generalized effects which may have only modest relevance to thermoregulation. One line of evidence that suggests that these effects may be generalized rather than specific is another preliminary finding: thermogenin mRNA in brown adipose tissue is greater in adult than in aged mice; and after cold exposure, both adult and aged mice show induction of thermogenin mRNA.

As scientific knowledge has accumulated, scientists have become more and more specialized. Thus, areas of research that may once have overlapped have drawn apart to the point that their common roots have been forgotten. Two such areas of science are exercise research, and research on the central nervous system.

Exercise was once considered a basic behavior which underlaid natural selection: an animal's capacity to survive rested on its ability to hunt or to evade predators successfully. The central nervous system was recognized as the morphological basis for all behavior including, of course, exercise. As physiological research in both of these areas became more technical, the integrative and regulatory principles linking the physiological research to behavioral research was ignored. The main focus of research in this program in LBS is to provide a scientific context for rapprochement between behavioral principles and physiolgical principles: in particular, our research has been directed at yielding a deeper understanding of the central neural regulation of the circulation, and we have used the cardiovascular adjustments to exercise as a model for analyzing these mechanisms.

Research completed this year has confirmed earlier work in our Laboratory which showed that it is possible to train monkeys to attenuate the tachycardia of exercise. Specifically, we showed that animals can be taught to dissociate the cardiovascular response to exercise, from the somato-motor response to exercise: they can learn to attenuate the tachycardia of exercise while maintaining the same or greater levels of physical work. Our current findings have added to this knowledge by showing that when animals are regulating their heart rates, they are performing the same levels of physical work at lower levels of cardiovascular work. In addition, our findings also have shown that the animals can perform the exercise task even when one or another aspect of their autonomic nervous

system is blocked pharmacologically. This last finding shows that the central neural regulation of the cardiovascular system is organized to accomplish the task the subject is performing. Thus, when one or another neural pathway is blocked, the behavior is maintained although the specific mechanism by which the behavior is accomplished may be different. A corollary of our findings is that the physiological concept of central command is closely related to the behavioral concepts of learning and memory. Since a great deal is known about learning and memory, this knowledge should be integrated into physiology.

The third area of research in this program is the analysis of the nocturnal patterns of hemodynamic change. Earlier and current research in this program has shown that at night, the monkey's cardiac output and central venous pressure falls while total peripheral resistance rises. Studies with sympathetic blocking drugs, with angiotensin II blocking agents, and with vasopressin blockers have shown that the fall is not the result of selective redistribution of blood volume, and in fact, when either the sympathetic nervous system or angiotensin II release is blocked pharmacologically, the hemodynamic effects noted above are exacerbated. Vasopressin in the intact animal has no effect on nocturnal hemodynamics. The only mechanism which appears to explain all of these phenomena is that plasma volume falls at night, and that the hemodynamic adjustments noted here are compensatory effects secondary to this fall. Since the fall in cardiac output is mediated by a fall in heart rate, we investigated the role of heart rate in this phenomenon by preventing the nocturnal fall in heart rate via atrial pacing. When heart rate is maintained at normal daytime levels, cardiac output still falls; however, under these conditions, the fall is mediated by an attenuation in stroke volume.

Additional research in our Laboratory has shown that the effect we have observed in monkeys, and that others have reported in rodents and man, is not present in the dog. In this species the nocturnal fall in heart rate is balanced by a rise in stroke volume so that cardiac output is conserved and total peripheral resistance does not change at night. We believe that this species difference is related to behavioral differences: rodents and primates have diurnal cycles of sleep and activity, whereas dogs, like other carnivores, have very different sleep/activity cycles characterized by occasional bursts of activity during hunting or eating, and extended periods of sleeping. The findings from this program may be clinically important as well as physiologically significant:

(1) The fact that plasma volume falls overnight suggests that plasma protein concentration may rise; if this is true, then it is possible that many long-acting drugs which are bound to proteins in the blood may show a nocturnal increase in concentration.

(2) It is well-known that various, clinically significant cardiovascular events such as strokes, myocardial infarctions, sudden death, angina pectoris, and silent ischemic episodes are more likely to occur either in the morning upon arising, or at night while the person is asleep. Many of the morning events are probably associated with the increase in sympathetic nervous activity; however, the nocturnal fall in plasma volume and the attendent hemodynamic changes noted here may contribute significantly to these events.

(3) In our studies of heart rate pacing, we also observed a week-to-week change in cardiac function characterized by a shift of the Starling curve to the right (in the direction of heart failure) which worsened throughout the night and improved in the morning. Since the relative rate at which we set our pacemaker is within the range set for many patients, it is possible that some of these patients may also show abnormal, noctural, cardiac patterns.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00063-21 LBS

PERIOD COVERED
October 1, 1988 to September 31, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Learned Modification of Visceral Functions in Animals

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Bernard T. Engel	Chief, Laboratory of Behavioral Sciences	LBS, NIA
OTHERS:	David E. Anderson	Chief, Behavioral Medicine Section	LBS, NIA
	Mark I. Talan	Medical Officer (Research)	LBS, NIA

COOPERATING UNITS *(if any)*
Depart. Comparative Physiology, Budapest Univ., Hungary (G. Adam, G. Bardos); Depart. Cardiology, Francis Scott Key Medical Center (P. Chew); Division of Digestive Diseases, Francis Scott Key Medical Center (M. Crowell, W. Whitehead)

LAB/BRANCH
Laboratory of Behavioral Sciences

SECTION
Behavioral Physiology Section

INSTITUTE AND LOCATION
NIA, NIH, Gerontology Research Center, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.2	1.3	2.9

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of this project is to investigate the role of the central nervous system in behavior. In some experiments we are studying the extent to which the cardiovascular system can be modified be instrumental conditioning. In other experiments, we are examining diurnal patterns of hemodynamic performance and intestinal motility.

We have established that learned modification of the cardiovascular adjustments to exercise results in better cardiac efficiency at comparable levels of exercise. Data also indicate that animals that learn to slow heart rate while exercising, acquire a motor skill which utilizes any available peripheral, physiological mechanism.

We have demonstrated that the normal diurnal hemodynamic pattern consists of an overnight fall in cardiac output mediated primarily by a decrease in heart rate and accompanied by an overnight rise in total peripheral resistance. We have reported a number of experimental results indicating that this diurnal hemodynamic pattern reflects an overnight reduction in total plasma volume.

Experiments to assess diurnal variation and associated behavioral aspects of intestinal motility are in progress.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00072-04 LBS

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Behavioral Assessment and Treatment of Incontinence in Nursing Home Residents

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: Bernard T. Engel Chief, Laboratory of Behavioral Sciences LBS, NIA

OTHERS: Kathleen A. McCormick Nurse-Director (Research) LBS, NIA
Andre M. Hawkins Psychologist LBS, NIA

COOPERATING UNITS *(if any)*

Univ. Pittsburgh School of Medicine, Pittsburgh, PA (L. Burgio); Francis Scott Key Medical Center (A.S. Scheve); Health Care Financing Administration; Office of the Surgeon General of the United States

LAB/BRANCH

Laboratory of Behavioral Sciences

SECTION

Behavioral Medicine Section

INSTITUTE AND LOCATION

NIA, NIH, Gerontology Research Center, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.7	.15	1.55

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Incontinence is a major reason for institutionalizing elderly persons and is common in nursing homes. This project is designed to evaluate the effectiveness of behavioral treatment techniques as well as staff management techniques.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00073-01 LBS

PERIOD COVERED

October 1, 1988 to September 31, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Physiology of Thermoregulation and Aging in Rodents

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Mark I. Talan	Medical Officer (Research)	LBS, NIA
OTHERS:	Bernard T. Engel	Chief, Laboratory of Behavioral Sciences	LBS, NIA
	Hal Tatelman	IRTA Fellow	LBS, NIA

COOPERATING UNITS *(if any)*

Laboratory of Cellular and Molecular Biology, NIA (D. Ingram); Univ. of California San Diego Medical School (F. Gage); Laboratory of Molecular Genetics, NIA (N. Holbrook)

LAB/BRANCH

Laboratory of Behavioral Sciences

SECTION

Behavioral Physiology Section

INSTITUTE AND LOCATION

NIA, NIH, Gerontology Research Center, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.6	1.65	1.95

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of this project is to investigate age-related changes in thermoregulation and to examine the physiological mechanisms underlying these changes.

We have demonstrated that aged mice have diminishing cold tolerance and are not able to adapt to repeated cold exposure. The cause of these age-related aberations in thermoregulation appears to be a reduction in metabolic heat production. The results from a number of experiments suggest that the mechanism responsible for diminished metabolic heat production in response to cold is an age-related change in brown adipose tissue.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00074-01 LBS

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Behavioral Factors in Transient Myocardial Ischemia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: David E. Anderson Chief, Behavioral Medicine Section LBS, NIA

OTHERS: Jennifer A. Haythornthwaite IRTA Fellow LBS, NIA

COOPERATING UNITS *(if any)*

Division of Cardiology, Francis Scott Key Medical Center, Baltimore, MD (S. Gottlieb)

LAB/BRANCH

Laboratory of Behavioral Sciences

SECTION

Behavioral Medicine Section

INSTITUTE AND LOCATION

NIA, NIH, Gerontology Research Center, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.7	1.0	0.7

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Transient myocardial ischemia is a manifestation of coronary heart disease. In recent years, episodes of silent (i.e., nonpainful) ischemia have been observed in the context of relatively low heart rates, suggesting mediation by acute coronary vasoconstriction rather than increased myocardial demand. The present project addresses the question of whether such episodes are triggered by specific behavioral interactions. A program has been developed for a portable computer which enables patients to regularly record behavioral interactions during periods of cardiac monitoring with a minimum of intrusion into daily activities. Identification of specific behavioral antecedents of episodes of transient myocardial ischemia could lead to the development of nonpharmacological interventions for their prevention.

PROJECT NUMBER

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00600-01 LBS

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Respiratory Factors in Blood Pressure Regulation

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: David E. Anderson Chief, Behavioral Medicine Section LBS, NIA

OTHERS: Kathleen A. McCormick, Nurse-Director (Research) LBS, NIA
Bernard T. Engel, Chief, Laboratory of Behavioral Sciences LBS, NIA

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Behavioral Sciences

SECTION

Section on Behavioral Medicine

INSTITUTE AND LOCATION

NIA, NIH, Gerontology Research Center, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.7	0.6	2.1

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Previous studies with animals have shown that blood pressure response to high sodium intake is correlated with sustained respiratory suppression resulting from aversive behavioral conditioning. The present project seeks to identify individual differences in tonic ventilation of human subjects as a predictor of individual blood pressure response to high sodium intake. A respiration monitor has has been devised which records tidal volume and breath-rate of ambulatory subjects in the natural environment. The monitor integrates methodology of inductive plethysmography with a portable microprocessor which can record respiratory measures continuously for days. Studies have shown significant differences between individuals in 24-hour breathing rate, tidal volume, and minute ventilation. Analysis of diurnal variations show that tidal volume and minute ventilation are significantly greater during the day than at night in all subjects studied to date but there are no consistent within-subject day-night differences in breathing frequency. By contrast, the within-subject coefficient of variation (sd/mean) of breathing frequency is significantly greater during the day than at night, while tidal volume and minute ventilation show no consistent day-night differences in this measure of variability. These observations suggest differential physiological control of rate and tidal volume and provide the basis for continued investigation of respiratory correlation of variations in blood pressure response.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 AG 00601-01 LBS

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Exercise Influences in Aging Man

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Kathleen A. McCormick	Nurse-Director (Research)	LBS, NIA
OTHERS:	David E. Anderson	Chief, Behavioral Medicine Section	LBS, NIA
	Bernard T. Engel	Chief, Laboratory of Behavioral Sciences	LBS, NIA
	Ricardo A. Brown	IRTA Fellow	LBS, NIA

COOPERATING UNITS *(if any)*
Dept. of Medicine, Francis Scott Key Medical Center and The Johns Hopkins School of Medicine (Fred Wigley); Baltimore Longitudinal Studies Branch, NIA (James Fozard) (Edward Lakatta, LCS, NIA)

LAB/BRANCH
Laboratory of Behavioral Sciences

SECTION
Behavioral Medicine Section

INSTITUTE AND LOCATION
NIA, NIH, Gerontology Research Center, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.0	.75	.25

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project is concerned with experimental differentiation of cardiopulmonary deficits associated with aging versus pathophysiology. One study has shown that longitudinal training in control of muscle associated with breathing has beneficial effects on cardiopulmonary function. A second study assesses the utility of Doppler technology in studies of the effects of aging on cardiac functions. A third project investigates the effects of sleep disturbance on behavior and activity of individuals with chronic diseases. Together, these studies define age-related cardiopulmonary function changes associated with training influences versus disease.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 AG 00602-01 LBS

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Diaphragmatic Breathing Challenge in Man

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Kathleen A. McCormick	Nurse-Director (Research)	LBS, NIA
OTHERS:	David E. Anderson	Chief, Behavioral Medicine Section	LBS, NIA
	Bernard T. Engel	Chief, Laboratory of Behavioral Sciences	LBS, NIA
	Ricardo A. Brown	IRTA Fellow	LBS, NIA

COOPERATING UNITS *(if any)*
Sleep Lab, Francis Scott Key Medical Center and The Johns Hopkins University School of Medicine (Phil Smith); Baltimore Longitudinal Studies Branch, NIA (James Fozard)

LAB/BRANCH
Laboratory of Behavioral Sciences

SECTION
Behavioral Medicine Section

INSTITUTE AND LOCATION
NIA, NIH, Gerontology Research Center, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.00	1.25	0.75

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project is concerned with the integration of behavioral principles with physiological measurement for application to clinical medicine. Subjects are normal volunteers recruited from the BLSA and/or the community who are studied to provide normative data on the response of persons with normal hearts and lungs to a breathing challenge using their diaphragm. Comparative groups are patients selected from various medical clinics who are characterized and compared with the normal volunteers. If the performance of those persons with pathophysiology is determined to be less than normal, volunteers or groups of persons who are high-performers, behavioral techniques can be applied in training subjects to breathe diaphragmatically and improve cardiopulmonary response. If the breathing challenge is an exercise, then the comparison of this test to standard graded-exercise tests could improve the description of cardiopulmonary performance in normal aged persons and those with pathophysiology.

ANNUAL REPORT OF THE LABORATORY OF BIOLOGICAL CHEMISTRY

NATIONAL INSTITUTE ON AGING

The Laboratory of Biological Chemistry conducts fundamental and original research on the molecular basis of life processes important to our understanding of aging and the pathophysiology of age-associated disorders. The Laboratory's scientists investigate the mechanisms regulating intracellular and extracellular environments; metabolism; structural integrity; cell division, growth and differentiation; physiological functions; and vitality. Particular attention is paid to the role of hormones and growth and differentiation factors, and signal transduction mechanisms eliciting cellular responses.

Significant Administrative Events

The Laboratory of Biological Chemistry is in a transition period since the death of its Laboratory Chief, Dr. Bertram Sacktor, in the summer of 1988. The Section Chief of the Membrane Biology Section, Dr. Jeffrey Froehlich, became Acting Laboratory Chief at that time. Dr. Froehlich left the Gerontology Research Center for a 6 month period in May of 1989 to continue collaborative studies with the staff at the Max Planck-Institute FÜr Biochemistry in Frankfurt, West Germany. Since May, the Scientific Director of the Gerontology Research Center, Dr. George Martin, has been Acting Chief of the Laboratory. Dr. Charles Filburn, Research Chemist, currently plans to spend between 9 and 12 months at Johns Hopkins University working with Dr. Peter Pedersen of the Department of Biological Chemistry starting in October of 1989. Dr. Filburn plans to initiate studies that will involve the cloning and sequencing of ATP binding proteins. Dr. James Kinsella, Research Physiologist, plans to work with Dr. Jacques Pouyssegur, CNRS, University of Nice, for one year starting in the Spring of 1990. Dr. Kinsella will pursue studies on the regulation of plasma membrane transport proteins expression.

The future direction of the Laboratory is unclear at this point, but the Laboratory may emphasize Neurobiology and/or Cell Biology. The selection of a new Laboratory Chief is in a preliminary stage and a Search Committee has not been organized. Some current staff may join other Laboratories in the Institute.

Scientific Accomplishments

<u>The Regulatory Mechanisms Section</u> examines how mineral metabolism is regulated at the cellular, subcellular and molecular biology levels and studies the mechanisms by which these systems become altered in age-related osteopenia and osteoporosis. Cell culture lines of bone, kidney and intestine are developed as models and exploited. In addition, various cell and membrane preparations are used to investigate the control of intracellular pH, calcium and

ion flux, factors essential for cell division, growth, differentiation and metabolism. Signal transduction mechanisms in mediating cell responses are investigated as well as the changes that occur in these systems during the aging process.

1. **Effect of L-triiodothyronine on Na^+-H^+ exchanger activity in cultured opossum kidney (OK) cells.** We demonstrated that thyroid hormones stimulated Na^+-H^+ exchanger activity in OK cells in a time and dose-dependent manner without changing Na^+-dependent glucose transport. Thyroid hormones increased the maximum velocity (V_{max}) for Na^+ flux but did not alter the apparent affinity (K_m). Thyroid treatment did not alter cell number, DNA, or protein per dish. These results indicate that thyroid hormones can stimulate Na^+-H^+ exchanger activity directly in a continuous cell line without apparent changes in pH_i, cellular hypertrophy or hyperplasia. These studies may be useful for examining the expression of specific plasma membrane proteins and in the control of fluid metabolism under pathophysiological conditions.

2. **Differentiation of intestinal crypt cells to villus cells.** An intestinal cell line, IEC-6, resembles crypt cells by both morphological and immunological criteria when grown on plastic dishes. When IEC-6 cells are plated onto dishes covered with a mixture of extracellular proteins (Matrigel), the cells stop dividing and differentiate into cells resembling intestinal villus cells. These changes reflect the changes that occur normally in the intestine, i.e. crypt cells are actively dividing and migrate up the villus where they stop dividing and change morphologically and functionally. We found that some individual components of Matrigel, i.e. laminin, fibronectin or collagen type IV, did not alter the growth or morphological characteristics of the cells. The cells respond to atrial natriuretic factor and heat stable enterotoxin by increasing cGMP production. The regulation of fluid reabsorption in the small intestine by different hormones through cAMP and cGMP dependent mechanisms in crypt and intestinal cells are important in the understanding of normal and pathological changes in the gut.

3. **Dopamine (DA) increased cAMP production and decreased phosphate uptake into cultured opossum kidney cells.** DA decreased Na^+ dependent phosphate uptake, but not Na^+ independent phosphate uptake in OK cells. DA also increased the cAMP level. Both the increased cAMP levels and the decreased phosphate transport were dependent upon DA binding to DA_1 receptors and not DA_2 or adrenergic receptors. DA dependent cAMP production in OK cells was independent of PTH dependent cAMP production. Forskolin increased the efficiency and the potency of DA. Our studies suggest that the increase cAMP production activated specific protein kinases leading to phosphate transport inhibition. Dopamine dependent phosphaturia is likely caused by decreased Na^+ dependent phosphate uptake in renal proximal tubule.

4. **Dopamine decreases sodium uptake in OK cells.** Dopamine (DA) is an endogenous catecholamine which has a vasodilatory effect on both

renal and general circulation. In addition, DA also inhibits Na^+ reabsorption in the renal proximal tubule by mechanisms which are not completely understood. The Na^+-H^+ exchanger is the major route for salt reabsorption in the proximal tubule and thought to be controlled by a number of protein kinases. We therefore examined OK cells to determine whether DA acting through cAMP may inhibit Na^+-H^+ exchanger activity. After incubation of OK cells with DA for 60 min, the initial rate (2 min) of amiloride-sensitive Na^+ uptake was decreased by 33% when compared to untreated cells. DA had no effect on amiloride-insensitive Na^+ uptake. This study shows that OK cells may be a useful model to study the physiological role of dopamine and other factors on proximal tubule Na^+ transport and on regulation of blood pressure.

5. **The role of renal disease in age-associated biochemical changes.** The possible influence of renal disease on functional parameters in various organs was evaluated by studying female rats from the GRC Wistar colony. Unlike their male counterparts; old female rats exhibited only a moderate degree of renal disease, with comparatively smaller increases in BUN, serum creatinine and immunoreactive PTH. However, a marked increase in proteinuria, a sensitive index of the onset of renal disease, was observed and was comparable to measurements in old male rats. Decreases previously found in old male rats in the activity of the Ca^{2+} pump in cardiac sarcoplasmic reticulum, serum 1,25-$(OH)_2$-vitaminD_3, duodenal cell Ca^{2+} transport and adrenergic stimulation of Ca^{2+} efflux from parotid acinar cells were not found in old female rats. Desensitization of renal cortical PTH responses was found and, unlike that in male rats, appeared to be independent of severity of renal disease but may be related to serum levels of PTH. These results indicate that absence of severe renal disease is associated with absence of decreases in functional parameters of some tissues and raises the questions of whether decreases observed in male rats are secondary to renal disease and are not universal but sex-dependent.

6. **Age-related changes in in vitro transcription rates of genes encoding message for GTP-binding proteins.** Previously, we quantitated the levels of proteins and messages for Gs(stimulatory) and Gi(inhibitory), two subclasses of GTP- binding proteins, in kidney of young and old rats. Changes in the protein and message levels of Gs or Gi during aging could explain the loss of the kidney response to parathyroid hormone in senescent rats. Our experiments measuring transcription rate showed there is an age-related decline in synthesis rates of Gs and Gi message. It appears that the loss of hormone response in aging can be related to changes in activity of genes producing the proteins involved in hormonal action.

7. **Ammoniagenesis in isolated glomeruli of young and old rats.** Ammoniagenesis was measured in glomeruli isolated from 6 and 24 mo GRC Wistar rats. Ammonia production in the proximal tubule, but not in the glomerulus, is enhanced during metabolic acidosis. We also found a correlation between glomerular ammoniagenesis and the

severity of the renal failure (serum creatinine and BUN). Ammoniagenesis in other nephron segments was unchanged in rats with varying degrees of renal failure. It is unclear whether or not this change in glomerular function reflects some important underlying mechanism related to renal failure.

8. **Effect of glucocorticoids on phosphate dependent glutaminase activity.** Brain, small intestine, and kidney all contain the same isozyme for phosphate dependent glutaminase (PDG). In the kidney as in the other tissues, PDG converts glutamine to glutamate and ammonium. During metabolic acidosis: glucocorticoid levels, PDG activity, and ammonium excretion all increase. Glucocorticoids also increase ammonium excretion from the kidney independent of acidosis. In the brain, glutamine is synthesized and released by astrocytes where it is taken up by specific neurons. Glutamine serves as the precursor for the amino acid transmitters glutamate and -aminobutyric acid (GABA). Abnormalities in glutamate metabolism have been implicated in a number of neurological diseases including epilepsy, Huntington's disease, olivopontocerebellar atrophy, and Alzheimer's disease. In addition, glucocorticoids are known to have both trophic and degenerative effects in the brain. We measured both the enzyme activity and the expression of PDG with an anti-PDG antibody in brain, intestine, and kidney from control, acidotic, and glucocorticoid treated rats. Both metabolic acidosis and glucocoticoids increased ammonium excretion from the kidney, but only acidosis increased the activity and the expression of renal PDG. Neither glucocorticoids nor acidosis increased the activity or the expression of PDG in the brain or small intestine. We concluded that 1) renal PDG is under different control than brain or intestinal PDG; 2) glucocorticoids alter ammonia metabolism through a PDG independent mechanism; and 3) glucocorticoid's effects on the brain are not likely to be due to alterations in PDG activity.

9. **Calcium metabolism in skin fibroblasts isolated from Alzheimer's disease patients and age matched controls.** Skin fibroblasts from Alzheimer's patients have been described to contain lower resting free intracellular Ca^{2+} but greater total Ca^{2+} when compared to age matched controls. In response to mitogens, cellular free Ca^{2+} is reported not to increase to the same extent as controls. We found in a preliminary study of individual cells from skin fibroblasts isolated from young adults, Alzheimer's patients and age matched controls that there were no differences in resting Ca^{2+} (range: 50 to 80 nM) and in response to 5% serum among the different groups. We examined three different cell lines in each group and observed considerable cell to cell heterogeneity. These preliminary data suggest that a generalized defect in intracellular Ca^{2+} does not occur in fibroblasts from patients with Alzheimer's disease.

10. **Purinergic regulation of cytosolic Ca2+ in bone cells.** Regulation of cyclic nucleotide and Ca^{2+} metabolism in bone cells (UMR-106) by calciotropic hormones, eicosanoids, and growth factors

is an area of intensive investigation by many laboratories. We previously confirmed stimulation of cytosolic Ca^{2+} by PTH in rat osteosarcoma cells but also showed similar effects by neurotransmitters and ATP or ADP. The Ca^{2+} response following activation of P2y purinergic receptors was much greater than previously studied effects of agonist on bone cells. The response was dependent upon stimulation of phosphoinositide metabolism, with marked generation of IP3 and IP4 that mobilization both intracellular and extracellular Ca^{2+}. Unlike other agonists studied, no change was observed in levels of cyclicAMP. While the physiological significance of purinergic regulation of bone cell Ca^{2+} metabolism is uncertain, it will serve as a useful tool in understanding the roles and possible crosstalk of the second messengers that mediate the effects of various agonists that regulate bone cell function.

11. **Regulation of protein kinases in cultured kidney cells**. Most agents that regulate renal cell function through generation or perturbation in second messengers ultimately exert their actions through stimulation of protein kinases A and C. Thus establishing and characterizing the degree of regulation of these protein kinases is essential to understanding the overall mechanisms of regulation. We studied both PTH and purinergic regulation of protein kinase activity in cultured kidney cells from the opossum kidney cells (OK). PTH was found to be a potent, rapid, and persistent activator of protein kinase A, but a much less potent and only transient activator of protein kinase C. PTH antagonist were found to differentially inhibit activation of protein kinase A compared to protein kinase C. ATP, acting through a purinergic receptor, was a much more potent activator of protein kinase C, but had negligible effects on protein kinase A. These studies show that protein kinases in kidney cells are subject to differential regulation by agonists that regulate phosphoinositide and cyclic nucleotide metabolism.

12. **Purification of duodenal vitamin D receptor**. Vitamin D regulates a number of important physiological functions by altering gene activity. Vitamin D binds to specific sites on DNA that control numerous physiological functions. Vitamin D receptors were extracted from rat duodenum and purified by various methods. This partially purified receptor (several thousand fold purification) can still bind vitamin D. The study of purified D receptor binding to DNA will be useful for clarifying the mechanism of vitamin D action.

The Membrane Biology Section seeks to determine the chemical nature and sequence of intermediate reactions controlling the movement of cations through ionic channels and pumps. The behavior of these systems with respect to energy utilization and energy transduction, ion selectivity, gating mechanisms, and sensitivity to hormones and pharmacological agents are characterized. Studies concern how the affinity, capacity and selectivity of ion translocation mechanisms are affected by aging.

1. **Absence of age-related decrement in the initial rate of Ca^{2+} accumulation in rat cardiac sarcoplasmic reticulum**. Last year we reported that the efficiency of energy coupling between ATP hydrolysis and Ca^{2+} transport in rat cardiac muscle SR may be diminished with age based on evidence showing that the overall CaATPase rate did not change even though the initial velocity of Ca^{2+} transport as measured by stopped-flow mixing showed an age-dependent decline in activity. The possibility that this may have resulted from a larger fraction of unsealed or poorly-sealed membrane vesicles in the old population was excluded by results showing identical passive Ca^{2+} loading capacities and passive efflux rates in SR membranes isolated from young and old hearts. To test whether the efficiency of energy utilization was altered at the high and low affinity ATP binding sites, the ATP concentration used in these studies was adjusted to 10 or 1000 μM which are sufficient to saturate these sites. At 2 μM Ca^{2+}, the time course of $^{45}Ca^{2+}$ accumulation consisted of a rapid exponential phase, which was complete within 20 msec at 1 mM ATP, and a linear phase which lasted several hundred milliseconds. Active Ca^{2+} transport at an ATP concentration sufficient to saturate the catalytic sites (10 μM) did not differ significantly in the 6-8 month and 24-26 month age groups, indicating that energy utilization at this site is unimpaired. Raising the ATP concentration to 1 mM more than doubled the rate of Ca^{2+} uptake, but did not reveal a significant age-related difference in transport activity as anticipated. Moreover, the observed rates at the higher ATP concentration are in excellent agreement with the predicted values (11.74 nmol/mg·sec for the young and 11.67 nmol/mg·sec for the old) based on the steady state phosphoenzyme levels and turnover rates measured in cardiac SR prepared from animals in these two age groups. These results indicate that the intrinsic kinetic properties of the SR Ca^{2+} pump are not altered during aging and that the difference in transport activity measured in the presence of oxalate may reflect an age-related difference in membrane permeability to anions. If the kinetic properties of the pump do not change and if the density of the transport sites in the SR membrane remain constant with age as the invariance of the phosphoenzyme levels suggest, then either the SR content of the myocardium declines with age or alteration of some other mechanism such as Ca^{2+} release from troponin is responsible for the prolongation of contraction duration in senescent myocardium. Consistent with the former possibility recent measurements by Charlotte Tate and George Taffet at Baylor University have demonstrated that the maximum, oxalate-dependent Ca^{2+} loading capacity of SR vesicles in cardiac muscle homogenates prepared from Fisher 344 rats is diminished in aging.

2. **Correlation of the NaK-ATPase partial reactions with transient pump currents generated during ATP hydrolysis**. Last year in collaboration with investigators at the Max-Planck-Institut FÜr Biophysik we began a study of the relationship between the enzymatic reactions of the Na^+ pump and the transient pump currents generated by the Na,K-ATPase in response to an ATP concentration jump. In the electrical experiments, Na,K-ATPase activity is initiated by laser photolysis of caged ATP, a photolabile inactive

derivative of ATP, and the resulting charge movement measured by capacitive coupling of the adsorbed Na,K-ATPase membrane fragments to an underlying planar block lipid membrane. Previous work by the Frankfurt group had established that Na^+-dependent ATP hydrolysis during the first turnover of the pump is associated with the appearance of a current transient that results from the movement of positive charge in the direction of Na^+ translocation. Analysis of the current transient showed that it could be fitted to two exponentials with rate constants of 12 s^{-1} and 100 s^{-1}. The smaller rate constant was ATP-dependent suggesting that it corresponds to the ATP binding step whereas the faster reaction, which is electrogenic, was assumed to represent the E_1P to E_2P transition which is believed to be coupled to Na^+ translocation. In order to establish the validity of these assignments, we investigated the time course of the enzymatic reactions using an Na,K-ATPase preparation and experimental conditions identical to those used in the electrical measurements. The results of these rapid mixing experiments clearly established that the slower of the two rate constants corresponds to the rate of phosphorylation which is slowed because of competition between ATP and the unphotolysed analogue for the catalytic site. The rate constant for the E_1P to E_2P transition evaluated from the rapid mixing experiments was ten times larger than the fast reactions rate constant in the bilayer experiments while K^+-activated dephosphorylation following the transition was at least five times larger. These results have two important implications for active ion transport by the Na,K pump. First, they suggest that Na^+ translocation consists of at least two steps with rate constants of 1000 and 100 s^{-1}. The first step represents a rapid conformational change in which Na^+ is transported from the cytoplasmic to the extracellular membrane surface while the slower reaction which follows it, may correspond to the release of Na^+ from an occluded state at the extracellular surface. This interpretation is quantitatively consistent with the results of $^{22}Na^+$ flux experiments using rapid filtration. Second, since K^+ activates a reaction (dephosphorylation) that is faster than Na^+ deocclusion, an intermediate state in the transport cycle must occur in which Na^+ and K^+ are simultaneously bound to their respective transport sites. This raises the possibility that Na^+ transport in one direction is coupled simultaneously to K^+ movement in the opposite direction, a situation that would tend to minimize charge accumulation during transport. In support of this interpretation, bilayer experiments by the Frankfurt group have shown that addition of K^+ reduces the amplitude of the current transient generated during Na^+ translocation. Future work will attempt to further quantitate the effects of K^+ on the properties of the Na^+-dependent pump current.
Dr. Froehlich is spending 6 months at the Max Planck-Institute familiarizing himself with these techniques.

3. **Pre-steady state studies of Na^+-H^+ exchanger using isolated renal brush border membranes.** Previous studies of pre-steady state kinetics for the exchanger suggested that the functional exchanger is a tetramer with each of the four subunits one quarter out of phase with the other subunits. This resulted in Na^+ cooperativity

during the initial turnover but apparent single site availability in subsequent turnovers (steady state conditions). We measured the disappearance of H^+'s from the isolated vesicle interior by pH sensitive dyes. Our results show that H^+'s disappear from the interior before the first complete Na^+ cycle and was dependent upon external Na^+. The rate of H^+ efflux is directly related to the external Na^+ and the interior H^+ concentrations. Our results suggest that H^+ transport binding sites of the exchanger are available after Na^+ binds to the exchanger but before Na^+ is transported to the vesicle interior.

4. Measurements of plasma membrane domains in human skin fibroblasts. A method has been developed for sufficient incorporation of long chain fluorescent phospholipids in the plasma membrane. The long chain fluorescent phospholipids remain in the membrane longer before internalizing when compared to short chain phospholipids. This enabled us to make long term observations of the fate of different phospholipids in the plasma membrane. The initial studies indicate that phospholipids are distributed in both discrete domains and within the lipid membrane continuum. For example, phosphatidylcholine seem distributed mainly in the continuum, while both phosphatidylserine and phophatidylethanolamine seem distributed predominantly in discrete domains. In addition, sphingomyalin is apparently able to cross domain barriers between the continuum and the domains.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 AG 00048-15 LBC

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Ion Transport Mechanisms and Aging

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)*

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Other:		
Phillip F. Heller	Chemist	LBC GRC NIA
Kinya Otsu	Visiting Fellow	LBC GRC NIA
Sandra Guggino	Senior Staff Fellow	LBC GRC NIA
James Kinsella	Research Physiologist	LBC GRC NIA
Elishalom Yechiel	Visiting Associate	LBC GRC NIA
Daniel Alexander	Summer Student	LBC GRC NIA

COOPERATING UNITS *(if any)*

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LAB/BRANCH

Gerontology Research Center, Laboratory of Biological Chemistry

SECTION

Membrane Biology Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
4.12	3.0	1.12

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

A rapid mixing technique was used to evaluate the kinetic properties of the Ca^{2+} pump in cardiac SR isolated from young and old rat hearts. Significant age-related differences in the initial rates of ATP-dependent $^{45}Ca^{2+}$ uptake were not observed, indicating that the intrinsic properties of the Ca^{2+} pump are not altered during aging. This suggests that the prolonged contraction duration interval in senescent myocardium may be the result of a decrease in SR content rather than a decline in Ca^{2+} pump turnover rate. A detailed comparison of the mammalian Na,K-ATPase partial reactions with the transient electrical currents generated by the Na^+ pump in response to an ATP concentration jump has demonstrated that the Na^+ translocation mechanism is a two step process, consisting of a rapid conformational change followed by a slower electrogenic Na^+ deocclusion reaction. Presteady state kinetic studies on Na^+-H^+-exchanger in renal brush border membrane vesicles have began to uncover details of the temporal relationship between Na^+ uptake and H^+ efflux. A new method has been developed for incorporating long chain fluorescent phospholipids into plasma membranes and following their distribution in membrane structural domains.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 AG 00051-09 LBC

PERIOD COVERED: October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*: Regulation of Mineral Metabolism

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory and institute affiliation)*

C. Tony Liang	Research Chemist	LBC GRC NIA
James Kinsella	Research Physiologist	LBC GRC NIA
Linda Cheng	Research Chemist	LBC GRC NIA
Katsuhiko Yonemura	Visiting Fellow	LBC GRC NIA
Daniel Lajeunesse	Visiting Fellow	LBC GRC NIA
Shunji Imanaka	Visiting Fellow	LBC GRC NIA
Teresa Molina	Special Volunteer	LBC GRC NIA
Tadashi Ishii	Special Volunteer	LBC GRC NIA

COOPERATING UNITS *(if any)*

LAB/BRANCH: Gerontology Research Center, Laboratory of Biological Chemistry

SECTION: Regulatory Mechanisms Section

INSTITUTE AND LOCATION: NIA, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS: 5.16	PROFESSIONAL: 2.0	OTHER: 3.16

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects
  - ☐ (a1) Minors
  - ☐ (a2) Interviews
- ☐ (b) Human tissues
- ☒ (c) Neither

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This report describes studies on the regulation of mineral metabolism in cells and tissues from the intestines, and the kidneys. Studies were carried out to characterize Na^+, PO_4^+, and Ca^{2+} homeostatic mechanisms. (A) Sodium homeostasis is controlled by a number of Na^+ transporting mechanisms in the kidney and the intestines that are regulated by a variety of hormones and factors. We have developed different model systems to study proximal tubule Na^+ reabsorption (where 2/3 of the 180 liters of filtrate are reabsorbed). This year we used the opossum kidney (OK) cell line as a model for the renal proximal tubule cell. We found that thyroid hormones, T_3 or T_4, added to thyroid hormone depleted media increased Na^+-H^+ exchanger activity by a mechanism similar to described changes in intact tissues. Dopamine which inhibits fluid reabsorption in the proximal tubule also inhibited the exchanger activity and Na^+-dependent $PO_4^=$ transport in OK cells. The small intestine can both secrete fluid (crypt cells) or reabsorb fluid (villus cell). We initiated studies of the differentiation of crypt cells to villus cells and begun to characterize the mechanisms for salt and fluid fluxes. (B) Vitamin D is a major hormone in the control of Ca^{2+} homeostasis. Humans are usually in negative Ca^{2+} balance from the third decade through the rest of life. For some of the elderly population, this is an important cause of bone fractures. Vitamin D is the major mechanism for controlling Ca^{2+} flux in the intestine. Studies conducted in this laboratory demonstrate that the Vit D receptor affinity for DNA decreases with age by changes in the receptor protein and the DNA binding site.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 AG 00052-09 LBC

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Regulatory Mechanisms in the Control of Cell Functions

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

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COOPERATING UNITS *(if any)*

LAB/BRANCH

Gerontology Research Center, Laboratory of Biological Chemistry

SECTION

Regulatory Mechanisms Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.0	2.1	1.9

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This report describes studies on the biochemical and physiological mechanisms by which cell functions are regulated by hormones, agonists, and in pathophysiological states, including aging. The presence of various Regulatory GTP-binding proteins that couple cell surface receptors to their effector systems were shown in the kidney. Decreases in vitro transcription rates of mRNAs for Gs and Gi were observed during aging, but a decrease in level was seen only for Gs. Receptor mediated effects on cyclic AMP and phosphoinositide metabolism and on second messenger regulation of protein kinases were described in cultured kidney and bone cells. PTH regulation of protein kinase C was shown in renal cells, along with differential regulation of protein kinase A and C activity by PTH antagonist. Dopamine regulation of cyclic AMP production was shown for the first time in an established renal cell line. Purinergic regulation of cytosolic Ca^{2+} in bone cells was shown to result from increased phosphoinositide metabolism without crosstalk from simultaneous changes in cyclic AMP metabolism. Considerable heterogeneity was observed in Ca^{2+} metabolism of individual skin fibroblast from Alzheimer's disease patients and age-matched controls, precluding at present firm conclusions regarding purported differences. Ammoniagenesis in the renal proximal tubule, unlike that in brain, small intestine, and the glomerulus, is regulated by acidosis and glucocoricoids. Glomeruli ammoniagenesis was increased in old rats and associated with the degree of renal failure.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00053-01 LBC

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Role of Renal Failure in Age-Associated Changes in Wistar Rats

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Jeffrey Froehlich	Medical Officer, Chief, Membrane Biol Sec	LBC GRC NIA
Linda Cheng	Research Chemist	LBC GRC NIA
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Bernard Bulos	Research Chemist	LBC GRC NIA

COOPERATING UNITS *(if any)*

LAB/BRANCH

Gerontology Research Center, Laboratory of Biological Chemistry

SECTION

Regulatory Mechanisms Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
2.2	1.7	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The possible influence of renal disease on functional parameters in various organs was evaluated by studying female rats from the GRC Wistar colony. Unlike their male counterparts, old female rats exhibited only a moderate degree of renal disease with comparatively smaller increases in BUN, serum creatinine and immunoreactive PTH. However, a marked increase in proteinuria, a sensitive index of onset of renal disease, was observed and was comparable to that seen in old male rats. Decreases previously found in old male rats in the activity of the Ca^{2+} pump in cardiac sarcoplasmic reticulum, serum 1,25-$(OH)_2$-vitaminD_3, duodenal cell Ca^{2+} transport and adrenergic stimulation of Ca^{2+} efflux from parotid acinar cells were not found in old female rats. Desensitization of renal cortical PTH responses was found and, unlike that in male rats, appeared to be independent of severity of renal disease but may be related to serum levels of PTH. These results indicate that absence of severe renal disease is associated with absence of decreases in functional parameters of some tissues and raises the questions of whether decreases observed in male rats are secondary to renal disease and are not universal but sex-dependent.

ANNUAL REPORT OF THE LABORATORY OF CARDIOVASCULAR SCIENCE

NATIONAL INSTITUTE ON AGING

The overall goals of the Laboratory of Cardiovascular Science are (1) to identify age-related changes that occur within the cardiovascular system and to determine the mechanisms for these changes; (2) to study myocardial structure and function, and response to pharmacological therapeutics in mechanical overload, altered thyroid state, and physical conditioning models, and to determine how age interacts with these chronically altered cardiac states to determine the level of myocardial function; and (3) to study basic mechanisms in excitation-contraction coupling and of energy-yielding oxidative pathways in cardiac muscle. In meeting these objectives, studies are performed in human volunteers, intact animals, isolated heart and vascular tissues, isolated cardiac cells, and subcellular organelles.

Studies in Man

Detection of Prognosis of Silent Myocardial Ischemia. To separate the effects of age and silent myocardial ischemia (SI), on the left ventricular (LV) response to maximal upright cycle ergometry, we compared 3 groups: 8 clinically healthy older men (mean age - 76) with prior abnormal ECG and thallium scan (TS) responses to maximal treadmill exercise (OSI); 16 age-matched men with normal ECG and TS responses (OC); and 21 young (mean age = 33) controls (YC). At rest LV ejection fraction (EF), end-diastolic volume index (EDVI) and end-systolic volume index (ESVI) were similar in the 3 groups. With cycle exercise LVEF increased markedly in the young controls, less in the older controls and least in the OSI. In contrast, exercise-induced LV dilatation (increased ESVI) was most pronounced in the OSI with a lesser increase in the OC; EDVI actually declined below baseline values by maximal effort in the YC. Thus, age-related cardiac dilatation and blunted EF response to upright cycling are exaggerated in older subjects with exercise-induced SI.

Age-Associated Changes in Cardiac Rhythm and Conduction. To determine the site of the PR interval prolongation associated with aging, we performed signal averaged high resolution surface ECGs in 161 clinical healthy Baltimore Longitudinal Study of Aging volunteers with normal atrioventricular (AV) conduction. An increase in PR interval with age was found in both sexes and was localized proximal to the His bundle depolarization but distal to the P wave inscription, suggesting block within the AV junction; a similar qualitatively similar but more pronounced delay was noted proximal to the His bundle in 7 older men with first degree AV block.

Studies in Animal Models

Excitation-Contraction Mechanisms in Isolated Cardiac Cells. We have developed a system for simultaneous measurement of changes in cytosolic free Ca^{2+}, cell length and membrane current/voltage, with high time resolution. The system uses the fluorescent probe Indo-1 to monitor cytosolic free Ca^{2+} transient. Cell length is measured from the bright-field image of the cell by an optical edge tracking method using a video edge detector and the membrane potential can be monitored simultaneously with patch electrodes. Salient recent results of

studies of the mechanisms of cardiac excitation-contraction (E-C) coupling include: (1) a demonstration that the sarcoplasmic reticulum (SR) is the source of the majority of Ca^{2+} ions that initiate myofilament activation both in guinea pig and rat Maoists; (2) the SR can selectively be depleted by ryanodine and can, still in the presence of ryanodine, be Ca^{2+} repleted by rapid electrical stimulation; (3) small (3-5 mV), sustained (seconds) depolarizations that cause small Ca^{2+} currents current are followed by small steady reductions in cell length measured via a photodiode array and small steady increases in cytosolic Ca^{2+} (Ca_i), The steady (nitrendipine sensitive) current and sustained increase in Ca_i and contraction exhibit a similar voltage-dependence over the voltage range between -40 and -20 mV. Ryanodine 2 μM, in the presence of intact Ca^{2+} channel activity, also abolishes the steady increase in Ca_i and contraction over this voltage range. Thus, when a sustained depolarization does not exceed about -20 mV the resultant steady, graded contraction is due to SR Ca^{2+} release graded by a steady ("window") Ca^{2+} current. The existence of appreciable, sustained, graded Ca^{2+} release in response to Ca^{2+} current generated by arbitrarily small depolarizations is not compatible with any model of Ca^{2+}-induced Ca^{2+} release in which the releasing effect of the Ca^{2+} channel current is mediated solely by Ca^{2+} entry into a common cytosolic pool. Our results therefore imply a distinction between the triggering and released Ca^{2+} pools and provide a boundary condition for mathematical models of cardiac E-C coupling.

Cytosolic Calcium Modulation of the Cardiac Action Potential. The role of the Ca_i transient in determining the configuration of the cardiac action potential was investigated in single isolated rat ventricular myocytes loaded with the Ca^{2+} sensitive fluorescent dye Indo-1. The magnitude of the Ca_i transient was graded by various physiologic and pharmacologic interventions and membrane voltage or current was recorded using patch-type microelectrodes. The peak of the Ca_i transient corresponded in time to the start of the action potential plateau. Although short in duration relative to the Ca_i transient, the plateau was followed by a slow tail of repolarization, only a few millivolts in amplitude, that decayed in parallel with the Ca_i transient. Stimulation from rest resulted in a negative staircase in the magnitude of the Ca_i transient, accompanied by a decrease in the duration of the action potential plateau and in the magnitude of the slow tail of repolarization. Space-plane loops of membrane potential (Vm) vs. Indo-1 ratio revealed that during the slow tail of repolarization there was a common relationship between Vm and Ca_i from all the beats of a stimulus train. Electronic subtraction of the action potential and Ca_i transient of a steady state beat from those of the first post-rest beat showed that the large positive difference in the action potential plateau had a similar waveform to the Ca_i transient difference, with both peaking at the same time. Identical results were seen when ryanodine was used to reduce the magnitude of the Ca_i transient. Under voltage clamp conditions, Ca_i transients elicited by brief pulses or caffeine occurred in phase with a small inward current. Like the Ca_i transient, this current exhibited a negative staircase during a train of brief voltage clamp pulses following a period or rest. It is concluded that this inward current, mediated by the Ca_i transient, modulates the plateau of the rat ventricular action potential and is responsible for the slow tail of repolarization.

Length/Load-Dependent Calcium Modulation of Contraction in Cardiac Myocytes. Multiple lines of evidence has established that contractile performance of cardiac tissue is governed by the intimate relationship between sarcomere length and Ca^{2+}-myofilament activation forming the basis of the Frank-Starling mechanism. In contrast, relaxation is governed by the competition between Ca^{2+}

-myofilament inactivation and the external restoring force associated with muscle strength and loading. In order to eliminate mechanical and electrical inhomogeneity of bulk tissue, prior studies of contractility have been performed in intact single myocytes, albeit at slack length (as no satisfactory method exists to alter length/load in this model), or in chemically-skinned cells. To examine the effect of strength on the twitch contraction and relaxation of single ventricular myocytes with intact sarcolemma, we developed a novel technique enabling reversible gradation in the resting cell length of up to 15-18%. Our initial results show (1) that the relative effect of bathing Ca^{2+} to augment shortening velocity varied with the cell length is consistent with the concept that myofilament-Ca^{2+} activation is length/load-dependent. A stretch of resting cell length increases twitch amplitude and accelerates relaxation without changing the Ca_i transient. Thus, a Ca_i-dependence of relaxation at slack length can be overridden by the external restoring force associated with stretch, consistent with the concept of a length/load-dependence of relaxation in bulk cardiac muscle, and, moreover, stretch represents a principal determinant of relaxation over Ca^{2+}-myofilament inactivation in tissue with "normal" Ca^{2+} homeostasis.

pH Regulation in Cardiac Myocytes. Physiological studies have been aided by the use of intracellular indicators. Indicators for intracellular Ca^{2+} and pH are used in monitoring physiological and pathophysiological properties of isolated cardiac myocytes and intact cardiac tissue. The purpose of this project was to characterize SNARF-1, seminaphthorhodafluor, a recently synthesized intracellular pH indicator, and modify our existing time resolved Ca^{2+} system for pH investigations.

The emission spectrum of SNARF-1 contains two well separated emission peaks at 590 and 640 nm. This feature allows the indicator to be used in the single excitation, dual emission, ratio mode; analogous to the Ca^{2+} indicator, INDO-1. The indicator is available in both the free acid form and as a cell permeate acetoxymethyl ester. We have found that isolated cardiac myocytes are easily loaded with the ester, and have the following characteristics: 1) the contractile properties are unchanged in the presence of the indicator, 2) the indicator is present primarily in the cytosol (95% to 100%) with virtually no partitioning into the mitochondria, 3) the indicator is retained for several hours at 20°C, and 4) steady-state and transient changes in pH are easily monitored. Preliminary results on myocytes exposed to anoxia indicate that pH changes can be monitored during important physiological and pathophysiological perturbations.

Pathophysiologic Effects of Spontaneous Calcium Release in the Heart. We have hypothesized that a single type of disorder among myocardial cells can produce the trilogy of common manifestations of heart failure that results from a variety of etiologies, that is, abnormal diastolic tonus, limited systolic function, and a high probability that arrhythmias will occur. This disorder is a spontaneous Ca^{2+} oscillation (OSC) that occurs locally within and asynchronously among cells constituting the myocardium. The focus of the present project is on how Ca^{2+} OSC affects membrane potential. Membrane potential OSC arising from the resting potential that occur either spontaneously at rest or that follow a previous action potential (or late diastolic after depolarization, DAD) and those occurring at the action plateau level ("early" after depolarization, EAD) have been implicated in cardiac arrhythmias. To determine the relationship of voltage or current OSC and Ca_i OSC occurring at different membrane potential we simultaneously measured membrane potential and Ca_i, via Indo-1 fluorescence, in single adult rat ventricular myocytes at the diastolic Vm or on action potential

plateau. For DAD the phase plane diagram of Vm versus Ca_i showed Ca_i and Vm OSC occur with no phase shift. For EAD the phase plane of Vm versus Ca_i is a clockwise loop, i.e. the onset of the Vm OSC precedes the Ca_i OSC. These results show, for the first time, that for DADs Ca_i OSC does not lag behind the Vm OSC confirming the hypothesis that the DADs result from Ca_i OSC; in contrast, the EAD causes a Ca_i OSC, most likely via Ca^{2+} current induced Ca^{2+} release from the SR. Verapamil, 10 μm, abolishes EAD but Ca^{2+} OSC can still occur, and under voltage clamp are associated with small (<100 pA) current OSC (that produce small voltage OSC. Verapamil plus EGTA (25 mm) pipette or 2 μm ryanodine in the bath abolish all OSC. In absence of verapamil neither EGTA nor ryanodine blocks the EAD. Thus, membrane potential OSC that occur around the rat action potential plateau (approximately -40 to -10 mV) can involve several interactive mechanisms including spontaneously L type Ca^{2+} channel activation, and SR generated Ca_i OSC.

Novel Positive Cardiac Inotropic Agents. All positive inotropic agents that are available for clinical use exercise their effect predominately via an increase in cell Ca^{2+} loading. However once the myocardial preparation has reached its peak contractile response a further increase in cell Ca^{2+} loading is associated initially with a plateau and then with a decline in the inotropic state of the muscle, an increase in diastolic tone, aftercontractions and arrhythmias. This condition which has been defined as "Ca^{2+} overload" represents the limiting factor in the clinical use of positive inotropic agents. Thus, it is desirable to develop drugs that increase the contractility of the heart via an enhancement in myofilament responsiveness to Ca^{2+} rather than by increasing the extent of cell Ca^{2+} loading. We tested the effect of the thiadiazinone EMD 54622, an experimental substance designed by E. Merck, Darmstadt, (FRG) which sensitizes isolated cardiac myofibrils to Ca^{2+}. We determined whether EMD 54622 increases twitch amplitude without increasing Ca_i in guinea pig ventricular myocytes. During stimulation at 1 Hz in 1 mM bathing Ca^{2+}, EMD 54622 (0.5-1.25 μM); (1) increases the twitch amplitude up to more than twofold over control but not the Ca_i transient, measured simultaneously as the 410/490 nm ratio of Indo-1 fluorescence, and this fully reversed after drug wash out; (2) shifts the twitch amplitude-Ca_i relationship (obtained by varying bathing Ca^{2+}) to the left. Thus the positive inotropic action of EMD 54622 in intact cells occurs via an increased myofilament responsiveness to Ca^{2+}.

Oxidant-Induced Intracellular Calcium Overload in Cardiac Myocytes. Reperfusion of ischemic myocardium limits ischemic damage but may induce cellular injury due to reperfusion itself. Recent evidence suggests that myocardial reperfusion is accompanied by an increase in intracellular Ca^{2+} and myocardial damage. Other studies have documented a burst of reactive oxygen radicals at the moment of reperfusion in the intact heart. Oxygen radicals may contribute to the Ca^{2+} overload and cellular injury of reperfusion but supportive data is lacking. Utilizing the laminar counterflow barrier well, developed in our laboratory, we observed a rise in intracellular Ca^{2+} and cellular injury in single rat cardiac myocytes exposed to anoxia and reoxygenation. The isolated cardiac myocyte allows the simultaneous study of cell function, intracellular Ca^{2+} and membrane potential from a single cardiac myocyte avoiding the problems associated with the multiple cell types found in bulk cardiac preparations. In separate experiments we exposed single cardiac myocytes to exogenously generated O_2 radicals/oxidants and observed an initial increase in the electrically stimulated twitch amplitude associated with a decrease in diastolic length. Aftercontractions later developed and finally the cell became inexcitable and underwent contracture. These mechanical changes appeared to be consistent with intracellular Ca^{2+} over-

load. Ca_i, measured in cells loaded with the fluorescent probe Indo-1, rose following the administration of oxidants. When the action potential was monitored with whole-cell current clamp there was marked progressive action potential plateau prolongation without depolarization of the resting potential. Thus, oxidants/O_2 radicals induce Ca^{2+} overload and cellular injury in cardiac myocytes and cause action potential changes that may relate to Ca^{2+} loading.

The Role of Opioid Peptides in Modulating Myocardial Function. The discovery of endogenous opioid peptides in the brain has resulted in extensive investigations to determine the physiologic role of these substances. With regard to the cardiovascular system it has been shown that myocardial cells possess specific opioid receptors and it has been suggested that opioids released from the adrenal medulla, from nerve terminals and possibly also synthesized within myocardial cells as a large amount of preproenkephalin mRNA has recently been identified in cardiac myocytes may directly effect myocardial cell function. The objectives of this study are: a) to define the role of opioid peptides to modulate myocardial cell function, b) to identify which of the known opioid receptors (delta, K and μ) mediate the action of these peptides. c) to characterize the steps involved in signal transduction subsequently to the binding of the opioid to its specific receptor, d) to determine whether the mechanisms for signal transduction identified in myocardial cells are common to other cell types such as neurons. Isolated rat ventricular myocytes were used to investigate the effect of leucine-enkephalin, methionine-enkephalin, DADLE (delta agonists), DAGO (μ agonist), and U-50 (K agonist) on myocardial cell function. Changes in contractility and Ca_i were simultaneously recorded in myocytes loaded with the Ca^{2+} probe Indo-1. Both the delta and K agonist had a marked negative inotropic action and prolonged the time course of the contraction. These changes were associated to a decrease in the amplitude and a prolonged duration of the Ca_i transient . The μ agonist had no effect. At rest the rapid (200 msec) addition of caffeine (15 mM) from a pipette above the cell releases Ca^{2+} from the SR and transiently increases Ca_i. This effect was abolished by 40 min exposure to 10 μM leucine-enkephalin or U-50 and preserved when leucine-enkephalin or U-50 were superfused with their specific antagonists, respectively naloxone or Mr-1452. Thus, SR Ca^{2+} depletion is a mechanism for the delta and K opioid receptor agonists in the myocardium.

Myocardial Reserve and Calcium Tolerance in the Cardiomyopathic Hamster. While the cardiomyopathic hamster (CMH), BIO14.6 strain, develops congestive heart failure with aging, the evolution of compromised myocardial reserve, Ca^{2+} intolerance, and response to catecholamines prior to overt failure remains to be fully understood and is investigated in this project. We used hearts from 28-52 day old male CMH and age-matched F1B strain control hearts. Isolated, isovolumic and AV blocked hearts were perfused with Hepes buffer at constant pressure and stimulated at 2 Hz at 37°C to investigate the effects of (1) an increasing in bathing [Ca^{2+}] (1-10 mM; n = 10 of each), β-adrenergic (isoproterenol, 1 nM - 1 μmM; n = 10 of each), (3) α-adrenergic (phenylephrine, 0.1 - 10 μ mM; n = 10 of each) agonists, and (4) Ca^{2+} channel agonist (BAYK8644, 5 nM - 1 μM; n = 10 of each) on contractile properties. In CMH, the peak developed pressure response saturates at a significantly ($p < 0.001$) smaller developed pressure and declines from maximum occurs at a significantly lower concentrations of α- or β-agonist, Ca^{2+} channel agonist or of perfusate [Ca^{2+}] compared to control. The rise in end-diastolic pressure with increasing in drug or perfusate [Ca^{2+}] concentration in CMH is also significantly ($p < 0.001$) greater than control. These results suggest that myocardium shows enhanced response to Ca^{2+} per se, and also that myocardial cell Ca^{2+} loading in response to catecholamines is greater in CMH than in

control hearts.

Cellular Calcium Ion Homeostasis and the Impact of Aging. The regulation of cellular free Ca^{2+} concentrations is of crucial importance to a host of cellular activities, including growth and replication, stimulus-secretion coupling and E-C coupling. There is evidence that some of mechanism responsible for the homeostasis of Ca^{2+} are deranged in old-age, leading to less effective neuronal and humoral signaling and thus a decreased capacity to respond to stresses and environmental changes. This project heading is a general rubric describing our investigations on mechanisms of cellular Ca^{2+} regulation and changes which occur in old-age. This year, we have addressed the following questions. (1) What is the mechanism whereby activity-oxidized substrates lead to a positive inotropic effect in cardiac muscle preparations ? Is this a function of an increased SR Ca^{2+} store? We have approached this by using individual rat cardiac myocytes, with measurement of contractility and of the increase in cytosolic free Ca^{2+} due to sudden addition of caffeine, which release SR Ca^{2+}. Substrates include pyruvate, to bypass limiting glycolytic steps, and mid-chain length fatty acids, as well as glucose. (2) Is the magnitude of the Ca^{2+} concentration gradient across the mitochondrial membrane affected by aging ? This derives from our earlier studies in which we showed that the specific activity of bath Ca^{2+}-uptake and release pathways of cardiac mitochondria is decreased in old-age. Changes in transport activity at the level of the mitochondrial membrane have the potential for affecting both the kinetics of changes in Ca_i and the regulation of intramitochondrial Ca^{2+}-dependent dehydrogenases. (3) Are there differences with senescence in the depolarization-induced phosphorylation of the neuronal protein synapsin I ? This Ca^{2+}-dependent phosphorylation forms part of the mechanism of exocytosis of transmitter-substance-containing vesicles and has been studied this year in synaptosomes (pinched off presynaptic terminals from cerebral cortex of rats of different ages (3,6 and 24 months).

Regulation of Energy Metabolism. This project is designed to assess the physiological importance of Ca^{2+} ions in the regulation of energy metabolism. The activation of muscle contraction by Ca^{2+} ions initiates the performance of intense work and establishes a demand for the more rapid synthesis of ATP. We have shown previously that the increased availability of Ca^{2+} ion to the mitochondria allows the activation of three dehydrogenases, viz pyruvate, isocitrate and 2-oxoglutarate dehydrogenases, which catalyze non-equilibrium steps in the terminal pathway of substrate oxidation. This allows the more rapid generation of NADH and, theoretically at least, minimizes the degree to which the tissue adenine nucleotide phosphorylation potential falls due to increased tissue work. This year we have further characterized the relationship between mitochondrial NADH levels and the flux through oxidative phosphorylation. Rat heart mitochondria were exposed to various concentrations of the oxidizable substrates pyruvate, 2-oxoglutarate and glutamate or to different extramitochondrial free Ca^{2+} concentrations, in the range of 10-500 nM, and O_2-uptake and $NADH/NAD^+$ ratios were measured. In general there was found to be a positive, linear relation between $NADH/NAD^+$ and O_2-uptake: anomalies obtained when Ca^{2+} concentration was varied, at unchanged substrate concentration, main point to an additional role of Ca^{2+} in activating the mitochondrial respiratory chain and/or ATP -synthase. This year, we have also studied the activation of pyruvate dehydrogenase by Ca^{2+} in work involving isolated, perfused guinea pig and rat hearts. We shown that electrical stimulation (2 to 5 Hz) results in an increased content of the active, dephospho form of the enzyme and a concomitant increase in the Ca^{2+}-content of a rapidly-isolated mitochondrial fraction. This falls within the

range of mitochondrial Ca^{2+} which we have previously shown to affect pyruvate dehydrogenase regulation, in in vitro studies with suspensions of rat heart mitochondria. Finally, we have initiated a collaboration with the Division of Cardiology, Department of Medicine, Johns Hopkins University in which the use of substrates enriched with ^{13}C allows a description by nmr techniques of flux through pyruvate dehydrogenase and the tricarboxylate cycle in intact hearts which are reperfused following a period of ischemia. This protocol, which is of obvious clinical relevance, gives rise to a period of impaired metabolism of ill-understood origin. Understanding of the state may allow pharmacological intervention to favor pyruvate oxidation over fatty acid oxidation, with a consequent increase in ATP formed per (scarce) O_2.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00226-07 LCS

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Excitation-Contraction Mechanisms in Isolated Cardiac Cells

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

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Gerontology Research Center, Laboratory of Cardiovascular Science

SECTION
Cardiac Function Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2	1.6	0.4

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

We have developed a system for simultaneous measurement of changes in cytosolic free $[Ca^{2+}]$, cell length and membrane current/voltage, with high time resolution. The system uses the fluorescent probe Indo-1 to monitor cytosolic free $[Ca^{2+}]$ transient. Cell length is measured from the bright-field image of the cell by an optical edge tracking method using a video edge detector and the membrane potential can be monitored simultaneously with patch electrodes. Salient recent results of studies of the mechanisms of cardiac excitation-contraction (E-C) coupling include: (1) a demonstration that the sarcoplasmic reticulum (SR) is the source of the majority of calcium ions that initiate myofilament activation both in guinea pig and rat myocytes; (2) the SR can selectively be depleted by ryanodine and can, still in the presence of ryanodine, be calcium repleted by rapid electrical stimulation; (3) small (3-5 mV), sustained (seconds) depolarizations that cause small calcium currents current are followed by small steady reductions in cell length measured via a photodiode array and small steady increases in cytosolic $[Ca^{2+}]$ (Ca_i), The steady (nitrendipine sensitive) current and sustained increase in Ca_i and contraction exhibit a similar voltage-dependence over the voltage range between -40 and -20 mV. Ryanodine 2 μM, in the presence of intact calcium channel activity, also abolishes the steady increase in Ca_i and contraction over this voltage range. Thus, when a sustained depolarization does not exceed about -20 mV the resultant steady, graded contraction is due to SR calcium release graded by a steady ("window") calcium current. The existence of appreciable, sustained, graded calcium release in response to calcium current generated by arbitrarily small depolarizations is not compatible with any model of calcium-induced calcium release in which the releasing effect of the calcium channel current is mediated solely by calcium entry into a common cytosolic pool. Our results therefore imply a distinction between the triggering and released calcium pools and provide a boundary condition for mathematical models of cardiac E-C coupling.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00228-06 LCS

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Age-Associated Changes in Cardiac Rhythm and Conduction

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	J. L. Fleg	Cardiologist	LCS, NIA
Others:	E. G. Lakatta	Chief	LCS, NIA
	J. Busby	Guest Researcher	LCP, NIA
	E. Shefrin	Computer Scientist	LSB, NIA

COOPERATING UNITS *(if any)*

Division of Cardiology, Johns Hopkins Hopsital (M. McIvor)

LAB/BRANCH
Gerontology Research Center, Laboratory of Cardiovascular Science

SECTION
Cardiac Function Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.3	0.2	0.1

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

A. To determine the site of the PR interval prolongation associated with aging, we performed signal averaged high resolution surface ECGs in 161 clinical healthy Baltimore Longitudinal Study of Aging (BLSA) volunteers with normal atrioventricular (AV) conduction. An increase in PR interval with age was found in both sexes and was localized proximal to the His bundle depolarization but distal to the P wave inscription, suggesting block within the AV junction; a similar qualitatively similar but more pronounced delay was noted proximal to the His bundle in 7 older men with first degree AV block.

B. We have determined the prevalence and significance of exercise-induced frequent or repetitive ventricular ectopic beats (VEB) in apparently healthy BLSA volunteers. Between 1974 and 1984, 80 of 1160 such asymptomatic subjects developed frequent VEB (> 10%) or salvos (> 3 in a row) on at least one maximal treadmill exercise test. These 80 subjects were significantly older than the larger group without such exercise-induced VEB (63.8±12.5 vs 50.0±16.1, $p<.0001$). Only 9 of 80 (11%) demonstrated an ischemic ST segment response to exercise. Over a mean followup of 4.6 years; only 8 cardiac events have occurred versus 10 events in 80 age- and sex-matched control subjects without such complex exercise-enduced VEB (p = NS)

(Formerly, Exercise-Induced Arrhythmias in Normal Volunteers)

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00231-05 LCS

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Regulation of Energy Metabolism

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	R. Hansford	Chief, EMBS	LCS, NIA
Others:	B. Hogue	Chemist	LCS, NIA
	R. Moreno-Sanchez	Visiting Fellow (DOD 11/88)	LCS, NIA

COOPERATING UNITS *(if any)*
Cardiac Function Section, LCS (B. Lewartowski), Cardiology Division, Department of Medicine, Johns Hopkins University (R. Weiss and G. Gerstenblith)

LAB/BRANCH
Gerontology Research Center, Laboratory of Cardiovascular Science

SECTION
Energy Metabolism and Bioenergetics Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.1	0.6	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project is designed to explore the importance of the regulation of dehydrogenases, in particular by Ca^{2+} ions, in the overall control of oxidative metabolism. This year we have quantitated the activation of pyruvate dehydrogenase which occurs when isolated, perfused rat hearts oxidizing glucose plus the fatty acid octanoate are electrically stimulated and/or made to perform external pumping work. The degree of activation of the dehydrogenase correlates with the increase in mitochondrial Ca^{2+} content which occurs under these conditions and which was described in last year's Annual Report. We have also completed a study in which flux through oxidative phosphorylation was related to the NADH/NAD^+ ratio, as the latter was varied by exposing suspensions of rat heart mitochondria to various concentrations of the substrates pyruvate, 2-oxoglutarate and glutamate, or to different extramitochondrial free Ca^{2+} concentrations, in the range 10 nM-500 nM. Displacement of the two sets of results indicates a role for Ca^{2+} in activating the mitochondrial respiratory chain and/or ATP-synthase, as well activating pyruvate and 2-oxoglutarate dehydrogenases. We have also begun a collaboration with the Cardiology Division, Department of Medicine, Johns Hopkins University in which use of substrates enriched with ^{13}C allows a description by nmr of flux through pyruvate dehydrogenase and around the tricarboxylate cycle in intact hearts that are reperfused following a period of ischemia: this protocol, which is of clinical relevance, gives rise to a period of impaired metabolism, of ill-understood origin.

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00233-05 LCS

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Beta-Adrenergic Modulation of Cardiac Function

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.)* *(Name, title, laboratory, and institute affiliation)*

PI:	E. G. Lakatta	Chief	LCS, NIA
Others:	M. C. Capogrossi	Medical Officer	LCS, NIA
	H. A. Spurgeon	Physiologist	LCS, NIA
	M. Sakai	Visiting Fellow (DOD 5/88)	LCS, NIA
	R. S. Danziger	Medical Staff Fellow (DOD 7/88)	LCS, NIA
	R. G. Hansford	Chief, EMBS	LCS, NIA
	D. J. Pelto	Biologist (DOD 7/88)	LCS, NIA
	J. M. Staddon	Visiting Fellow, EMBS (DOD 5/88)	LCS, NIA

COOPERATING UNITS *(if any)*
Division of Cardiology, Johns Hopkins University School of Medicine, Baltimore, MD (M. McIvor)

LAB/BRANCH
Gerontology Research Center, Laboratory of Cardiovascular Science

SECTION
Cardiac Function Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.5	1.3	.2

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Beta-adrenergic agonists increase the myocardial contraction amplitude and enhance relaxation. Our studies examine the autonomic modulation of the calcium-myofilament interaction to determine whether it could account for enhanced twitch relaxation. In single cardiac myocytes we found that for a given amplitude of cytosolic calcium twitch amplitude was less in isoproterenol (Iso) than in control. In myocytes suspensions norepinephrine (NE, 10 μM) increased troponin-I phosphorylation fourfold and under similar conditions decreased twitch relaxation time in individual myocytes by 20%. After propranolol (1.0 μM) troponin slowly dephosphorylated (half time 16.9±1.7 min) but relaxation time fully returned to control within 5 min. Thus, the extent of troponin-I phosphorylation by NE is not directly proportional to its effect on relaxation time.

In isolated, aequorin-injected ferret cardiac muscle the calcium tension relation was determined from the peak aequorin luminescence and peak tension measured across a broad range of bathing calcium in the presence and absence of acetylcholine (ACh, 1 μM) or Iso (1 μM) or both drugs. Ach shifted the relationship of peak tension to (peak) aequorin light leftward, suggesting an increase in myofilament calcium sensitivity, but did not alter twitch relaxation (t1/2R). Iso shifted the relationship of peak tension to peak aequorin light rightward and decreased t1/2R. Ach added to Iso abolished the Iso effect on peak tension-aequorin light relationship but did not reverse the effect of Iso to decrease t1/2R. Thus perturbations of the apparent myofilament calcium interaction in the intact muscle do not necessarily relate to twitch relaxation time.

Combined into Z01 AG 00259-01 LCS

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00243-03 LCS

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Pathophysiologic Effects of Spontaneous Ca^{2+} Release in the Heart

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	E. G. Lakatta	Chief	LCS, NIA
Others:	H. A. Spurgeon	Physiologist	LCS, NIA
	M. C. Capogrossi	Medical Officer	LCS, NIA
	M. D. Stern	Guest Researcher	LCS, NIA

COOPERATING UNITS *(if any)*
Department of Biology, University of Turku, Finland (A. Talo)

LAB/BRANCH
Gerontology Research Center, Laboratory of Cardiovascular Science

SECTION
Cardiac Function Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.5	2.2	0.3

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

We have hypothesized that a single type of disorder among myocardial cells can produce the trilogy of common manifestations of heart failure that results from a variety of etiologies, that is, abnormal diastolic tonus, limited systolic function, and a high probability that arrhythmias will occur. This disorder is a spontaneous calcium oscillation (OSC) that occurs locally within and asynchronously among cells constituting the myocardium. the focus of the present project is on how calcium OSC affects membrane potential. Membrane potential (vM) OSC arising from the resting potential that occur either spontaneously at rest or that follow a previous action potential (AP) (or late diastolic after depolarization, DAD) and those occurring at the action plateau level ("early" after depolarization, EAD) have been implicated in cardiac arrhythmias. To determine the relationship of voltage or current OSC and cytosolic calcium (Ca_i) OSC occurring at different vM we simultaneously measured vM and Ca_i, via Indo-1 fluorescence, in single adult rat ventricular myocytes at the diastolic Vm or on AP plateau. For DAD the phase plane diagram of Vm versus Ca_i showed Ca_i and Vm OSC occur with no phase shift. For EAD the phase plane of Vm versus Ca_i is a clockwise loop, i.e. the onset of the Vm OSC precedes the Ca_i OSC. These results show, for the first time, that for DADs Ca_i OSC does not lag behind the Vm OSC confirming the hypothesis that the DADs result from Ca_i OSC; in contrast, the EAD causes a Ca_i OSC, most likely via Ca current induced calcium release from the sarcoplasmic reticulum (SR). Verapamil, 10 μm, abolishes EAD but calcium OSC can still occur, and under voltage clamp are associated with small (<100 pA) current OSC (that produce small voltage OSC. Verapamil plus EGTA (25 mm) pipette or 2 μm ryanodine in the bath abolish all OSC. In absence of verapamil neither EGTA nor ryanodine blocks the EAD. Thus, vM OSC that occur around the rat AP plateau (approximately -40 to -10 mV), can involve several interactive mechanisms including spontaneously L type calcium channel activation, and SR generated Cai OSC.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00246-03 LCS

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Effect of Alpha$_1$-Adrenergic Stimulation on Isolated Ventricular Myocytes

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	M. C. Capogrossi	Medical Officer	LCS, NIA
Others:	W. A. Kachadorian	Staff Scientist	LCS, NIA
	E. G. Lakatta	Chief	LCS, NIA
	H. A. Spurgeon	Physiologist	LCS, NIA

COOPERATING UNITS *(if any)*

LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

SECTION

Cardiac Function Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1	.9	.1

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The effect of alpha$_1$-adrenergic stimulation on the inotropy of the myocardium is still controversial. A positive inotropic effect has been well documented and it is often preceded by a short lived decrease in contractility. Additionally a persistent negative inotropic effect of alpha$_1$ stimulation has also been described in multicellular cardiac preparations. The purpose of this study was to characterize the effect of alpha$_1$ stimulation on the cytosolic Ca transient and on the contractile properties of single ventricular myocytes under condition leading either to an enhancement or a decrease in twitch amplitude. Isolated rat ventricular myocytes, pretreated with propranolol were used to investigate the effect of alpha$_1$-adrenergic stimulation with phenylephrine on contractility, cytosolic Ca homeostasis and on the frequency of spontaneous contractile waves (CW), which represent the mechanical expression of spontaneous calcium release from the sarcoplasmic reticulum (SR). a) In 1 mM bathing [Ca^{2+}] (Ca_o), during field stimulation at 0.2 Hz, alpha$_1$ had a positive inotropic effect which was reversibly abolished by prazosin and appeared related to an increased myofilament responsiveness to calcium in addition to some enhancement in the amplitude of the cytosolic Ca transient associated with the twitch. b) During stimulation at 0.2 Hz, in 5 mM Ca_o, CW appeared in some of the diastolic intervals. Phenylephrine abolished them and decreased twitch amplitude. In similar experiments with myocytes loaded with the Ca probe Indo-1 AM the negative effect of alpha$_1$ on TA was associated with a decrease in the amplitude of the cytosolic Ca transient. c) In the absence of stimulation, in 5 mM Ca_o, alpha$_1$ significantly and reversibly reduced cytosolic and CW frequency. This effect could be prevented by the alpha$_1$ blocker prazosin. No effect of pheylephrine on cytosolic Ca was observed at rest in 1 mM Ca_o. These findings are consistent with the view that the effect of alpha$_1$-adrenergic stimulation of cardiac cells can vary in relation to intracellular Ca.
Discontinued.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00247-03 LCS

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Detection and Prognosis of Silent Myocardial Ischemia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	J. L. Fleg	Cardiologist	LCS, NIA
Others:	A. Zonderman	Senior Staff Fellow	LPC, NIA
	P. Costa	Chief	LPC, NIA
	E. G. Lakatta	Chief	LCS, NIA
	E. Shefrin	Computer Scientist	LSB, NIA
	L. Brant	Mathematical Statistician	LSB, NIA

COOPERATING UNITS *(if any)*

Division of Cardiology, Johns Hopkins Hospital, Baltimore (G. Gerstenblith, L. Becker, M. L. Weisfeldt), Akron Cardiology Consultants. Ohio (R. Josephson)

LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

SECTION

Cardiac Function Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.5	0.6	0.9

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Among 726 apparently healthy Baltimore Longitudinal Study of Aging (BLSA) men and women who have undergo serial maximal exercise testing since 1969, the risk of future cardiac events was compared in those whose initial test was positive (Group I), those who converted from negative to positive (Group II and those who remained negative over a 6.4 year mean follow-up (Group III). By proportional hazards analysis, Groups I and II had a nearly identical enhanced risk of a cardiac event (RR of 2.78 and 2.72 respectively) compared to Group III subjects. Thus, in asymptomatic volunteers, serial conversion from a negative to a positive exercise ECG has a similar predictive value for a future coronary event as an initially positive ECG response.

To separate the effects of age and silent myocardial ischemia (SI), on the left ventricular (LV) response to maximal upright cycle ergometry, we compared 3 groups: 8 clinically healthy older men (mean age - 76) with prior abnormal ECG and thallium scan (TS) responses to maximal treadmill exercise (OSI); 16 age-matched men with normal ECG and TS responses (OC); and 21 young (mean age = 33) controls (YC). At rest LV ejection fraction (EF), end-diastolic volume index (EDVI) and end -systolic volume index (ESVI) were similar in the 3 groups. With cycle exercise LVEF increased markedly in the YC, less in the OC and least in the OSI. In contrast, exercise-induced LV dilatation (increased ESVI) was most pronounced in the OSI with a lesser increase in the OC; EDVI actually declined below baseline values by maximal effort in the YC. Thus, age-related cardiac dilatation and blunted EF response to upright cycling are exaggerated in older subjects with exercise-induced SI.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

PROJECT NUMBER

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00248-03 LCS

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(90 characters or less. Title must fit on one line between the borders.)*
Factors Detecting Maximal Exercise Performance in Man

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.)* *(Name, title, laboratory, and institute affiliation)*

PI:	J. L. Fleg	Cardiologist	LCS, NIA
Others:	E. G. Lakatta	Chief	LCS, NIA
	J. Busby	Guest Researcher	LCP, NIA
	D. Drinkwater	Visiting Fellow	LCP, NIA
	R. Andres	Chief	LCP, NIA
	L. Fried	Guest Researcher	LCP, NIA
	J. Tobin	Chief, APS	LCP, NIA
	F. O'Connor	Chemist	LCS, NIA

COOPERATING UNITS *(if any)*
Div. Cardiol., Johns Hopkins Hospital (G. Gerstenblith, S. Schulman, L. Becker, M. L. Weisfeldt); Sch. Hygiene, Johns Hopkins Hospital (S. Fortney); Div. Geriat. Med., Francis Scott Key Med. Ctr. (A. Goldberg)

LAB/BRANCH
Gerontology Research Center, Laboratory of Cardiovascular Science

SECTION
Cardiac Function Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.2	1.8	2.4

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

We have recently demonstrated in 184 non endurance trained non obese men and women from the Baltimore Longitudinal Study of Aging (BLSA) with normal maximal exercise ECGs that the age-associated decline in maximal oxygen consumption (VO_2max) was markedly attenuated after VO_2max was normalized for total muscle mass instead of body weight. These results suggested an important role of peripheral (vs central circulatory) factors in the age-related reduction of maximal aerobic performance. A closely related issue is whether the well documented marked increase in VO_2max of older endurance trained men relative to that of age-matched peers is mediated primarily by central versus peripheral adaptations. We performed radionuclide ventriculography and VO_2 measurements during maximal upright bicycle ergometry in 8 endurance trained (mean age = 65 + 5 yr, treadmill VO_2max = 51 + 4 ml/kg/min) and 6 age-matched sedentary (treadmill VO_2max = 31 + 4 ml/kg.min) men. The maximum workload (MWL), the measured VO_2 at MWL (peak VO_2) and cardiac output (CO) at MWL and derived average arteriovenous oxygen difference [(A-V)O2] at MWL are shown below (mean ± S.D.).

	Endurance Trained	Sedentary	p
MWL (watts)	172 + 31	129 + 19	.02
Peak VO_2 (L/min)	2.27 ± 0.33	1.52 ± 0.30	.003
CO (L/min)	17.6 ± 4.2	15.9 ± 3.4	NS
(A-V)O_2 (vol. %)	13.4 ± 2.9	9.9 ± 2.7	.05

Thus, the augmented aerobic capacity of endurance trained seniors at exhaustion during upright bicycle exercise is due primarily to peripheral rather than central adaptations.

Discontinued (Description in Contract Progress Report).

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00249-03 LCS

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Cellular Calcium Ion Homeostasis and the Impact of Aging

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	R. G. Hansford	Chief, EMBS	LCS, NIA
Others:	B. Hogue	Chemist	LCS, NIA
	D. Guyker	Stay-in-School Student (EOD 3/89)	LCS, NIA

COOPERATING UNITS *(if any)*
Cardiac Function Section, LCS

LAB/BRANCH
Gerontology Research Center, Laboratory of Cardiovascular Science

SECTION
Energy Metabolism and Bioenergetics Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS.	PROFESSIONAL.	OTHER:
1.1	0.5	0.6

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project constitutes an investigation into mechanisms whereby cells achieve the homeostasis of cytosolic free Ca^{2+} concentrations ($[Ca^{2+}]_c$), and allow perturbations in $[Ca^{2+}]_c$ in response to hormones and neurotransmitters. Further, it addresses derangements in these control mechanisms which may occur in old-age. This year, we have asked the following questions. (1) What is the mechanism whereby actively-oxidized substrates lead to a positive inotropic effect in cardiac muscle preparations? Is this a function of an increased sarcoplasmic reticulum (SR) Ca^{2+} store? We have approached this using individual rat cardiac myocytes, with measurement of contractility and of the increase in cytosolic free Ca^{2+} ($[Ca^{2+}]_c$) due to sudden addition of caffeine, which releases SR Ca^{2+}. (2) Is the functioning of the SR obligatory for the development of the force-frequency relationships which are characteristic of cardiac muscle preparations from different mammalian species? In a collaboration with the Cardiac function Section, we have approached this by disabling the SR with caffeine or ryanodine and studying force-frequency relationship in single cardiac myocytes from guinea pig and rat. (3) Is the magnitude of the Ca^{2+} concentration gradient in cardiac mitochondria affected by the aging process? This derives from our earlier studies in which we have shown that the activity of both Ca^{2+} uptake and egress pathways is diminished in old-age. (4) Are there differences with senescence in the depolarization-induced phosphorylation of the protein synapsin I? This Ca^{2+}-dependent phosphorylation forms part of the mechanism of exocytosis of transmitter-substance vesicles and has been studied this year in synaptosomes (pinched-off presynaptic vesicles) from cerebral cortex of rats of different ages (3,6, and 24 months).

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00250-02 LCS

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Age-Related Changes in Cardiac Structure and Function

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	J. L. Fleg	Staff Cardiologist	LCS, NIA
Others:	R. S. Danziger	Medical Staff Fellow DOD 7/88	LCS, NIA
	E. G. Lakatta	Chief	LCS, NIA
	S. P. Schulman	Medical Staff Fellow DOD 2/89	LCS, NIA
	C. Swinne	Guest Researcher	LCS, NIA

COOPERATING UNITS *(if any)*
Division of Cardiology, Johns Hopkins Hospital (J. A. Lima, G. Gerstenblith, M. Waclawiw), Division of Cardiology, Frances Scott Key Medical Center (D. Bush)

LAB/BRANCH
Gerontology Research Center, Laboratory of Cardiovascular Science

SECTION
Cardiac Function Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.0	1.0	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

We have previously shown that left ventricular (LV) wall thickness increases with age in normotensive BLSA men. To determine whether this finding relates to the increase in systolic blood pressure (SBP) which also accompanies normal aging, LV wall thickness (Th) was measured in short axis 2-dimensional echocardiogram (2-D echo) echoes obtained from 74 participants of the Baltimore Longitudinal Aging population without evidence of hypertensive (BP < 140/90) or ischemic heart disease. The average of 3 contigous septal wall Th measurements normalized for body surface area (WTS) was related to age (WTS = 0.66 + 0.0029 [age], $r = 0.26$, $p < 0.03$), but more strongly to SBP (WTS = 0.32 + 0.0039 [SBP], $r = 0.39$, $p < 0.001$). When WTS was regressed against age and SBP (multivariate analysis) the effect of age became insignificant ($p = 0.28$) while SBP remained a strong determinant of WTS ($r = 0.41$, $p = 0.0045$). These data suggest that the normal LV hypertrophy associated with aging is mediated via an increase in SBP. Doppler echocardiography during isometric handgrip in 25 healthy BLSA subjects revealed that advanced age was associated with a greater rise in systolic blood pressure ($r = .53$, $p = .008$), greater increases in LV end diastolic dimension ($r = .59$, $p = .002$) and end systolic dimensions ($r = .50$, $p = .01$), blunted fractional shortening ($r = .42$, $p = .04$) and a further augmentation of atrial contribution to LV filling ($r = .48$, $p = .014$). In a related study, MUGA end-diastolic volume (EDV) and ejection fraction (EF) in 47 women (W) and 104 men (M), and average LV end-diastolic wall thickness (EDWT) by 2-D echo (31 W and 43 M) were obtained in BLSA subjects. Both EDV and EDWT were smaller in W than in M (117±30 vs 146±38 ml $p<0.001$ and 0.97± 0.14 vs 1.17±0.16 cm, $p<.001$ respectively). EF was greater in W than in M (68±7 vs 64±7%, $p<.005$). Gender differences were eliminated by adjustment for body surface area (BSA) and systolic blood pressure (SBP). Thus, there is no distinctive gender difference in cardiac structure or function.

Discontinued. Description in Contract Progress Report.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00251-02 LCS

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Mechanisms of Anoxic Contractile Failure in Cardiac myocytes

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI	M. D. Stern	Guest Researcher	LCS, NIA
Others	H. S. Silverman	Senior Staff Fellow	LCS, NIA
	R. A. Josephson	Medical Staff Fellow DOD 6/88	LCS, NIA
	M. C. Capogrossi	Medical Officer	LCS, NIA
	E. G. Lakatta	Chief	LCS, NIA

COOPERATING UNITS *(if any)*

Department of Physiology, Temple University, Philadelphia, PA (S. R. Houser), Department of Physiology, University of Maryland, Baltimore, MD (C. G. Nichols and W. J. Lederer)

LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

SECTION

Cardiac Function Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.5	1.4	0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Anoxia of the heart causes failure of contraction prior to any irreversible injury. The mechanism by which anoxia blocks cardiac excitation-contraction coupling is unknown. Studies in whole muscle are confounded by heterogeneity; however it has not previously been possible to achieve the low oxygen tensions required to study anoxia in single myocytes during electrophysiology recordings. Guided by calculations of oxygen transport, we developed a system in which myocytes in an open dish are insulated from oxygen by a laminar counterflowing column of argon, permitting free access by microelectrodes while maintaining a PO_2 less than 0.02 torr. In the absence of glucose, the amplitude of stimulated contraction of anoxic ventricular myocytes fell to zero over two minutes, after a lag period attributable to consumption of endogenous glycogen. The cytosolic calcium transient, measured by Indo-1 fluorescence, fell to zero simultaneously with the contraction. After the twitch had failed, microinjection of caffeine around the cell still caused a large calcium release and contraction, indicating that sarcoplasmic reticulum calcium stores were not depleted. Failure of the twitch was accompanied by shortening and then failure of the action potential; under voltage clamp, large outward currents, reversing at the resting potential, developed during contractile failure. After failure of action potential -mediated contraction, voltage clamp depolarization, using a large command voltage to compensate for the series resistance error due to the outward currents, restored a normal twitch contraction. We conclude that anoxic contractile failure in the rat myocyte is due to alteration of the action potential, and the distal pathways of excitation-contraction coupling remain essentially intact.

Combined into Z01 AG 00257-01 LCS.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00252-02 LCS

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Mechanisms of Ethanol Depression of Myocardial Contractility

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.)* *(Name, title, laboratory, and institute affiliation)*

PI:	E. G. Lakatta	Chief	LCS, NIA
Others:	R. S. Danziger	Medical Staff Fellow (DOD 7/88)	LCS, NIA
	M. C. Capogrossi	Medical Officer	LCS, NIA
	M. Sakai	Visiting Fellow (DOD 4/88)	LCS, NIA
	S. Schulman	Medical Staff Fellow (DOD 2/89)	LCS, NIA
	O. Hano	Guest Researcher	LCS, NIA
	S. Raffaeli	Guest Researcher (DOD 12/87)	LCS, NIA

COOPERATING UNITS *(if any)*
Division of Cardiology, Johns Hopkins University School of Medicine, Baltimore, MD (T. Guarnieri and G. Gerstenblith)

LAB/BRANCH
Gerontology Research Center, Laboratory of Cardiovascular Science

SECTION
Cardiac Function Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.0	2.9	.1

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The mechanisms of acute ethanol depression of myocardial contractility were examined in intact hearts, isolated cardiac muscle and in suspensions in individual isolated cardiac myocytes. In the isolated, rat heart, ethanol (0.75 - 6.0 vol%) caused a concentration-dependent decline in developed pressure without a change in ATP (adenosine triphosphate), phosphocreatine, inorganic phosphate, or pH measured by NMR techniques. The functional decline could be rapidly and completely reversed by perfusing the ethanol-free solution and significantly, although not completely, reversed by increasing perfusate calcium to 4 mM. In single rat cardiac myocytes and myocyte suspensions the acute effects of ethanol (1-5%) on cytosolic $[Ca^{2+}]$ (Ca_i) transient and contraction and on sarcoplamic reticulum (SR) calcium content were examined. During stimulation at 1 Hz ethanol decreased the amplitude of the Ca_i transient and decreased the amplitude of contraction. The Ca_i transient amplitude was decreased to a lesser extent than the contraction amplitude. In myocyte suspensions, ethanol caused a concentration dependent initial increase in Ca_i and a subsequent depletion of SR calcium content, manifest as a diminution in the Ca_i increase elicited by caffeine in the presence of extracellular EGTA and zero added calcium. Thus, in rat cardiac myocytes high ethanol concentrations induces SR calcium release and depletes the SR of calcium, attenuates the Ca_i transient elicited by electrical stimulation and alters the myofilament calcium interaction possibly due to a decrease in myofilament calcium sensitivity. These combined effects contribute to the high concentration ethanol depression of contraction. In additional studies in isolated ferret cardiac muscle the threshold ethanol concentration (0.15±0.05%) which produced a 10% decline in contractile force did not change the transient. This decline in contraction strength with no change in Cai transient suggests that the negative inotropic effect of low concentrations of ethanol is due to an altered myofilament response to calcium.

Discontinued.

GPO 814-818

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00253-02 LCS

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Diminished Cardiac Response to Chronic Volume Overload in Older Adult Rats

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	H. A. Spurgeon	Physiologist	LCS, NIA
Others:	E. G. Lakatta	Chief	LCS, NIA

COOPERATING UNITS *(if any)*

Division of Cardiology, Johns Hopkins University School of Medicine, Baltimore, MD (G. W. Walford)

LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

SECTION

Cardiac Function Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.2	1.2	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The effects of long term hemodynamic overload in middle-aged or older animals is unclear because most studies have used relatively young animals or, when older ones were used, did not compare different age groups with the same duration of the hemodynamic load. There is good reason to believe that the adaptive process of hypertrophic growth may be modified by the age of the animal. Atrioventricular block (B) causes a volume overload state that can be tolerated for long periods of time and induces considerable cardiac hypertrophy that can be related to the amount which the heart rate is slowed. To examine the effect of this type of chronic hemodynamic overload in animals of different ages, we used closed chest electrocautery to induce complete B in male, Sprague-Dawley rats of 5, 12, and 16 months of age for mean duration of 7 months. The results indicate aging over this adult period modified the influence of long term B on cardiac size and the function of isolated cardiac muscle. Chronic B: (1) caused cardiac hypertrophy that was greater in the younger than older animals; (2) prolonged contraction duration that was correlated with the extent of hypertrophy regardless of age and (3) resulted in age-related alterations in contractile function of isolated intact and "chemically skinned" muscle, with the youngest B have more force than control (C) and the older B having equal or less force than C. Differences between younger and older B in both excitation -contraction coupling and myofilament force production are required to explain the observed results. These findings indicate an age-related difference in the chronic myocardial adaptive response to chronic atrioventricular B. The age-related differences in force development in the present study cannot be attributed to the age-related differences in hypertrophy. The ultimate explanation for these findings will require a better understanding of how the myocardium "restructures" itself under the influence of any given hemodynamic stress and how aging affects this process.

Discontinued.

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PROJECT NUMBER

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00254-02 LCS

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Effect of Polyamines on Isolated Ventricular Myocytes

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.)* *(Name, title, laboratory, and institute affiliation)*

P.I.	M. C. Capogrossi	Medical Officer	LCS, NIA
Others:	E. G. Lakatta	Chief	LCS, NIA

COOPERATING UNITS *(if any)*
INRCA, Ancona, Italy (C. Ferroni)

LAB/BRANCH
Gerontology Research Center, Laboratory of Cardiovascular Science

SECTION
Cardiac Function Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.5	.5	.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Polyamines have been shown to be present in many cell types and their concentration within the tissue changes in response to a variety of stimuli. β-adrenergic stimulation and hypoxia are associated with an increase in the activity of ornithine decarboxylase, the enzyme responsible for the formation of polyamines, while aging is associated to a decrease in the activity of that enzyme. Additionally, it has been suggested that polyamines may modulate the inotropic state of the myocardium and in particular its response to β-adrenergic stimulation. We have attempted to define the role of polyamines on the cardiac cell function.

Isolated rat ventricular myocytes were used to investigate the effect of putrescine, spermidine and spermine on the twitch and the associated cytosolic calcium transient and, in the unstimulated state, on the frequency of spontaneous calcium release from the sarcoplasmic reticulum (SR) and on resting cytosolic calcium. While putrescine had no effect on contraction and cytosolic calcium spermidine and spermine had a negative inotropic effect which was due to a decrease in the cytosolic calcium transient and not to a change in myofilament responsiveness to cytosolic calcium. In the unstimulated state there was no effect of spermine either on spontaneous SR calcium release or on resting cytosolic calcium.

Discontinued.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00255-02 LCS

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Mechanism of Action of Antidiuretic Hormone

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory and institute affiliation)*

PI:	W. A. Kachadorian	Research Physiologist	LCS, NIA
Others:	K. R. Spring	Research Physiologist	LKEM, NHLBI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Gerontology Research Center, Laboratory of Cardiovascular Science

SECTION
Cardiac Function Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS: 0.2	PROFESSIONAL: 0.1	OTHER: 0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Antidiuretic hormone (ADH) increases the permeability of the distal nephron to water. Water reabsorption in this part of the kidney occurs in response to ADH provided an osmotic gradient from tubule lumen to blood is present. The toad urinary bladder has been used extensively as a structural and functional analogue of the distal nephron for assessing the mechanism of action through which the hydrosmotic response to ADH is achieved. This tissue was used in the present study to evaluate the possibility that ADH action involves regulation of water permeability not only by altering the luminal plasma membrane barrier of cells forming the mucosal surface of this tissue, but also regulation of one or more resistances beyond or "distal" to this site. Previous freeze fracture studies which have defined luminal membrane water permeability in morphologic terms, suggest that this may be a valid hypothesis. The current experiments demonstrate directly the validity of this hypothesis and provide insight about the functional nature of the intramembrane structural entities that gain appearance in the luminal membrane in response to ADH and are considered as sites for transluminal membrane water movement.

Discontinued.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 AG 00256-01 LCS

PERIOD COVERED: October 1, 1988 to September 30, 1989

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.): Myocardial Reserve and Calcium Tolerance in the Cardiomyopathic Hamster

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	E. G. Lakatta	Chief	LCS, NIA
Others:	O. Hano	Guest Researcher	LCS, NIA

COOPERATING UNITS (if any): Division of Cardiology, Johns Hopkins Hospital, Baltimore (E. Kasper, H. F. Weisman)

LAB/BRANCH: Gerontology Research Center, Laboratory of Cardiovascular Science

SECTION: Cardiac Function Section

INSTITUTE AND LOCATION: Baltimore, Maryland 21224

TOTAL MAN-YEARS: 1.0	PROFESSIONAL: 0.9	OTHER: 0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

While the cardiomyopathic hamster (CMH), BIO14.6 strain, develops congestive heart failure with aging, the evolution of compromised myocardial reserve, calcium intolerance, and response to catecholamines prior to overt failure remains to be fully understood and is investigated in this project. We used hearts from 28-52 day old male CMH and age-matched F1B strain control (C) hearts. Isolated, isovolumic and AV blocked hearts were perfused with Hepes buffer at constant pressure and stimulated at 2 Hz at 37°C to investigate the effects of (1) an increasing in bathing $[Ca^{2+}]$ (1-10 mM; n = 10 of each), β-adrenergic (isoproterenol, 1 nM - 1 μmM; n = 10 of each), (3) α-adrenergic (phenylephrine, 0.1 - 10 μ mM; n = 10 of each) agonists, and (4) Ca^{2+} channel agonist (BAYK8644, 5 nM - 1 μM; n = 10 of each) on contractile properties. In CMH, the peak developed pressure response saturates at a significantly ($p < 0.001$) smaller developed pressure and declines from maximum occurs at a significantly lower concentrations of α- or β-agonist, Ca^{2+} channel agonist or of perfusate $[Ca^{2+}]$ compared to control. The rise in end-diastolic pressure with increasing in drug or perfusate $[Ca^{2+}]$ concentration in CMH is also significantly ($p < 0.001$) greater than control. These results suggest that myocardium shows enhanced response to Ca^{2+} per se, and also that myocardial cell Ca^{2+} loading in response to catecholamines is greater in CMH than in C hearts.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 AG 00257-01 LCS

PERIOD COVERED: October 1, 1988 to September 30, 1989

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Oxidant-Induced Intracellular Calcium Overload in Cardiac Myocytes

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory and institute affiliation)

PI:	H. Silverman	Senior Staff Fellow	LCS, NIA
Others:	E. G. Lakatta	Chief	LCS, NIA
	M. D. Stern	Guest Researcher	LCS, NIA

COOPERATING UNITS (if any)

LAB/BRANCH: Gerontology Research Center, Laboratory of Cardiovascular Science

SECTION: Cardiac Function Section

INSTITUTE AND LOCATION: NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS: Man hours 1.0	PROFESSIONAL: 0.6	OTHER: 0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Reperfusion of ischemic myocardium limits ischemic damage but may induce cellular injury due to reperfusion itself. Recent evidence suggests that myocardial reperfusion is accompanied by an increase in intracellular calcium and myocardial damage. Other studies have documented a burst of reactive oxygen radicals at the moment of reperfusion in the intact heart. Oxygen radicals may contribute to the calcium overload and cellular injury of reperfusion but supportive data is lacking. Utilizing the laminar counterflow barrier well, developed in our laboratory, we observed a rise in intracellular calcium and cellular injury in single rat cardiac myocytes exposed to anoxia and reoxygenation. The isolated cardiac myocyte allows the simultaneous study of cell function, intracellular calcium and membrane potential from a single cardiac myocyte avoiding the problems associated with the multiple cell types found in bulk cardiac preparations. In separate experiments we exposed single cardiac myocytes to exogenously generated oxygen radicals/oxidants and observed an initial increase in the electrically stimulated twitch amplitude associated with a decrease in diastolic length. Aftercontractions later developed and finally the cell became inexcitable and underwent contracture. These mechanical changes appeared to be consistent with intracellular calcium overload. Cytosolic calcium, measured in cells loaded with the fluorescent probe Indo-1, rose following the administration of oxidants. When the action potential was monitored with whole-cell current clamp there was marked progressive action potential plateau prolongation without depolarization of the resting potential. Thus oxidants/oxygen radicals induce calcium overload and cellular injury in cardiac myocytes and cause action potential changes that may relate to calcium loading.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00258-01 LCS

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Cytosolic Calcium Modulation of the Cardiac Action Potential

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	W. duBell	IRTA Fellow	LCS, NIA
Others:	E. G. Lakatta,	Chief	LCS, NIA
	H. A. Spurgeon	Physiologist	LCS, NIA
	M. C. Capogrossi	Medical Officer	LCS, NIA

COOPERATING UNITS *(if any)*

Department of Biology, University of Turku, Finland (A. Talo); Department of Physiology, University of Leeds, England (M. Boyett)

LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

SECTION

Cardiac Function Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.8	0.7	0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The role of the cytosolic Ca^{2+} (Ca_i) transient in determining the configuration of the cardiac action potential was investigated in single isolated rat ventricular myocytes loaded with the Ca^{2+} sensitive fluorescent dye Indo-1. The magnitude of the Ca_i transient was graded by various physiologic and pharmacologic interventions and membrane voltage or current was recorded using patch-type microelectrodes. The peak of the Ca_i transient corresponded in time to the start of the action potential plateau. Although short in duration relative to the Ca_i transient, the plateau was followed by a slow tail of repolarization, only a few millivolts in amplitude; that decayed in parallel with the Ca_i transient. Stimulation from rest resulted in a negative staircase in the magnitude of the Ca_i transient, accompanied by a decrease in the duration of the action potential plateau and in the magnitude of the slow tail of repolarization. Space-plane loops of membrane potential (Vm) vs. Indo-1 ratio revealed that during the slow tail of repolarization there was a common relationship between Vm and Ca_i from all the beats of a stimulus train. Electronic subtraction of the action potential and Ca_i transient of a steady state beat from those of the first post-rest beat showed that the large positive difference in the action potential plateau had a similar waveform to the Ca_i transient difference, with both peaking at the same time. Identical results were seen when ryanodine was used to reduce the magnitude of the Ca_i transient. Under voltage clamp conditions, Ca_i transients elicited by brief pulses or caffeine occurred in phase with a small inward current. Like the Ca_i transient, this current exhibited a negative staircase during a train of brief voltage clamp pulses following a period or rest. It is concluded that this inward current, mediated by the Ca_i transient, modulates the plateau of the rat ventricular action potential and is responsible for the slow tail of repolarization.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 AG 00259-01 LCS

PERIOD COVERED: October 1, 1988 to September 30, 1989

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.):
The Role of Opioid Peptides in Modulating Myocardial Function

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	C. Ventura	Guest Researcher	LCS, NIA
Others:	E. G. Lakatta	Chief	LCS, NIA
	M. C. Capogrossi	Medical Officer	LCS, NIA

COOPERATING UNITS (if any)

Department of Biochemistry, University of Bologna Medical School, Bologna, Italy

LAB/BRANCH: Gerontology Research Center, Laboratory of Cardiovascular Science

SECTION: Cardiac Function Section

INSTITUTE AND LOCATION: NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.0	0.8	0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The discovery of endogenous opioid peptides in the brain has resulted in extensive investigations to determine the physiologic role of these substances. With regard to the cardiovascular system it has been shown that myocardial cells possess specific opioid receptors and it has been suggested that opioids released from the adrenal medulla, from nerve terminals and possibly also synthesized within myocardial cells as a large amount of preproenkephalin mRNA has recently been identified in cardiac myocytes may directly effect myocardial cell function. The objectives of this study are: a) to define the role of opioid peptides to modulate myocardial cell function, b) to identify which of the known opioid receptors (delta, K and μ) mediate the action of these peptides. c) to characterize the steps involved in signal transduction subsequently to the binding of the opioid to its specific receptor, d) to determine whether the mechanisms for signal transduction identified in myocardial cells are common to other cell types such as neurons. Isolated rat ventricular myocytes were used to investigate the effect of leucine-enkephalin, methionine-enkephalin, DADLE (delta agonists), DAGO (μ agonist), and U-50 (K agonist) on myocardial cell function. Changes in contractility and cytosolic $[Ca^{2+}]_i$, Ca_i, were simultaneously recorded in myocytes loaded with the calcium probe Indo-1. Both the delta and K agonist had a marked negative inotropic action and prolonged the time course of the contraction. These changes were associated to a decrease in the amplitude and a prolonged duration of the Ca_i transient . The μ agonist had no effect. At rest the rapid (200 msec) addition of caffeine (15 mM) from a pipette above the cell releases calcium from the sarcoplasmic reticulum and transiently increases Ca_i, This effect was abolished by 40 min exposure to 10 μM leucine-enkephalin or U-50 and preserved when leucine-enkephalin or U-50 were superfused with their specific antagonists, respectively naloxone or Mr-1452. Thus, SR calcium depletion is a mechanism for the delta and K opioid receptor agonists in the myocardium.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 AG 00260-01 LCS

PERIOD COVERED: October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*: Novel Positive Cardiac Inotropic Agents

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	C. Ventura	Guest Researcher	LCS, NIA
Others:	O. Hano	Guest Researcher	LCS, NIA
	E. G. Lakatta	Chief	LCS, NIA
	R. Miller	Biologist DOD 8/89	LCS, NIA
	M. C. Capogrossi	Medical Officer	LCS, NIA

COOPERATING UNITS *(if any)*: E. Merck, Darmstadt, West Germany (M. Klockow)

LAB/BRANCH: Gerontology Research Center, Laboratory of Cardiovascular Science

SECTION: Cardiac Function Section

INSTITUTE AND LOCATION: NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS: 1.0	PROFESSIONAL: 0.8	OTHER: 0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

All positive inotropic agents that are available for clinical use exercise their effect predominately via an increase in cell calcium loading. However once the myocardial preparation has reached its peak contractile response a further increase in cell calcium loading is associated initially with a plateau and then with a decline in the inotropic state of the muscle, an increase in diastolic tone, aftercontractions and arrhythmias. This condition which has been defined as "calcium overload" represents the limiting factor in the clinical use of positive inotropic agents. Thus, it is desirable to develop drugs that increase the contractility of the heart via an enhancement in myofilament responsiveness to calcium rather than by increasing the extent of cell calcium loading. We tested the effect of the thiadiazinone EMD 54622, an experimental substance designed by E. Merck, Darmstadt, (FRG) which sensitizes isolated cardiac myofibrils to calcium. We determined whether EMD 54622 increases twitch amplitude without increasing cytosolic calcium in guinea pig ventricular myocytes. During stimulation at 1 Hz in 1 mM bathing calcium, EMD 54622 (0.5-1.25 μM); (1) increases the twitch amplitude up to more than twofold over control but not the cytosolic calcium transient, measured simultaneously as the 410/490 nm ratio of Indo-1 fluorescence, and this fully reversed after drug wash out; (2) shifts the twitch amplitude-cytosolic calcium relationship (obtained by varying bathing calcium) to the left. Thus the positive inotropic action of EMD 54622 in intact cells occurs via an increased myofilament responsiveness to calcium.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 AG 00261-01 LCS

PERIOD COVERED: October 1, 1988 to September 30, 1989

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Length/Load-Dependent Calcium Modulation of Contraction in Cardiac Myocytes

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	S. J. Sollott	Medical Staff Fellow	LCS, NIA
Others:	E. G. Lakatta	Chief	LCS, NIA
	H. A. Spurgeon	Physiologist	LCS, NIA

COOPERATING UNITS (if any)

LAB/BRANCH: Gerontology Research Center, Laboratory of Cardiovascular Science

SECTION: Cardiac Function Section

INSTITUTE AND LOCATION: NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.0	0.8	0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Multiple lines of evidence has established that contractile performance of cardiac tissue is governed by the intimate relationship between sarcomere length and calcium-myofilament activation (LDA) forming the basis of the Frank-Starling mechanism. In contrast, relaxation is governed by the competition between calcium-myofilament inactivation and the external restoring force associated with muscle strength and loading. In order to eliminate mechanical and electrical inhomogeneity of bulk tissue, prior studies of contractility have been performed in intact single myocytes, albeit at slack length (as no satisfactory method exists to alter length/load in this model), or in chemically-skinned cells. To examine the effect of strength on the twitch contraction and relaxation of single ventricular myocytes with intact sarcolemma, we developed a novel technique enabling reversible gradation in the resting cell length of up to 15-18%. Our initial results show (1) that the relative effect of bathing calcium to augment shortening velocity varied with the cell length is consistent with the concept that myofilament-calcium activation is length/load-dependent. A stretch of resting cell length increases twitch amplitude and accelerates relaxation without changing the cytosolic calcium transient. Thus, a cytosolic calcium-dependence of relaxation at slack length can be overridden by the external restoring force associated with stretch, consistent with the concept of a length/load-dependence of relaxation in bulk cardiac muscle, and, moreover, stretch represents a principal determinant of relaxation over calcium-myofilament inactivation in tissue with "normal" calcium homeostasis.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00262-01 LCS

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Title pH Regulation in Cardiac Myocytes

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	P. S. Blank	IRTA Fellow DOD 7/89	LCS. NIA
Others:	H. Silverman	Senior Staff Fellow	LCS, NIA
	M. D. Stern	Guest Researcher	LCS, NIA
	M. C. Capogrossi	Medical Officer	LCS, NIA
	R. G. Hansford	Chief, EMBS	LCS, NIA
	E. G. Lakatta	Chief	LCS, NIA
	O. Chung	Guest Researcher	LCS, NIA

COOPERATING UNITS *(if any)*

LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

SECTION

Cardiac Function Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.5	0.5	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Physiological studies have been aided by the use of intracellular indicators. Indicators for intracellular calcium and pH are used in monitoring physiological and pathophysiological properties of isolated cardiac myocytes and intact cardiac tissue. The purpose of this project was to characterize SNARF-1, seminaphthorhodafluor, a recently synthesized intracellular pH indicator, and modify our existing time resolved calcium system for pH investigations.

The emission spectrum of SNARF-1 contains two well separated emission peaks at 590 and 640 nm. This feature allows the indicator to be used in the single excitation, dual emission, ratio mode; analogous to the calcium indicator, INDO-1. The indicator is available in both the free acid form and as a cell permeate acetoxymethyl ester. We have found that isolated cardiac myocytes are easily loaded with the ester, and have the following characteristics: 1) the contractile properties are unchanged in the presence of the indicator, 2) the indicator is present primarily in the cytosol (95% to 100%) with virtually no partitioning into the mitochondria, 3) the indicator is retained for several hours at 20°C, and 4) steady-state and transient changes in pH are easily monitored. Preliminary results on myocytes exposed to anoxia indicate that pH changes can be monitored during important physiological and pathophysiological perturbations.

CONTRACT

Name and Number : JOHNS HOPKINS UNIVERSITY (NO1-AG-4-2109)

Title : Non-Invasive Assessment of Cardiac Structure and Function in Aging Men and Women

Date Contract Initiated: September 30, 1977

Current Annual Level : $268,327

During the past 11½ years, rest and exercise thallium and gated blood pool cardiac scans have been performed respectively on over 700 and 250 participants in the BLSA. These studies have provided unique insights concerning the prevalence and prognostic significance of exercise-induced myocardial blood flow abnormalities (i.e. ischemia) as well as the effect of age, gender, life-style and disease on cardiac structure and function at rest and during aerobic exercise. The contract has been renewed for 9 years, during which cardiac blood pool and thallium scans be continued in the following groups of individuals.

A. Gated Cardiac Blood Pool Scans

1. Repeat Scans. In 100 men and women who have had blood pool scans at least 5 years previously, the test will be repeated, with simultaneous measurement of oxygen consumption (VO_2). This will allow insight into longitudinal changes in cardiac function at rest and during exercise. The VO_2 data will provide information regarding central (cardiac) versus peripheral (arteriovenous oxygen difference) mechanisms for maintaining VO_2 with advancing age.

2. Scans in Highly Trained Seniors, Sedentary Subjects Pre- and Post-Training, and Obese individuals Pre- and Post-Weight Loss. These scans, all performed with simultaneous VO_2 measurements, will allow determination of the central and peripheral effects of conditioning status and obesity on aeorbic exercise performance, and the interrelations of such lifestyle variables with the aging process.

3. Scans in Patients with Latent Coronary Artery Disease (CAD) Preliminary data from such individuals with abnormal exercise ECG's and or exercise thallium scans, suggest that ischemia and advanced age have additive effects on certain cardiac parameters. Extension of these studies will allow more accurate characterization of this interaction between age and latent CAD and help to clarify discrepancies in the cardiovascular aging literature which have resulted from the inclusion of such individuals with latent CAD in some studies but not others.

4. Additional Studies in Normals with simultaneous measurement of VO_2. In other BLSA volunteers who have no evidence of CAD by all available criteria, these scans should be made:

a. To contrast the effect of age in men with its effect in women on the cardiovascular response to stress.

b. To evaluate the effect of age on the response to other commonly employed drugs used to treat large numbers of elderly individuals, e.g., vasodilators.

c. To provide a base of 350-400 individuals for a longitudinal evaluation of the effect of age itself on cardiovascular function.

B. Thallium Perfusion Scans

Participants in the Baltimore Longitudinal Study of Aging would continue to undergo exercise thallium tests as they become eligible to do so in the next 4 years. This would include those who become 40 years of age, those who enter the program, and those who are capable of undergoing a treadmill test but who for one reason or another did not have a thallium test during the past 5 years. This would enable us to continue to identify asymptomatic reversible ischemia in the BLSA participants and allow us to better assess the accuracy of a positive test in asymptomatic individuals in predicting the future development of clinical ischemic events. In addition, repeat thallium scans will be initiated on subjects who last underwent such scans at least 10 years previously. These repeat scans will allow assessment of the longitudinal development and progression of both latent and overt CAD, identification of risk factors associated with disease progression and determination of the prognostic significance of longitudinal changes in these perfusion scans.

The following abstracts summarize the scientific program that has resulted from the contract during FY89:

Danziger RS, Lakatta EG, Tobin J, Fleg JL. The age-related decline in creatinine clearance is not due to a decline in cardiac output. The Physiologist 1988;31:(4),A108.

Schulman SP, Lakatta EG, Fleg JL, Becker LC, Weisfeldt ML, Gerstenblith G. Beta blockade alters the exercise-induced increase in diastolic filling rate in young, but not old, healthy men. The Physiologist 1988;31:(4),A129.

Fleg JL, Schulman S, Gerstenblith G, Goldberg A, Tankersley C, Becker L, Clulow LJ, Drinkwater D, Lakatta L, Lakatta EG. Central versus peripheral adaptations in highly trained seniors. The Physiologist 1988;32:(4),A158.

Lima JA, Fleg JL, Waclawiw M, Lima SD, Gerstenblith G. Cardiac structure and function in elderly women. Is there a distinctive profile? Circulation 1988;78:(4)Suppl. II, II-63.

Josephson RA, Shefrin E, Fleg JL. Is conversion from negative (-) to positive (+) exercise ECG a specific marker for future coronary events in asymptomatic subjects? Circulation 1988;78:(4)Suppl. II, II-246.

Schulman SP, Gerstenblith G, Fleg JL, Becker LC, Lakatta L, Drinkwater D, Lakatta EG. Vigorous exercise training does not prevent slowed and delayed early diastolic filling in healthy older men. Circulation 1988;78:(4)Suppl. II, II-247.

Publications:

Lakatta EG, Goldberg AP, Fleg JL, Fortney SM, Drinkwater DT. Reduced cardiovascular and metabolic reserve in older persons: disuse, disease, or aging. In: Chernoff R, Lipschitz DA, eds. Health Promotion and Disease Prevention in the Elderly. New York: Raven Press, 1988;75-87.

Fleg JL, Gerstenblith G, Lakatta EG. Pathophysiology of the aging heart and circulation: In: Messerli FH, ed. Cardiovascular Disease in the Elderly, 2nd Edition, Boston:Martinus Nijhoff, 1988;9-35.

Fleg JL, Gerstenblith G, Zonderman AB, Becker LC, Weisfeldt ML, Costa PT, Lakatta EG. Prevalence and prognostic significance of exercise-induced silent myocardial ischemia detected by thallium scintigraphy and electrocardiography in asymptomatic volunteers. Circulation (in press).

Fleg JL, Goldberg AP. Exercise in older people; cardiovascular and metbolic adaptations. In: Hazzard WR, Andres R, Bierman EL, Blass JP, eds. Principles of Geriatric Medicine and Gerontology. 2nd edition. (in press).

Lakatta EG, Maughan WL. Cardiovascular function and ventricular function and muscle mechanics. In: Garfein OB, ed. Cardiovascular Physiology: A Review. Academic Press, (in press).

Lakatta EG. Heart and Circulation. In: Schneider EL, Rowe J, eds. Handbook of the Biology of Aging. 3rd Edition, Orlando, FL:Academic Press, (in press).

Lakatta EG. Arterial Pressure and Aging. Internat J Cardiol (in press).

Josephson RA, Lakatta EG. Cardiovascular changes in the elderly. In: Katlic MA ed. Surgical Management of the Elderly Patient (in press)

Lakatta EG. Normal Changes of Aging. In: Merck Manual of Geriatrics (in press).

Gerstenblith G, Lakatta EG. Disorders of the heart. In: Hazzard WR, Andres R, Bierman EL, Blass JB, eds. Principles of Geriatric Medicine and Gerontology. 3rd Edition, New York:McGraw-Hill, (in press).

Lakatta EG, Gerstenblith G. Alterations in circulatory function. In: Hazzard WR, Andres R, Bierman EL, Blass JP, eds. Principles of Geriatric Medicine and Gerontology 3rd Edition, New York:McGraw-Hill, (in press).

Lakatta EG. Mechanisms of hypertension in the elderly. Am J Geriat (in press).

Laboratory of Cellular and Molecular Biology

This laboratory conducts fundamental research on some of the basic systems of molecular biology as well as studies designed to understand the biology of aging. The laboratory was not designed to operate in a pyramidal mode, in which the labortory chief formulates a grand design. Rather it was organized to bring together sections led by investigators with a diversity of goals but also a community of interests. Every section in the laboratory has engaged in successful collaborations with other sections.

The Inorganic Biochemistry Section has conducted many studies on nucleic acid structure and function as well as a variety of studies on molecular structural changes in aging. A particular emphasis at the moment is the project on the mechanism of RNA synthesis at the site of internucleotide bond formation, leading to a model of structure in the active site of RNA polymerase that is compatible with the functions of the enzyme. The section has just completed a monumental effort to compile all the data on the interaction of metal ions with DNA and RNA. The section has begun a systematic study of the metabolic effects of exercise as part of the Baltimore Longitudinal Study on Aging.

The Molecular Dynamics Section shares the commitment to structural studies with the Inorganic Biochemistry Section, and is actively collaborating on the RNA synthesis study. Its importance is signified by its title - the emphasis on the dynamics, i.e. molecular motion that occurs during - and is required for - biological function. The section is presently involved in characterizing the dynamics of the interaction of hemoglobin with oxygen and other ligands, having identified distal perturbations and subunit interactions across the $\alpha_1\beta_1$ interface as important components in the process. It is also engaged in studying the consequences of the discovery of enhanced hemoglobin oxidation rate under hypoxic stress resulting in the formation of superoxide.

The Macromolecular Chemistry Section has carried out a variety of activities designed to understand the molecular basis of drug action and to lead to the design of better drugs. The work has been entered on the reaction of α and β blockers with their receptors and on the synthesis of macromolecular drugs based on cyclodextrin. Recent work has been focused on the cyclodextrin studies, and has led to the development of techniques for binding adducts to specific sites on the cyclodextrin molecule.

The Molecular Physiology and Genetics Section is dedicated to the study of the regulation of physiological functions during aging. The studies on age changes in hormone and transmitter action involve adrenergic receptors and are therefore related to the work of the macromolecular chemistry section. The section is also studying age changes in central nervous system responsiveness, behavioral biology, gene expression and the biology of human longevity. It is also involved in determining whether caloric modification increases lifespan in primates as well as in previously studied rodents.

Following are some of the highlights of the research in each section:

Inorganic Biochemistry Section

Mechanism of RNA Synthesis.

A major emphasis of the section at present is the determination of the geometric relationships between the substrates in the i and i+1 sites of RNA polymerase, how the geometry changes during the course of RNA synthesis, and how this geometry may have a place in the regulation of RNA synthesis to insure the fidelity of transcription. The geometry is determined by measuring distances between metals in the i and i+1 sites, and between these metals and points on the substrates in both sites, using NMR and EPR techniques. We have been able to work out the geometry under a variety of conditions. The model we have constructed for interaction at the active site is in accord with the measured

distances, and meets a variety of conditions essential for correct RNA synthesis: (1) the reactive groups on the substrates (3'OH in i and α-phosphate in i+1) are in position to form an internucleotide bond through an S_N2 mechanism, (2) only the 3'OH group is in this position, and not the 2'OH group, and (3) the bases in the two sites are in a position in which they can H-bond to complementary bases on the DNA template. The metal in the i site is too far from the i substrate for bond formation, and is probably a structural element that places the enzyme into its proper conformation. The metal in the i+1 site binds to the triphosphate group, and is probably active in the cleavage of pyrophosphate form that group. Since we have discovered flexibility in the enzyme, i.e., a change in structure under different conditions, we hypothesize that the flexibility may have a purpose in producing optimal geometry for bond formation with "correct" substrates, and suboptimal geometry with "incorrect" ones.

Active and Inactive Forms of RNA Polymerase.

A large proportion of the enzyme molecules in apparently physically homogeneous preparations of E. coli RNA polymerase almost invariably behaves as if incompetent to enter the processive elongation stage. We are interested in differentiating the inactive from the active enzyme molecules, and make use of a competition between DNA template and heparin in binding the enzyme. Heparin readily binds unbound or weakly bound enzyme, but not enzyme strongly bound to DNA during elongation. In principle, inactive enzyme can be identified by extractability with heparin during the elongation phase, and active enzyme by extraction after termination, when the enzyme has dropped off the DNA. A sizeable proportion of the total RNAP was rapidly extracted by heparin during

the elongation phase without affecting the measured activity, and the proportion of the total RNAP becoming heparin-extractable after termination appeared to account for the overall activity.

Those results do in fact appear to differentiate between active and inactive enzyme. We next asked whether the dichotomy arises from irreversible change affecting a portion of the enzyme molecules, or whether an equilibrium condition exists between the active and inactive forms. We have attempted to determine whether the "active" enzyme molecules retain their activity during a second transcription cycle. We therefore added σ-factor to the portion of the enzyme that survived the heparin-treatment during the initial elongation, and found that a second cycle of RNA synthesis did occur, but at greatly reduced rate. This experiment does suggest the possibility of an equilibrium, but more work is necessary to confirm that possibility.

Simplification of Large-Scale Production of T7 DNA.

DNA from T7 bacteriophage is used as a template for quantitative RNA polymerase assay. In the usual large-scale preparation procedure phage is precipitated from the lysate by poly(ethyleneglycol), then purified on a CsCl gradient. We substituted relatively rapid filtration for the laborious and time-consuming centrifugation steps previously used to remove cellular debris from the crude lysate and to isolate the poly(ethyleneglycol) precipitate, and at the same time eliminated losses that occurred on poly(ethyleneglycol) precipitation. Using a Pellicon (Millipore) tangential-flow device, cellular debris was removed on a 0.4 μm pore filter then phage concentrated using a filter having a 300,000 dalton cutoff. All the filtration steps were completed within 2 h, saving a least 3 person-days. (Developed in collaboration with Dr. E. Sybert and Mr. M. Conner at the Bio-Scale-Up facility, University of Maryland - College Park.)

Comprehensive Compilation of Data for Interaction of Metal Ions with DNA and RNA.

Our laboratory began to work on the effects of metal ions on nucleic acids in 1959, and we were asked to prepare a compilation of data on this subject for a nucleic acid section in Landoldt-Börnstein. The field has grown to such an extent that we produced a 300+ page volume. We prepared comprehensive tables of metal binding sites and binding constants, the structural effects of metal binding and metal-catalyzed degradation. We believe this material will be extremely useful for researchers in molecular biology, biophysics, physical chemistry, and inorganic chemistry.

In Vivo NMR Studies of Aging in Animals.

We have initiated the longitudinal study involving participants from the Baltimore Longitudinal Study on Aging (BLSA). Results at this point are incomplete because too few subjects aged 70 or greater have been examined. Thus no age-related effects have been identified. However, we have observed an initial increase in pH upon the initiation of light (30% of maximum workload) exercise followed by a more intense acidosis as work is continued. This effect had been observed previously, but non consistently, in other laboratories. We feel the higher time resolution of our study will allows us to effectively investigate this and other such transient phenomena.

One of our two exercise protocols requires the subject to squeeze a hand dynamometer at 30, 40, 50 and 60% of his maximum for 30 seconds followed by a 60 second rest period between contractions. Typically the PCr/Pi ratio declines during exercise and recovers toward the initial value during the resting portions of the protocol. In many of our subjects the initial recovery period following the 30% contraction is interrupted by a drop in the PCr/PPi ratio (see Figure).

These studies demonstrate that the isometric exercise method can be successfully applied to the determination of metabolic changes during exercise.

Molecular Dynamics Section

Transmission of Subunit Interactions in Hemoglobin Across the $\alpha_1\beta_1$ Interface

By comparing different valence hybrids it was shown that binding of ligands to the reduced chains perturbed the oxidized chain across the $\alpha_1\beta_1$ interface but not across the $\alpha_1\beta_2$ interface. This observation provides the basis for a new mode of subunit interactions through the $\alpha_1\beta_1$ interface. This interface contains the largest number of subunit contacts, but has been neglected in earlier studies because unlike the $\alpha_1\beta_2$ interface, no structural changes at the $\alpha_1\beta_1$ are resolved by x-ray analysis.

Transmission of Distal Perturbations in Hemoglobin

A number of studies have considered the effect of distal interactions in regulating ligand affinity. However, the transmission of distal interactions between subunits and thereby a contribution to cooperative interactions have been neglected.

We have found that the time dependent changes in the EPR spectra of oxidized hemoglobin are particularly sensitive to protein fluctuations on the distal side of the heme. In our studies on valence hybrids the binding of ligands to the reduced chains are found to produce dramatic perturbations in these protein fluctuations on the distal side of the oxidized heme even when no alterations on the proximal side of the heme are expected to take place. These results demonstrate for the first time the transmission of distal effects between subunits.

Oxidation of Hemoglobin

We have previously reported that reduced oxygen pressure produces an increased rate of oxidation with the concomitant formation of superoxide. It was further

found that hemoglobin with three oxygens bound is the primary species responsible for the enhanced rate of oxidation under hypoxic conditions.

These results were completely unexpected. Oxyhemoglobin with three ligands bound is expected to possess an "R"-like quaternary conformation very similar to that of oxyhemoglobin. What is then the explanation for a dramatic increase in the rate of oxidation when one oxygen is removed? Our results on the transmission of distal effects between subunits within the "R" conformation suggest a possible explanation. If the removal of one oxygen and the resultant rearrangements within the ligand pocket can be transferred to other subunits, the configuration and environment of the bound oxygen will be altered. Further evidence for enhanced oxidation, when the "R" conformation is perturbed, was provided by the observation that hemoglobin dissociation into dimers at low concentrations produced a twenty-fold increase in the rate of oxidation. Dissociation of hemoglobin maintains an "R"-like conformation but perturbs the subunit interface. An increased rate of oxidation indicates that the interface perturbation is transmitted to the oxygen binding site. An analogous effect is observed in the oxygenation reaction, in which dissociation changes the oxygen affinity.

The Hypoxic Stress on Erythrocytes

We have previously found that reduced oxygen pressures result in an enhanced rate of oxidation and leakage of superoxide from the erythrocyte. In our initial studies the determination of oxidation was performed on lysed cells. In order to further delineate the hypoxic stress on erythrocytes and the mechanism for the leakage of superoxide, detailed studies have been performed on intact cells as a function of oxygen pressure. By centrifugation of samples incubated under various oxygen pressures, it was possible to show an enhanced rate of lysis at reduced oxygen pressure with a maximum rate in the region of 20 mm Hg.

This lysis is inhibited by superoxide dismutase and therefore associated with oxyradical membrane damage. However, the maximum rate of superoxide leakage is at appreciably lower pressures where the amount of lysis is negligible. Additional visible spectroscopy and electron paramagnetic resonance studies suggest that it may be possible to distinguish different classes of oxidized hemoglobin responsible for the lysis and superoxide leakage, respectively. These results suggest specific oxygen dependent hemoglobin-membrane interactions which determine the fate of the superoxide formed in the cell.

Macromolecular Chemistry Section

Synthesis of Cyclodextrin Derivatives.

Hydroxypropylcyclodextrins, compounds introduced through the work of this section (Pitha J for US Government, **US Patent 4,596,795**: Administration of Sex Hormones in the Form of Hydrophilic Cyclodextrin Derivatives, June 24, 1986; Pitha J for US Government, **US Patent 4,727,064**: Pharmaceutical Preparations Containing Cyclodextrin Derivatives, February 23, 1988; Pitha J and Pitha J, J Pharm Sci 1985;74:987-90), are now in production and used extensively. In spite of that, the detailed composition of these mixtures has remained unclear. Presently, the preparative work of Dr. Rao (a visiting fellow in this section) and analyses of the products by Professor Lindberg and his collaborators (University of Stockholm) has enabled us to formulate substitution rules for cyclodextrins. Substituents can be directed either to the 2-oxygen or the 6-oxygen positions depending on reaction conditions, and thus cyclodextrin can be substituted on the wide or the narrow entry to the toroidal cavity.

Cyclodextrins and Lipids of the Cell Membrane.

A limited study of these interactions was performed locally by Dr. Irie and in greater detail by Dr. Ohtani, a collaborator from Tokyo. Alpha-cyclodextrin and its derivatives show limited specificity for phospholipids, whereas

beta-cyclodextrin and its derivatives show specificity for cholesterol. Specificity of gamma-cyclodextrin is rather low but the solubilization also encompasses triglycerides. Interactions of cyclodextrins with lipid components of membranes was obviously stronger than that with membrane proteins.

Intravenous Hydroxypropylcyclodextrins.

When administered to Watanabe hereditary hyperlipidemic rabbits these compounds somewhat lessened atherosclerotic lesions in aorta. Dr. Irie and Mr. Fukunaga also found that after such administration free cholesterol is detected in urine, a clear sign that injected hydroxypropyl-beta-cyclodextrin assists in the transport of this lipophile. The work of Jan Pitha narrowed the possible untoward effects of such administration, at very high doses, to osmotic nephrosis.

Sex Hormones and hydroxypropylcyclodextrins.

Complexed forms of estradiol, progesterone, and testosterone enable the administration of these hormones in a manner which leads to a very high concentration in the bloodstream for a fraction of a day. Dr. Taylor was supplied with these complexed forms and his collaborator, C. Rupich, evaluated the effectiveness of these in the prevention of osteroporosis in ovariectomized rats. Positive effects were obtained.

Molecular Physiology and Genetics Section

Regulation of calcium mobilization during aging.

Alpha$_1$-adrenergic stimulated, calcium dependent secretion by rat parotid cells decreases 40-50% during aging while cholinergic stimulated secretion is reduced by 20% or less. Alterations in alpha$_1$-adrenergic receptors and/or inositol trisphosphate (IP_3) generation, which initiate the secretory signal transduction process, are not of sufficient magnitude to explain age changes. We have recently determined that alpha$_1$-adrenergic and cholinergic stimulated

calcium mobilization can be dissociated at the post receptor level based on differential neomycin inhibition of IP_3 production. In addition, other second messengers (e.g. arachidonate) can mediate the parotid secretory process. No age changes can be detected in microsomal IP_3 receptors or the microsomal calcium refilling mechanism, further suggesting that differential age changes in adrenergic and cholinergic regulation may occur through different post-receptor pathways. However, since direct IP_3 stimulation of calcium mobilization declines by 40% during aging, the possibilities of changes in post-IP_3 receptor signal transduction as well as differential compartmentalization of the IP_3 generated by different stimuli cannot be eliminated.

LHRH stimulation of LH release from isolated pituitary cells is also calcium dependent, utilizing intracellular stores in the first 15 minutes and extracellular calcium uptake through plasma membrane channels over the following hours. Age related reductions in LHRH stimulation are most pronounced after 4 hours of stimulation, but can be essentially abolished if pituitary cells from senescent rats are stimulated directly with the ionophore A23187 coupled with phorbol myristic acid (PMA). Thus, impaired regulation of membrane calcium channels rather than release from intracellular stores appears to be the site of this secretory dysfunction.

We have also established that dopaminergic inhibition of prolactin (PRL) release, another calcium dependent pituitary secretory function, is greater in cells obtained from young than old rats. This differences is not due to age associated alterations in dopamine receptors (in contrast to changes in control of motor function at the striatal level, which is detailed elsewhere in the MPGS Annual Report).

In total, these observations suggest that age related impairment in control of calcium dependent functions are quite selective in nature. Most such

dysfunctions can be at least partially reversed by appropriate manipulation of calcium fluxes, but the exact sites of age associated lesions are dependent on the tissue/cell type and response under examination.

Steroid action during aging.

During the past year we have confirmed our observation that estrogenic stimulation of hepatic apolipoprotein A1 production is essentially abolished during aging. This dysfunction may be due to the elevation of basal apolipoprotein A1 levels in serum *in vivo* as well as in cultured hepatocytes. In fact, at estrogen concentrations above 20 nM (physiological range) *in vitro* production of this protein is actually impaired in hepatocytes from aged rats while remaining elevated in cells from young counterparts. Very preliminary results suggest that regulatory impairments may be related to decreased nuclear binding of hepatic estrogenic receptors, but cannot explain the elevated basal expression of the apolipoprotein A1 gene in aged cells. The relationship of these regulatory dysfunctions to the increased susceptability to cardiovascular disease in elderly humans remains to be established.

It is interesting to note that age related increases in expression of the pituitary gene for prolactin (PRL) have been previously shown not to be due to increased PRL mRNA production, but probably due to enhanced translation. Age differences in processing of the PRL gene transcript also are also not detectable. Like hepatic apolipoprotein A1, the PRL gene is under estrogenic control.

Striatal Dopamine Receptors and Motor Function in Senescence.

The results from experiments in which ^{3}H-spiperone labeled D_2 receptors in rat striatal sections were assessed using computerized autoradiographic and cell quantitation techniques indicated that total cell numbers in the striatum increased by 13% during aging. This increase was the result of an approximately

19% loss of neurons and 58% increase in non-neuronal cells. D_2 receptor concentrations in four arbitrarily determined striatal regions indicated significant, age-related loss of receptors in these regions. There was a medial to lateral gradient in the concentration of these receptors and the greatest loss was in the most dense medial region (44%). These findings, coupled with those previously obtained, suggest that D_2 receptor loss most likely proceeds through two mechanisms: 1. decreased synthesis and 2. selective loss of striatal neurons which contain D_2 receptors. Unfortunately, limitations of the present autoradiographic techniques precluded determinations of receptor density from specific neurons. Thus, the degree of receptor decline from different neuronal populations may not be uniform. The resolution of this problem awaits further analysis.

In this regard, attempts were also made to determine the intrastriatal neuronal location of D_2 receptors by using the neurotoxin, kainic acid, to selectively destroy striatal interneurons and examine whether differences in DA receptor concentrations between young and old animals would still be observed. The reasoning was as follows: if there were no age-related differences in D_2-receptor concentrations following the lesions it might imply that the population of receptors lost as a function of age were located on the interneurons. The results indicated that this was the case and we are presently pursuing this line of research to determine precisely which receptor populations are lost in aging.

We also assessed the efficacy of prolactin (PRL) and estradiol (E_2) in inducing striatal D_2-receptor up-regulation and improvement of inclined screen (motor) performance. The results indicated that E_2 was a more reliable inducer of rat striatal D_2 receptors and improved motor performance than PRL. There were indications, however, from separate analyses that improvements in inclined

screen performance were seen prior to any increases in striatal D_2 receptor concentrations. These early performance increases seemed instead to be the result of improved muscarinic receptor control over striatal DA autoreceptor function. Later improvements in inclined screen performance were more dependent on increased striatal DA receptor concentrations. Therefore, there appear to be two important processes that may be involved in mediating enhanced inclined screen performance following E_2 administration: 1. enhancement of muscarinic receptor regulation of DA autoreceptor function and 2. increases in striatal DA receptor density.

Effects of Aging on Sensori-Motor Performance in Rodents.

As a model of age-related decline in motor performance, we have been investigating in mice the effects of various pharmacologic manipulations of the nigro-striatal dopaminergic system. Young (6-mo) C57BL/6J mice treated with the selective nigral dopaminergic neurotoxin, n-methlyl-4-phenyl-1,2,3,6-tetrahydropyridine hydrochloride (MPTP), show symptoms of motor dysfunction similar to senescent mice. Aged mice (24-mo) also showed impaired motor function but the impairments were not exaggerated compared to young mice. Final analysis of these data await confirmation of the extent of MPTP-induced damage to dopaminergic cells using immunocytochemical techniques.

Assuming that loss of function in the nigrostriatal system is responsible in part for age-related decline in motor performance, we are also investigating possible mechanisms for this decline. MPTP is thought to exert its toxic effects through a mechanism of oxygen radicals produced when the catacholaminergic degradative enzyme, monoamine oxidase-B, acts on the compound. The toxic effects of MPTP can be eliminated with sufficient doses of monoamine oxidase-B inhibitors, such as deprenyl. We have administered deprenyl in the drinking water of 18-mo old male C57BL/6J mice and observed these mice in a

battery of motor tests at 24 mo of age. No evidence of toxicity was noted as the treated mice exhibited normal fluid intake and body weights. Analysis of monoamine oxidase-B activity indicated significant reduction of enzyme activity as early as 3 weeks after initiation of treatment and maintenance of reduced levels over a 9-mo interval. No significant deprenyl effects were observed in any psychomotor parameter except in the rotodrum test in which mice treated with 1 mg/kg of deprenyl maintained their maximum running speed over 9 mo compared to the age-related decline observed in the other groups.

Effects of Aging on Learning/Memory Function in Rodents.

We have well established the involvement of the septo-hippocampal cholinergic system in accurate performance in the 14-unit T-maze. We have expanded our lesion work in young animals to assess the involvement of neocortical regions in maze learning and retention. To this end, aspiration lesions were provided to young (3-4 mo) male F-344 rats to remove parietal neocortex one day after acquisition and to test for retention performance in the maze. Extensive damage to the parietal cortex had no significant effect on maze retention when assessed one week after surgery. However, if parietal cortical lesions were combined with small lesions to the dorsolateral hippocampus, a profound amnesia resulted. The nature of the defect did not at all appear to be sensory-motor in nature as removal of the rat's vibrissae, which may be used to navigate through the maze, also did not affect retention performance, although the rats moved slightly more slowly through the maze.

Effects of Fetal Neural Tissue Transplants on Behavioral Aging in Rodents.

We are undertaking a large study to assess the behavioral and physiological effects of fetal hypothalamic grafts placed into the third cerebral ventricles of middle-aged (16-18 mo) and aged (26 mo) male C57BL/6J mouse hosts. Our initial experiments involve testing of 30-mo old mice that have received grafts

at 26-mo of age. Control groups include grafts of neocortical tissue, pieces of fat or muscle, and operated and unoperated controls. Histological examination has verified that some survivors have viable grafts (adult-size neurons, minimal gliosis, interfaced to host tissue) when the hypothalamic transplant was made to the dorsal or ventral aspect of the third ventricle. The difference between the two treatments is that in the dorsal aspect of the ventricle, the graft can exert only distal influence possibly through the portal or ventricular system; whereas, with the ventrally placed graft, there is the greater possibility of direct neural contact with the target hypothalamus of the host. The behavioral and physiological battery includes open-field activity, tightrope test, rotorod test, water consumption, body temperature, oxygen consumption, cold tolerance, runwheel activity, and running speed test. Consistent with theories hypothesizing a decline in hypothalamic function as a mechanism of mammalian aging, the objective was to determine whether the hypothalamic grafts would restore or prevent further age-related decline compared to controls. When surviving hosts judged to have viable grafts in or out of the targeted locations were compared to control groups, little evidence of functional improvement was observed. In fact, further functional decline was often noted among these aged hosts with grafts in the ventral third ventricle in some tests including reduced body temperature, cold tolerance, and increased water consumption. In addition, a much greater rate of mortality was observed among grafted mice compared to unoperated controls. The analysis of mice receiving grafts at 16-18 mo of age and tested at 24-mo has not been completed.

We are also utilizing the technology of fetal neural tissue grafting to assess the neurobiology of the age-related impairment in complex maze learning. Specifically, aged rats (22-mo) receive injections of septal cellular suspensions adjacent to or directly into the hippocampus. These animals along

with controls were tested in an extensive battery of motor and learning tests to determine the impact of the grafting procedure. Results indicate that the grafts had little favorable impact upon performance in motor or learning tests except in a few animals in which the graft did not interface with the hippocampus, but rather it touched the fimbria-fornix, the major pathway between the septum and the hippocampus.

Stability of proper gene expression.

Various techniques utilizing recombinant DNA technology has been utilized for the study of improper gene expression and physico/chemical alterations of the genome. Our major challenge in the gene expression studies has been the unusually low amount of mRNA associated with retroviral and oncogene expression as well as the low amount of altered nucleosides in the genome. Most techniques, as they are commonly employed, are required to work at the limits of their resolution, detection and specificity to pick up any age-dependent changes. Thus, much of our work has continued to be placed on improving existing methods to meet our specific research objectives. Recent results in other laboratories using amplification of cDNA by the polymerase chain reaction (PCR technique) shows promise of offering the sensitivity required in detecting improper gene transcription.

Previous studies in our laboratory suggest an age-dependent increase in expression of c-type retroviruses with age (MuLV and MMTV) in mouse tissues (liver, brain). We have continued these studies by investigating possible age-dependent derepression of the myc family of oncogenes (N- and c-myc) in various tissues of the C57BL/6J Mus musculus. Using both slot blot and Northern blot DNA-RNA hybridization techniques, a significant age-dependent change in c-myc gene expression but little or no change in the N-myc genes was found. Our most interesting result was the high levels of c-myc expression found in many of

the tissues of the oldest animals. We now plan on investigating the possible age-dependent expression of other oncogenes, particularly c-fos oncogene, which is frequently coexpressed with c-myc in cancerous tissues and along with c-myc is inducible by active oxygen species. Furthermore, we plan to extend our c-myc studies by carrying out in situ hybridization in liver tissue to determine the cellular distribution of c-myc expression as it increases with age in the C57BL/6J male mice.

Measurement of oxidative DNA damage.

We have been studying the possible age-dependent frequency of oxidized nucleic acid components in the urine and DNA of mice and primate species. Using both the HPLC/EDC and the GC/MS techniques for measuring oxidized nucleosides in urine and DNA, previous results suggest that steady state levels in DNA and the urinary output of thymidine glycol and 8-OHdG per creatinine is least in human and increases as the species life span decreases. We are now in the process of repeating these experiments using the same as well as new DNA and urine samples. Results measuring 8-OHdG by the GC/MS and HPLC-EDC have been similar and have so far confirmed our previous results.

Urinary content of oxidized nucleosides is interpreted as representing the average rate of removal of oxidized DNA damage for all cells in the organism. DNA content of oxidized nucleosides represents the steady state level of damage which is determined by both the rate of input and the rate of removal (DNA repair). Our results suggest that longer-lived species have a smaller rate of DNA repair of oxidized damage because there is less oxidized damage to be repaired. Thus, longer-lived species appear to have evolved strategies primarily to protect DNA from oxidized damage in favor of increasing rate of repair.

These result also suggest that oxidative damage to DNA does not remain for longer periods of time in shorter-lived species but instead has a higher turnover or repair rate. Thus, the DNA in shorter-lived species appears to be both damaged at a higher rate and repaired at a higher rate. This unexpected result leads to a novel concept that, in spite of oxidative damage not accumulating with age, high turnover rate of this DNA damage nevertheless could promote increased chromosomal rearrangements and other genomic perturbations contributing towards gene instability and dysdifferentiation. thus, prevention of damage rather than increase of repair might have been the preferred method to protect the integrity of the DNA and thus the differentiated state of a cell during the evolution of longer life span. This result, if it continues to be confirmed in our present studies using newly prepared DNA samples, could be of fundamental importance in understanding both the mechanisms of aging and of those processes governing aging rate.

Primate Aging; Effects of Caloric Modification.

After one year on full 30% caloric restriction, both the rhesus and squirrel monkeys appear to be quite healthy. Rates of weight gain are approximately proportional to food intake, and food consumption studies reveal that most restricted monkeys are eating roughly 70% as much as ad libitum fed counterparts of comparable body weight. According to a regression analysis of absolute body weight growth, the rate of weight gain in all control groups appears normal. In particular, the juvenile groups are gaining weight at rates on target for normal adults within 3 years. The degree of relative body weight growth (controlling for differences in baseline body weights) of experimental groups as a percent of that for control groups is 46% and 49% for juvenile and young adult Rhesus monkeys, respectively. Among squirrel monkeys, these estimates are 27% for both age groups. Thus, when assessed on a relative basis, the degree of restriction in body weight growth is clearly higher among squirrel monkeys.

However, within both species, no age difference in relative growth rate is observed. During the 3 month phase-in period for the restricted diet (10% reduction in the first month, 20% in the second, full 30% in the third), no acute effects of reduction were observed in any of the parameters measured. These included blood chemistries and cell counts, endocrine status, and immune function.

Many parameters have been found to differ as a function of cross-sectional chronological age in both species. We continue to observe a 70-80% decrease in blood alkaline phosphatase levels over the lifespan of both rhesus and squirrel monkeys. In addition, BUN, blood phosphorous, T_4, and Thymocyte mitogenesis decline significantly with increasing age. All of these measurements have yielded fairly consistent values during quarterly bleedings over the past year.

It is, thus, too early to observe any longitudinal age changes in individual monkeys. Likewise, it appears to be too early to determine whether the restricted diet has any effect on the rate of change of the parameters examined.

We have initiated a number of new measurements in the past year on a trial basis. These include rates of fingernail growth, rectal body temperature, red blood cell density, membrane fluidity and lipid composition, blood catecholamines, calcitropic hormones, and body composition. At present, nail growth, body temperature and red blood cell density profiles appear to show the most promising cross-sectional age differences, although not all data from the other measurements have yet been tabulated. Autoantibody, immunoglobulin and bone density studies have been temporarily halted, pending refinement of techniques and data analysis. Within the next year we hope to expand our studies on the most promising aging indices, de-emphasize less promising measurements and initiate several new studies. The latter include, collagen cross linking and locomotor activity measurements.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00044-16 LCMB

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Effect of Metals and Proteins on Nucleic Acids, Information Transfer and Aging

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Gunther L. Eichhorn	Chief, LCMB	IBS LCMB NIA
Others:	Richard B. Beal (EOD 2/1/88)	IRTA Fellow	IBS LCMB NIA
	James J. Butzow	Commissioned Officer	IBS LCMB NIA
	Peter P. Chuknyisky (EOD 5/1/87)	Sr. Staff Fellow	IBS LCMB NIA
	Patricia Clark	Research Chemist	IBS LCMB NIA
	Yong A. Shin	Research Chemist	IBS LCMB NIA

COOPERATING UNITS *(if any)* Johns Hopkins University (L. Liu, E. Freire, E. Moudrianakis, M. Beer); Max Planck Institute (M. Soumpasis); University of Oregon (C. Johnson); Wichita State University (R.P. Singhal); University of Western Ontario (S.J. Karlik); University of Toronto (U. DeBoni)

LAB/BRANCH

Laboratory of Cellular and Molecular Biology

SECTION

Inorganic Biochemistry Section

INSTITUTE AND LOCATION

National Institute on Aging, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
7.5	5.5	2

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project focuses on the interaction of molecules concerned with genetic information transfer. A primary objective is to determine under what conditions metal ions are essential for information transfer, and under what conditions they impact on the information in such a way as to influence biological aging. Topics of interest are: (1) the effects of metal ions on the structure of nucleic acids, nucleoproteins and chromatin; (2) the mechanism of involvement of aluminum in Alzheimer's disease; (3) crosslinking of nucleic acid strands by metal ions; (4) the structure of the active site of RNA polymerase; (5) metal ions and cellular aging.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00046-19 LCMB

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Molecular Recognition of Lipids and Lipophiles by Cyclodextrin Derivatives

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Josef Pitha	Section Chief	MCS LCMB NIA
Others:	John Kusiak (reassigned 6/30/89)	Research Chemist	MCS LCMB NIA
	Yasuhiro Chida DOD 1-31-89	Visiting Fellow	MCS LCMB NIA
	J. Torres-Labandeira EOD 6-9-89	Visiting Fellow	MCS LCMB NIA
	C. Trinadha Rao EOD 10-27-87	Visiting Fellow	MCS LCMB NIA
	Yan Xia EOD 1-23-89	Visiting Fellow	MCS LCMB NIA

COOPERATING UNITS *(if any)* Univ. Stockholm, Sweden (Dr. B. Lindberg); DKFZ, Inst. Exptl. Pathology, Heidelberg, West Germany (Drs. G. Taylor and J. Weiss); Kumamoto Univ., Japan (Drs. K. Uekama and T. Irie); NHLBI, NIH, Bethesda, MD (Dr. H. Fales); V.A., Hospital, Oklahoma City, OK (Dr. Jan Pitha)

LAB/BRANCH

Laboratory of Cellular and Molecular Biology

SECTION

Macromolecular Chemistry Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
5.0	4.0	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Alpha-, beta-, and gamma-cyclodextrins are cyclic hexa-, hepta-, and octamers of glucose which form host-guest complexes with lipophiles. These compounds were chemically derivatized to increase their solubility and decrease their toxicity. Basic interactions of cyclodextrins with components of cell membranes were evaluated. Furthermore, derivatized cyclodextrins were used to effectively administer lipophilic drugs, a problem which often cannot be solved using standard pharmaceutical materials. Some of that work has already entered into phase-1 trials. Derivatized cyclodextrins were furthermore administered intravenously with the aim of affecting redistribution of lipids/lipophiles within the organism.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00047-19 LCMB

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Structure-Function Relationships in Hemoglobin and Erythrocytes

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Joseph M. Rifkind	Chief, MDS	MDS LCMB NIA
Others:	Abraham Levy	Sr. Staff Fellow	MDS LCMB NIA
	Lu Zhang	Visiting Fellow	MDS LCMB NIA

COOPERATING UNITS *(if any)* NIA/LCS/CFS (E. Lakatta); IR TD/NHLBI (R. Berger); LMC/NCI (F. Friedman); Indian Inst. of Technology, Madras, India (P.T. Manoharan); Univ. California - San Diego, La Jolla CA (V.S. Sharma); Letterman Army Inst. of Research, San Francisco CA (R. Winslow); Benedict College, Columbia SC (K. Alston)

LAB/BRANCH

Laboratory of Cellular and Molecular Biology

SECTION

Molecular Dynamics Section

INSTITUTE AND LOCATION

National Institute on Aging, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.11	3.11	1

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project focuses on the mechanism involved in regulating the binding of oxygen to hemoglobin and the transport of oxygen to the tissues. Emphasis is placed on ways in which these functions are impaired and change with age. These studies have focused on the oxidation of hemoglobin, which produces non-functional hemoglobin and the simultaneous release of oxyradicals. The enhancement of these oxidative processes under hypoxic conditions is being explored as a possible source of tissue and organ damage, which would be exacerbated during aging. Studies are also included which are directed at the stability of the entire erythrocyte and the erythrocyte membrane.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00113-6 LCMB

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

In Vivo NMR Studies of Aging in Cells and Animals

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Gunther L. Eichhorn	Chief, LCMB	IBS LCMB NIA
Others:	Richard B. Beal (EOD 2/1/88)	IRTA Fellow	IBS LCMB NIA

COOPERATING UNITS *(if any)*

Cardiovascular Section, Clinical Physiology Branch, National Institute on Aging; Department of Radiology, Johns Hopkins University (J.L. Fleg)

LAB/BRANCH

Laboratory of Cellular and Molecular Biology

SECTION

Inorganic Biochemistry Section

INSTITUTE AND LOCATION

National Institute on Aging, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.5	0.5	0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

NMR Spectroscopy is used to study the metabolic changes associated with exercise in the flexor muscle of the forearm of human volunteers. Isometric exercise at variable workloads as well as constant workload are carried out using a hand dynamometer which is interfaced to a personal computer and a display unit. Changes in phosphocreatine (PCr) and inorganic phosphate (P_i) as well as intracellular pH are monitored via ^{31}P NMR spectroscopy during the exercise. Age-related differences in these parameters during exercise are studied in subjects of the BLSA using these protocols.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

ZO1-AG 00301-6 LCMB

PERIOD COVERED: October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*: Regulation of Physiological Functions During Aging: I. Hormone and Neurotransmitter Action.

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: G.S. Roth, Chief, Molecular Physiology and Genetic Section, LCMB, NIA

Others:

T. Maki (D.O.D. 1/89)
B. Baum
M. Blackman
A. Miyamoto (E.O.D. 7/89)
Z. Han (D.O.D. 9/89)

COOPERATING UNITS *(if any)*

Patient Care Branch, National Institute of Dental Research; Clinical Physiology Branch,

LAB/BRANCH

Gerontology Research Center,

SECTION

Molecular Physiology and Genetics Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.0	2.5	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project is mainly involved in elucidating those mechanisms by which the ability of hormones and neurotransmitters to regulate physiological functions is altered during aging.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 AG 00302-6 LCMB

PERIOD COVERED: October 1, 1988 to September 30, 1989

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.): Regulation of Physiological Functions During Aging: III. Behavioral Biology

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: Donald K. Ingram, Research Psychologist MPGS, LCMB, NIA

Others:

C. Barnes	E. Bresnahan	B. Davis	F. Gage
M. Gupta	J. Joseph	M. Jucker	H. Kametani
H. Kleinman	S. Kobayashi	T. McNeill	D. Olton
M. Talan	G. Wenk	H. Wiener	

COOPERATING UNITS (if any): Dept. Psychology, Johns Hopkins U., (D. Olton, G. Wenk); Essex Community College, (E. Bresnahan); Neuroanatomy Lab U. Rochester Sch. Med. (T. McNeill, B. Davis); F. Gage (U. C. San Diego, Sch. Med.) U. Louisville Sch. of Med. (M. Gupta) U. of Colorado (C. Barnes); Tokyo Metropolitan Institute of Gerontology (S. Kobayashi); Swiss Federal Institute of Technology (M. Jucker); N.S. Kline Inst. for Psychiat. Res. (H. Wiener); Nat'l Inst Dental Res. (H. Kleinman).

LAB/BRANCH: Gerontology Research Center,

SECTION: Molecular Physiology and Genetics Section

INSTITUTE AND LOCATION: NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS: 3.8	PROFESSIONAL: 3.5	OTHER: 0.3

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The purpose of this project is to assess the effects of aging at a behavioral level of analysis in animal models, to identify neurobiological mechanisms associated with these effects, and to test interventions which might alter age-related performance decrements. Rodent models are tested in a battery of sensori-motor and learning/memory tasks. Neurochemical and neurohistological assays are conducted to determine neurobiological correlates of functional losses. Interventions include dietary restriction, environmental enrichment, various pharmacologic treatments, and neural tissue grafting. Multiple genotypes are examined to determine possible genetic involvement in the pattern of age-related behavioral impairment.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG-00303-6 LCMB

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)* Regulation of Physiological Functions during Aging: IV Gene Expression and the Biology of Human Longevity

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: Richard G. Cutler Research Chemist LCMB, NIA

Others:

D.K. Ingram G.S. Roth A. Ayala

COOPERATING UNITS *(if any)* J. Vijg and A. Brower, TNO; D. Bergtold and M. Simic, NBS; A.H. Goldfarb, U. of NC; H. Alessio, Miami U.; A.S. Khan, NIH, NIAID; Alessio H, Miami, U.

LAB/BRANCH

Gerontology Research Center,

SECTION

Molecular Physiology and Genetics Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.0	2.0	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The objective of our research program is to search for unique characteristics of human biology which determine their extraordinary capacity for general health maintenance and longevity as compared to all other mammalian species. This research program has been guided by theoretical studies suggesting that a common set of specific longevity determinant processes exists in all mammals. Work has centered on two basic but interrelated questions: (1) is the cause of aging largely the result of dysdifferentiative processes and (2) is the rate of aging governed by mechanisms acting to stabilize the proper differentiated state of cells? With reference to the first question, stability of gene regulation has been investigated by measuring the steady state levels of mRNA for the genes coding for the endogenous retroviruses (human 4-1, mouse MuLV) and oncogene (c-myc) as a function of age in a number of tissues from mice and human. Results indicate that changes in expression of these genes do occur throughout the life span in both of these species. With reference to the second question, active oxygen species may be a cause of improper gene regulation. This possibility has been investigated by measuring the steady state level of specific oxidative damage products in DNA (8-hydroxydeoxyguanosine, 8-OHdG, and thymidine glycol) and in protein (5-hydroxy-2-aminovaleric acid, HAVA). Results indicate that these specific types of DNA damage products are highest in young rather than old individuals and that longer-lived species have, on average, less damage products over their life span. Methods to detect specific oxidative products of protein, including a GC/MS technique for detection of HAVA with sensitivity at the femtomole level, have been successfully developed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG-00304-3 LCMB

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Regulation of Physiological Functions During Aging: V. Assessment of Primate Aging: Effects of Caloric Modification

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI's	G. S. Roth	Chief, MPGS	LCMB, NIA
	D. K. Ingram	Research Psychologist, MPGS	LCMB, NIA
	R. G. Cutler	Research Chemist, MPGS	LCMB, NIA

Others:

R. Weindruch, H.S.A., NIA; D. Renquist, J, Knapka, Animal Center Section, DRS; M. April, Primate Unit, ACS, DRS; J. Tobin, S. Sherman, M. Blackman, LCP, NIA; M. Talan, LBS, NIA; W. Ershler, U. Wisconsin, Madison, WI; W. Stone, Trinity Univ, San Antonio, TX; W. Wood, H. Armbrecht, R. Strong, V.A.M.C., St. Louis, MO; J. Conway, U.S.D.A., Beltsville, MD; D. Danon, Weizmann Inst., Rehovot, Israel

COOPERATING UNITS *(if any)*

Dept. of Med. Univ. of Wisc. Madison, WI
~~Dept. of Biol. Trinity Univ., San Antonio, TX~~

LAB/BRANCH

~~LCMB, GRC~~

SECTION

~~Molecular Physiology and Genetics Section~~

INSTITUTE AND LOCATION

~~NIA, NIH, Baltimore, MD. 21224~~

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
~~4.0~~	~~2.0~~	~~2.0~~

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project is attempting to determine whether caloric modification of the diets of Rhesus and squirrel monkeys can affect aging rate as assessed by various physiological, biochemical and behavioral indices.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01-AG 00306-1 LCMB

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Regulation of Physiological Functions During Aging: II. Central Nervous System Responsiveness

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: J.A. Joseph, Research Pharmacologist, Molecular Physiology and Genetics Section LCMB, NIA, G.S. Roth, Chief, MPGS, LCMB, NIA

Others:

N. Appel
Z. Han (D.O.D. 9/89)
M. Blake
D. Ingram

COOPERATING UNITS *(if any)*

LAB/BRANCH

Gerontology Research Center,

SECTION

Molecular Physiology and Genetics Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.0	2.5	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project attempts to understand those mechanisms involved in age related changes in central nervous system responsiveness.

LABORATORY OF MOLECULAR GENETICS

Overview:

The Laboratory of Molecular Genetics was created to bring the powerful new recombinant DNA technology to bear on problems of aging and of diseases associated with aging. The Laboratory was reviewed in 1988 and a number of changes meant to streamline the program of the Laboratory were suggested. In addition, Dr. Edward Schneider who had been serving as the Acting Laboratory Chief on a part-time basis with the National Institute on Aging decided to leave that position, and the Scientific Director of the National Institute on Aging, Dr. George Martin, assumed the role of Acting Laboratory Chief. The principal aims of the current researchers in the group are primarily directed towards studying genes that are expressed by cells in response to injury or stress and genes that are involved in the regulation of cellular proliferation.

As discussed above, there have been notable achievements in the Laboratory in 1988 and we report the isolation and characterization of a gene which when injected into cells stops the proliferation of these cells. The gene is normally expressed in cells that are not proliferating and in a wide variety of non-dividing tissues. This gene product has been named prohibitin and it is possible that it plays a role in cell senescence and aging, although this has not yet been studied directly.

The heat shock response is a universal response found in cells from bacteria to human cells and involves the expression of a specific set of genes which appear to be involved in protecting the cell against a variety of toxic and stressful situations. We have shown that the heat shock response is altered in old animals exposed to hyperthermic conditions. A collaboration between the Laboratory of Molecular Genetics and the Laboratory of Behavioral Sciences has shown that the defect in the ability of old animals to withstand cold stress is associated with the failure to express at least one member of this gene family. Studies in the Laboratory of Molecular Genetics are currently directed toward characterization of the defect in the old animals.

Also, scientists in this Laboratory have isolated and characterized a gene which is expressed both in response to damage to DNA and when cells stop proliferating. It is likely that this gene, part of a larger family of genes referred as the GADD genes (growth arrest - DNA damage inducible genes), ensures that damaged DNA is not replicated.

ANNUAL REPORT OF THE LABORATORY OF MOLECULAR GENETICS

Cloning of a gene involved in shutting off cell growth

J. Smith at Baylor has shown that when poly(A)+ RNA derived from human diploid fibroblasts at late passage is microinjected into cells of the same type at early passage, the growth of the early passage cells is halted. A functionally identical activity derived from rat liver (by C. Lumpkin, J.K. McClung, and J. Smith) has a single molecular weight peak of activity on sucrose gradients. These data suggest that a single messenger RNA has the ability to shut off cell growth, and dilution experiments suggest that the message is abundant (1/100-1/1000 of total message). We have recently cloned a full-length cDNA that may correspond to this mRNA: synthetic mRNA from this cDNA shuts off DNA synthesis in fibroblasts, and the cognate mRNA is made *in vivo* in a cell cycle dependent manner, lowest in S phase.

Characterization of a Novel Gene Expressed in Response to DNA Damage and Growth Arrest

We have cloned a full length cDNA from Chinese hamster ovary (CHO) cells corresponding to a transcript which displays a unique pattern of expression during cell growth and in response to DNA damage. The mRNA corresponding to the cDNA referred to as GADD 153 is highly conserved throughout mammalian species and is induced to high levels following treatment with DNA damaging agents and when cell growth is arrested by a variety of means. We have isolated the genomic DNA corresponding to Gadd 153 from CHO cells. The gene spans about 6 kilobases and contains 4 exons. The promoter region of the gene has been sequenced and examined in detail. It contains no TATA or CCAAT consensus sequences. It is relatively GC rich (70%) and contains seven Sp 1 transcription factor binding sites within the region from -500 to +1. It also contains an AP-1 binding site for c-Jun at -270. An 800 bp fragment in this region has been shown to drive expression of the reporter gene chloramphenicol acetyl transferase in an orientation dependent fashion. It is active basally and is inducible by treatment with the DNA damaging agent methyl methane sulfonate (MMS). This fragment also confers MMS inducibility on an unrelated promoter consistent with an enhancer element. Deletion analysis of the 800 bp region indicates that the MMS responsive element lies within a region between -250 and -50 relative to the transcription start site. Further studies are aimed at determining 1) the specific site within this 200 bp region responsible for activation of the gene by MMS and 2) identifying the transactivating with which it interacts.

HSP 70 Expression in Cultured Fibroblasts from Young and Aged Rats

Physiological aging is characterized by decreased responses to

stress. This project examined the effect of aging on the cellular response to heat stress at the molecular level. This in vitro system was chosen to avoid the influence of complex physiological mechanisms associated with thermoregulation in intact animals.

The effect of aging on the heat-induced expression of the heat shock protein HSP 70 was studied in skin and lung fibroblast cultures from young (5 months) and aged (24 months) male Wistar rats. The kinetics of the heat shock response were found to be similar in the two age groups but cells from aged animals showed significantly lower levels of heat-induced HSP 70 mRNA compared to those from younger animals. Experiments analyzing HSP 70 protein showed a correlative decrease in HSP 70 protein in cells from aged animals. The response was specific for HSP 70 as other heat shock proteins were unaffected. Additional experiments with freshly excised lung tissue showed a similar age-related decline in the heat-induced expression of HSP 70 .

While their name is derived from the response to heat stress, the heat shock proteins are induced by a variety of cellular stresses and are presumed to play a role in protecting cells against these stresses. Our studies demonstrating an age-related reduction in HSP 70 expression following heat stress in fresh lung tissue and cultured cells suggest that these protective roles of HSP 70 may be impaired with aging.

DNA Fingerprinting of Subpopulations of Transformed Cells

We studied the genetic variation among subpopulations of cultured HeLa and RAT-1 cells with the DNA fingerprint technique. The technique makes it possible to screen for differences among scores of loci scattered throughout the genome.

We compared the fingerprint patterns of mass populations of HeLa cells with those of individual clones selected from the populations. We found differences in band patterns in 3% of the loci examined. We then made similar comparisons with RAT-1 cells, finding no differences in any of the bands studied.

Heat Shock Protein Gene Expression in Response to Physiological Stress

Heat and other stressors are known to induce the expression of a set of highly conserved proteins termed the heat shock proteins (HSPs) in virtually all organisms ranging from bacteria to man. While they have been extensively studied in cultured cells, little is known concerning their expression in response to stress in intact mammalian systems. In this project we have begun to examine the expression of two such HSPs, HSP 70 and HSP 27, in tissues of young and old rats and mice

following exposure to either hyperthermic or hypothermic conditions. We have characterized the kinetics of mRNA expression for these two HSPs in skin, lung, brain and liver after exposing rats to various elevated temperatures for different lengths of time. Reduced levels of HSP 70 and HSP 27 RNA were observed in tissues of aged rats when compared to young animals exposed to identical conditions. This decline appears to reflect a deficit in the thermal response to heat stress by aged animals rather than an alteration in their ability to express HSPs. We have further defined HSP 70 induction in-vivo in brain by determining the anatomical localization of expression using in-situ hybridization. Specific induction was observed in the dentate gyrus of the hippocampus and the paraventricular nucleus of the hypothalamus suggesting a link between the cellular HSP 70 response and the classic neuroendocrine stress responses generated via the hypothalamic-pituitary-adrenal axis. Exposure of young mice to hypothermic conditions also resulted in HSP 70 induction in brown fat, lung and heart. This induction did not occur in aged mice and again appears to reflect a problem with mechanisms of thermoregulation.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

PROJECT NUMBER

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00702-04 LMG

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Effect of In Vivo and In Vitro Aging on Neoplastic Transformation

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) Name, title, laboratory, and institute affiliation)

P.I.- E. L. Schneider, Acting Chief, LMG, NIA
Others - T. Kunisada, Former Fogarty Fellow, LMG, NIA
D. B. Danner, Senior Staff Fellow, LMG, NIA
V. Friedman, Fogarty Fellow, LMG, NIA

COOPERATING UNITS (if any)

LAB/BRANCH

Laboratory of Molecular Genetics

SECTION

INSTITUTE AND LOCATION

National Institute on Aging, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This project has been terminated.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

PROJECT NUMBER

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00703-04 LMG

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Molecular Basis for Decreased Immune Function in Aging Humans and Rats

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I. - Nikki J. Holbrook, Senior Staff Fellow, LMG, NIA
Others - Edward L. Schneider, Chief, LMG, NIA
Mike McCoy, Research Associate, LMG, NIA

COOPERATING UNITS *(if any)*

Laboratory of Clinical Physiology, Clinical Immunology Section, NIA (Drs. William Adler and James Nagel)

LAB/BRANCH

Laboratory of Molecular Genetics

SECTION

INSTITUTE AND LOCATION

National Institute on Aging, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project has been terminated.

Publications:

Holbrook NJ, Chopra RK, McCoy MT, Nagel, JE, Powers DC, Adler WH, Schneider EL. Expression of Interleukin 2 and the Interleukin 2 receptor in aging rats, Cellular Immunology 1989;120:1-9.

Chopra RK, Holbrook NJ, Powers DC, McCoy, MT, Adler, WH, and Nagel JE. Interleukin 2, Interleukin 2 receptor and interferon-synthesis and mRNA expression in phorbol myristate acetate and calcium ionophore A23187 stimulated T cells from elderly humans, Clin Immunol Immunopath 1989 (in press).

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

PROJECT NUMBER

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00704-04 LMG

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Molecular Genetic Analysis of Alzheimer's Disease

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: D. B. Danner Senior Staff Fellow LMG, NIA

COOPERATING UNITS (if any)

Dementia Research Service, Division of Chronic and Degenerative Diseases, Cornell Medical College (J. Blass, R. Shue)

LAB/BRANCH

Laboratory of Molecular Genetics

SECTION

INSTITUTE AND LOCATION

National Institute on Aging, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This project has been terminated.

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00705-04 LMG

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Cloning of a gene involved in shutting off cell growth.

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory and institute affiliation)

P.I.:	D.B. Danner	Senior Staff Fellow	LMG, NIA
Others:	M.J. Nuell	Senior Staff Fellow	LMG, NIA
	D.A. Stewart	Research Associate	LMG, NIA
	V. Friedman	Fogarty Fellow	LMG, NIA
	C.M. Wood	NRC Fellow	LMG, NIA

COOPERATING UNITS (if any)

Dept. of Virology, Baylor College of Medicine (J.R. Smith)
Noble Foundation, Ardmore, Oklahoma (J.K. McClung)

LAB/BRANCH

Laboratory of Molecular Genetics

SECTION

INSTITUTE AND LOCATION

National Institute on Aging, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
4.5	4.5	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

J. Smith at Baylor has shown that when poly(A)+ RNA derived from human diploid fibroblasts at late passage is microinjected into cells of the same type at early passage, the growth of the early passage cells is halted. A functionally identical activity derived from rat liver (by C. Lumpkin, J.K. McClung, and J. Smith) has a single molecular weight peak of activity on sucrose gradients. These data suggest that a single messenger RNA has the ability to shut off cell growth, and dilution experiments suggest that the message is abundant (1/100-1/1000 of total message). We have recently cloned a full-length cDNA that may correspond to this mRNA: synthetic mRNA from this cDNA shuts off DNA synthesis in fibroblasts, and the cognate mRNA is made in vivo in a cell cycle dependent manner, lowest in S phase.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00707-04 LMG

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Isolation of Genes Differentally Expressed in Brain of Old and Young Rats

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I. - Nikki J. Holbrook, Senior Staff Fellow, LMG, NIA
Others - Joseph Fargnoli, Senior Staff Fellow, LMG, NIA
Michael Blake, National Research Council Fellow, LMG, NIA

COOPERATING UNITS *(if any)*

Laboratory of Radiation Oncology, NCI (Dr. Albert J. Fornace, Jr.)

LAB/BRANCH

Laboratory of Molecular Genetics

SECTION

INSTITUTE AND LOCATION

National Institute on Aging, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS.	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project has been terminated.

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00708-04 LMG

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Identification of age-related transcripts in the mouse

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) Name, title, laboratory, and institute affiliation)

P.I.:	D. B. Danner	Senior Staff Fellow	LMG, NIA
Others:	V. Friedman	Fogarty Fellow	LMG, NIA

COOPERATING UNITS (if any)

LAB/BRANCH

Laboratory of Molecular Genetics

SECTION

INSTITUTE AND LOCATION

National Institute on Aging, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This project has been terminated.

Pulbications:

Friedman V, Wagner JW, Danner DB. Isolation and identification of age-related transcripts in the mouse, Mech Ageing Dev (in press)

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

PROJECT NUMBER

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00709-04 LMG

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Analysis of changes in hormone expression with age

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

P.I.:	D. B. Danner	Senior Staff Fellow	LMG, NIA
Others:	David Stewart	Research Associate	LMG, NIA

COOPERATING UNITS (if any)

Laboratory of Clinical Physiology, NIA (S. M. Harman, M. Blackman); Laboratory of Cellular and Molecular Biology, NIA (G. Roth).

LAB/BRANCH

Laboratory of Molecular Genetics

SECTION

INSTITUTE AND LOCATION

National Institute on Aging, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This project has been terminated

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00710-03 LMG

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Regulation of Interleukin 2 Gene Expression in Lymphoid and Nonlymphoid Cells

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I. Nikki Holbrook, Senior Staff Fellow, LMG, NIA
Others - Jennifer Luethy, Research Associate

COOPERATING UNITS *(if any)*

Alberto Gulino, Dipartmento di Medicina Spermentale, Universita "LaSapienza", Roma, Italy

LAB/BRANCH

Laboratory of Molecular Genetics

SECTION

INSTITUTE AND LOCATION

National Institute on Aging, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project has been terminated.

GPO 914-010

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

PROJECT NUMBER

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00713-02 LMG

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Characterization of a Novel Gene Expressed in Response to DNA Damage and Growth Arrest

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

(Isolation of a New Gene Associated with Cessation of Growth)

P.I. - Nikki J. Holbrook, Senior Investigator, LMG, NIA
Others - Joseph Fargnoli, Senior Staff Fellow, LMG, NIA
Jong Sung Park, Visiting Fellow, LMG, NIA
Jennifer D. Leuthy, Biologist GS-11, LMG, NIA

COOPERATING UNITS (if any)

Radiation Oncology Branch, NCI (Dr. Albert J. Fornace, Jr.)

LAB/BRANCH

Laboratory of Molecular Genetics

SECTION

INSTITUTE AND LOCATION

National Institute on Aging, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
2.5	1.5	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

We have cloned a full length cDNA from Chinese hamster ovary (CHO) cells corresponding to a transcript which displays a unique pattern of expression during cell growth and in response to DNA damage. The mRNA corresponding to the cDNA referred to as GADD 153 is highly conserved throughout mammalian species and is induced to high levels following treatment with DNA damaging agents and when cell growth is arrested by a variety of means. We have isolated the genomic DNA corresponding to Gadd 153 from CHO cells. The gene spans about 6 kilobases and contains 4 exons. The promoter region of the gene has been sequenced and examined in detail. It contains no TATA or CCAAT consensus sequences. It is relatively GC rich (70%) and contains seven Sp 1 transcription factor binding sites within the region from -500 to +1. It also contains an AP-1 binding site for c-Jun at -270. An 800 bp fragment in this region has been shown to drive expression of the reporter gene chloramphenicol acetyl transferase in an orientation dependent fashon. It is active basally and is inducible by treatment with the DNA damaging agent methyl methane sulfonate (MMS). This fragment also confers MMS inducibility on an unrelated promoter consistent with an enhancer element. Deletion analysis of the 800 bp region indicates that the MMS responsive element lies within a region between -250 and -50 relative to the transcription start site. Further studies are aimed at determining 1) the specific site within this 200 bp region responsible for activation of the gene by MMS and 2) identifying the transactivating with which it interacts.

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

PROJECT NUMBER

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00714-02 LMG

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Aging and aberrant gene expression

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

P.I.:	D. B. Danner	Senior Staff Fellow	LMG, NIA
Others:	A. I. Sato	Biologist GS-7	LMG, NIA
	E. L. Schneider	Chief	LMG, NIA

COOPERATING UNITS (if any)

LAB/BRANCH

Laboratory of Molecular Genetics

SECTION

INSTITUTE AND LOCATION

National Institute on Aging, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This project has been terminated

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 AG 00717-02 LMG

PERIOD COVERED: October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)* HSP 70 Expression in Cultured Fibroblasts from Young and Aged Rats

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I. - Joseph Fargnoli, Senior Staff Fellow, LMG, NIA
Others - Nikki J. Holbrook, Senior Investigator, LMG, NIA

COOPERATING UNITS *(if any)*

LAB/BRANCH
Laboratory of Molecular Genetics

SECTION

INSTITUTE AND LOCATION
National Institute on Aging, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.75	.75	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Physiological aging is characterized by decreased responses to stress. This project examined the effect of aging on the cellular response to heat stress at the molecular level.

The effect of aging on the heat-induced expression of the heat shock protein HSP 70 was studied in skin and lung fibroblast cultures from young (5 months) and aged (24 months) male Wistar rats. The kinetics of the heat shock response were found to be similar in the two age groups but cells from aged animals showed significantly lower levels of heat-induced HSP 70 mRNA compared to those from younger animals. Experiments analyzing HSP 70 protein showed a correlative decrease in HSP 70 protein in cells from aged animals. The response was specific for HSP 70 as other heat shock proteins were unaffected. Additional experiments with freshly excised lung tissue showed a similar age-related decline in the heat-induced expression of HSP 70.

While their name is derived from the response to heat stress, the heat shock proteins are induced by a variety of cellular stresses and are presumed to play a role in protecting cells against these stresses. Our studies demonstrating an age-related reduction in HSP 70 expression following heat stress in fresh lung tissue and cultured cells suggest that these protective roles of HSP 70 may be impaired with aging.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00718-01 LMG

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

DNA Fingerprinting of Subpopulations of Transformed Cells

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I. Edward L. Schenider, Acting Chief, LMG, NIA

Others: C. Dennis Miller, National Research Service Fellow
John White, Biologist, LMG, NIA

COOPERATING UNITS *(if any)*

Andrus Gerontology Center (Edward Schneider)

LAB/BRANCH

Laboratory of Molecular Genetics

SECTION

INSTITUTE AND LOCATION

National Institute of Aging NIH, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.5	0.5	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

We studied the genetic variation among subpopulations of cultured HeLa and RAT-1 cells with the DNA fingerprint technique. The technique makes it possible to screen for differences among scores of loci scattered throughout the genome.

We compared the fingerprint patterns of mass populations of HeLa cells with those of individual clones selected from the populations. We found differences in band patterns in 3% of the loci examined. We then made similar comparisons with RAT-1 cells, finding no differences in any of the bands studied.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00719-01 LMG

PERIOD COVERED

January 1, 1989 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)* Heat Shock Protein Gene Expression in Response to Physiological Stress

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I. - Michael J. Blake, National Research Council Fellow, LMG, NIA

Others - Nikki J. Holbrook, Senior Investigator, LMG, NIA
David Gershon, Visiting Professor, LMG, NIA
Joseph Fargnoli, Senior Staff Fellow, LMG, NIA

COOPERATING UNITS *(if any)*

Laboratory of Behavioral Sciences, Behavioral Physiology Section, NIA (Dr. Hal Tatelman and Mark Talan)

LAB/BRANCH

Laboratory of Molecular Genetics

SECTION

INSTITUTE AND LOCATION

National Institute on Aging, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.75	1.75	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Heat and other stressors are known to induce the expression of a set of highly conserved proteins termed the heat shock proteins (HSPs) in virtually all organisms ranging from bacteria to man. While they have been exstensively studied in cultured cells, little is known concerning their expression in response to stress in intact mammalian systems. In this project we have begun to examine the expression of two such HSPs, HSP 70 and HSP 27, in tissues of young and old rats and mice following exposure to either hyperthermic or hypothermic conditions. We have characterized the kinetics of mRNA expression for these two HSPs in skin, lung, brain and liver after exposing rats to various elevated temperatures for different lengths of time. Reduced levels of HSP 70 and HSP 27 RNA were observed in tissues of aged rats when compared to young animals exposed to identical conditions. This decline appears to reflect a deficit in the thermal response to heat stress by aged animals rather than an alteration in their ability to express HSPs. We have further defined HSP 70 induction in-vivo in brain by determining the anatomical localization of expression using in-situ hybridization. Specific induction was observed in the dentate gyrus of the hippocampus and the paraventricular nucleus of the hypothalamus suggesting a link between the cellular HSP 70 response and the classic neuroendocrine stress responses generated via the hypothalamic-pituitary-adrenal axis. Exposure of young mice to hypothermic conditions also resulted in HSP 70 induction in brown fat, lung and heart. This induction did not occur in aged mice and again appears to reflect a problem with mechanisms of thermoregulation.

ANNUAL REPORT OF THE LABORATORY OF NEUROSCIENCES
NATIONAL INSTTITUTE ON AGING
1988-1989

I. ORGANIZATION AND MISSION STATEMENTS:

The Laboratory of Neurosciences (LN) at the National Institute on Aging was formed in 1978, and is involved in research on the central and peripheral nervous systems in healthy, aging and disease, including Alzheimer's disease. The Laboratory is located at the Clinical Center in Bethesda, Maryland, and is divided into three sections entitled, (1) Cerebral Physiology and Metabolism, (2) Brain Aging and Dementia, and (3) Neurochemistry and Brain Transport. In addition, there are four Units which were formed in 1987 and 1988, entitled (1) Positron Emission Tomography, (2) Neuropsychology, (3) Pharmacology and Pharmacokinetics, and (4) Brain Imaging and Computers. In September 1982, a six-bed temporary Patient Care Unit (PCU) was established to study inpatients with Alzheimer's disease and other dementias, as well as healthy subjects. The PCU, now on the 12E Ward of the Clinical Center, should move to permanent quarters on the 6D Ward in FY 1989. An Outpatient Clinic also was started in 1982 to screen subjects for inpatient protocols and to carry on outpatient-related research.

A. REPORT ON SECTION ON CEREBRAL PHYSIOLOGY AND METABOLISM (STANLEY I. RAPOPORT, CHIEF).

This section investigates the function, structure, physiology, biochemistry, and pharmacology of the central and peripheral nervous systems and the changes that take place during development and aging. Areas of investigation include the application of in vivo techniques to study brain glucose and lipid metabolism (using radioactive 2-deoxy-D-glucose or fatty acids); examination of the structure and function of the blood-brain and blood-nerve barrier, in disease models and before and following modification, in relation to chemotherapy of central nervous system disease; the design of appropriate drugs to enhance entry and action within the central nervous system; the use of tissue culture techniques to examine neuronal electrical properties in relation to altered genetic composition (trisomy 16 mice); the use of histological techniques to examine neuronal morphology and plasticity; neurochemical and molecular biological techniques to examine the Alzheimer brain.

B. REPORT ON SECTION ON BRAIN AGING AND DEMENTIA (MARK B. SCHAPIRO, DEPUTY CHIEF). This section examines the metabolic, anatomical, neurochemical and neuropsychological parameters that characterize cerebral function in the following subject groups, so as to understand aging and disease of the brain and to provide a differential diagnosis of Alzheimer's disease and other dementias: (1) healthy men and women at different ages; (2) treated chronic hypertensives, (3) dementia of the Alzheimer type, (4) multiple infarct dementia, (5) Down syndrome, (6) depression in the elderly. The section employs positron emission tomography to examine cerebral metabolic rates for glucose and cerebral blood flow, computerized CT and magnetic resonance

imaging to evaluate brain anatomy, analytical techniques to explore the composition of cerebrospinal fluid, and neuropsychological tests to evaluate the details of cognitive function. The program has initial cross-sectional studies followed by longitudinal studies with post-mortem followup.

C. REPORT ON UNIT OF POSITRON EMISSION TOMOGRAPHY (MARK B. SCHAPIRO, CHIEF; CHERYL L. GRADY, DEPUTY CHIEF). This Unit is responsible for conducting research involving positron emission tomography on human subjects in relation to developmental abnormalities of the brain, including retardation; aging; and dementia, including Alzheimer's disease and multiple infarct dementia (see Section heading). Clinical protocols are formulated to examine brain glucose utilization using 18-F-2-deoxy-D-glucose; and blood flow using 15O-water, as positron-emitting tracers. Studies are performed on subjects at rest, with reduced visual and auditory inputs; to obtain baseline measures of cerebral metabolism; and in repeated fashion with well-defined cognitive or physiological stimulus paradigms to determine patterns of activation during different task conditions. Metabolic data are related to data obtained with CT and neuropsychological measures.

D. REPORT ON UNIT ON NEUROPSYCHOLOGY (JAMES V. HAXBY, CHIEF). This Unit is responsible for the design, implementation and analysis of neuropsychological research on memory, language, cognition and attention in healthy subjects and in patient groups noted above. A goal is to identify and describe changes in mental abilities that are a function of age or age-related disease, to propose and test cognitive models for these changes, and to relate them to neuroanatomical, neurochemical and physiological changes that are concurrently measured. The Unit participates in clinical protocols to evaluate cognitive and behavioral effects of centrally acting drugs, including possible therapeutic agents for the treatment of Alzheimer's disease.

E. REPORT ON UNIT ON PHARMACOLOGY AND PHARMACOKINETICS (TIMOTHY SONCRANT, CHIEF). This Unit is responsible for conducting research on the sites and modes of action of centrally acting drugs, in animals and humans, in relation to peripheral pharmacokinetics, behavioral and cognitive responses, and metabolic changes within the brain. Animals are examined using behavioral testing and quantitative autoradiographic procedures with various isotopes to localize central drug action. Humans are studied in relation to age and with neurodegenerative disorders, including Alzheimer's disease, depression, and extrapyramidal signs. Drugs are evaluated for therapeutic efficacy, using cognitive and other measures. Cerebrospinal fluid concentrations of neurotransmitters and their metabolites are measured by analytical techniques, often developed by the Unit. The Unit also trains clinicians in the proper conduct of research in clinical pharmacology and therapeutics.

F. REPORT ON SECTION ON NEUROCHEMISTRY AND BRAIN TRANSPORT (QUENTIN R. SMITH, CHIEF). The function of this section is to conduct research on the transport, distribution, metabolism, and physiological actions of critical solutes within the central and peripheral nervous systems in relation to brain function, aging and disease. The program examines the cerebral uptake, distribution and actions of environmental toxins, such as heavy

metals, which may have a key role in brain aging and dementia. In addition, the program explores the mechanisms that regulate cerebral metabolism, protect the brain from circulating toxins, and maintain a stable ionic environment for neuronal function.

G. REPORT ON UNIT ON BRAIN IMAGING AND COMPUTERS (BARRY HORWITZ, CHIEF). This Unit is responsible for conducting research involving in vivo structural imaging of the human brain in healthy subjects and in the patient groups noted above. Images are obtained using X-ray computer-assisted tomography (CT) and magnetic resonance imaging (MRI). Quantitative volumetric analyses are performed in order to assess differences in volumes of significant brain structures (e.g., ventricles, basal ganglia), and to determine volumetric changes in individuals followed longitudinally. In addition, this Unit conducts research involving the use of multivariate statistical methods and computer computational techniques for analyzing functional brain activity as measured by PET.

II. RESEARCH HIGHLIGHTS

This section summarizes selected research accomplishments from the Office of the Chief (Stanley I. Rapoport) and Section on Cerebral Physiology and Metabolism, not summarized under later Section or Unit Headings.

000 A. BRAIN FUNCTION IN AGING AND DEMENTIA.

00 1. Phylogenetic hypothesis for Alzheimer's disease. PET demonstrates disproportionate metabolic involvement of the frontal, parietal and temporal association neocortices in Alzheimer patients, with little involvement of primary and sensory motor regions. Furthermore, neurofibrillary tangles are selective to the association as compared to primary sensory and motor cortical regions, and Alzheimer neuropathology is found in non-neocortical brain regions which underwent rapid changes during recent hominid and higher primate evolution. These and other observations suggest that Alzheimer's disease is a phylogenetic disease which involves brain regions which underwent rapid expansion during evolution of higher primates. This work was done by S. Rapoport.

000 B. FUNCTIONAL INTERACTIONS BETWEEN BRAIN REGIONS.

00 1. Application of correlation matrix to clinical subject groups. The correlation matrix approach to PET-derived cerebral metabolic rates was related to assumptions that the brain is composed of networks of neuronal units whose integrated activities subserve cognition and behavior. Its application to different subject groups was evaluated. Matrix analysis suggests that functional interactions between ipsilateral parietal and frontal association areas are reduced in the elderly, consistent with reduced "fluid" intelligence and visuospatial ability; that cortical-cortical and noncortical-cortical interrelations

are altered in autism, consistent with altered directed attention; and that Broca's area is functionally disconnected in young adults with Down syndrome, as are thalamic regions, consistent with language problems and increased distractibility in these subjects. In view of studies following corpus callosotomy in rats, reductions of both interhemispheric and intrahemispheric correlations within the Alzheimer brain are consistent with a primary defect of pyramidal association neurons which contribute to both sets of correlations. Hypotheses concerning network abnormalities, derived from resting matrix data, have to be tested in subjects performing tasks proposed to be mediated by those networks. This work was done by S. Rapoport and B. Horwitz.

000 C. BRAIN ANATOMY IN AGING AND DEMENTIA.

00 1. Down syndrome. Adult Down subjects with trisomy 21 karyotype were compared by quantitative computer assisted tomography (CT) to controls. In young Down subjects (21 to 35 yr), the volumes of gray matter and individual intracerebral structures when normalized to height did not differ significantly from control volumes. Older Down subjects demonstrated increased CSF volume indicative of brain atrophy. Thus, no observable differences exist between brains of young Down subjects and controls, after normalization for height, but aging in Down syndrome is accompanied by brain atrophy. This work was conducted by M. Schapiro.

00 2. Serial computer assisted tomography in Down syndrome. Serial CT studies over periods of 2 years or more demonstrated no significant difference in the mean rate of lateral ventricular dilatation between older, nondemented DS subjects and younger healthy DS adults. On the other hand, older demented DS subjects show accelerated ventricular dilatation, indicative of progressive brain atrophy and neuronal loss; just as we have reported in patients with dementia of the Alzheimer type. This work was done by M. B. Schapiro and colleagues.

00 3. Obsessive-compulsive disorder. Ten men with severe primary obsessive-compulsive disorder (OCD) and 10 controls were compared using quantitative CT. Caudate nucleus volume in the OCD patients was less than in the controls, but other brain morphometric measures did not differ. Reduced caudate volume supports other evidence of involvement of this structure in OCD. This work was done by J. Luxenberg and colleagues.

000 D. CEREBROSPINAL FLUID CHEMISTRY IN AGING AND DEMENTIA.

00 1. CSF monoamines in DAT with extrapyramidal features (EDAT). Monoamine metabolites and biopterin in lumbar CSF were determined in DAT patients with (EDAT) and without extrapyramidal signs, and in controls. The concentrations of biopterin and of homovanillic acid were significantly less in the EDAT patients than in either the DAT patients or controls, suggesting that EDAT patients have a specific biopterin-dopaminergic central deficiency related to motor dysfunction. This work was conducted by J. Kaye and C. May.

00 2. CSF acetylcholinesterase and peptides in DAT and EDAT (see 1). CSF acetylcholinesterase was significantly reduced in DAT and EDAT patients as compared with controls. Somatostatin-like immunoreactivity was reduced only in DAT patients, whereas neuropeptide Y-like immunoreactivity was unaffected in both diseases. The results indicate selective deficits in DAT, cholinergic and somatostatinergic but not of neuropeptide Y. This work was conducted by J. Atack and C. May.

00 3. CSF markers in the myoclonic subtype of DAT. In DAT patients with myoclonus, as compared with DAT patients without myoclonus and controls, the mean concentration of homovanillic acid was reduced, as was the mean concentration of biopterin. 5-Hydroxyindole acetic acid (serotonin) concentration was higher in the myoclonic as compared to nonmyoclonic DAT group, matched for age and severity. DAT patients with myoclonus or extrapyramidal signs (see above) represent distinct subgroups with similar deficits in dopamine and biopterin, but differing with respect to serotonin metabolism. This work was done by A. Kaye, C. May and J. Atack.

00 4. CSF alpha-melanocyte stimulating hormone in Alzheimer's disease. Mean alpha-melanocyte stimulating hormone-like immunoreactivity was reduced in the CSF of DAT patients with late onset (> 65 years) dementia as compared with controls, and individual values were correlated inversely with CSF concentrations of homovanillic acid, a metabolic product of dopamine. It is likely therefore that hypothalamic neurons which produce pro-opiomelanocortin peptides are involved in Alzheimer's disease, and that a functional relation exists between central dopaminergic and melanotropinergic systems. This work was done by I. Raniero and colleagues.

00 5. CSF production in healthy aging. The rate of CSF production, measured using a draining method from lumbar CSF, was reduced by half in older as compared with younger healthy subjects, from 0.4 to 0.2 ml/min. Rostrocaudal gradients of protein did not differ, however, between old and young subjects. As CSF spaces are larger in the elderly, a lower production rate indicates that turnover of CSF, which acts as a sink for washout of brain substances, is reduced in the elderly. This work was done by C. May and colleagues.

000 E. BRAIN LIPID METABOLISM, RELATION TO FUNCTION AND AGING.

00 1. Mathematical model for brain incorporation of plasma palmitate. A multicompartment mathematical model was developed by P. Robinson to interpret and calculate, from experimental data, the rate of palmitate uptake by brain from plasma, Jpalm. The model includes entry of palmitate from plasma into brain, de novo synthesis from acetate, and turnover of palmitate-containing brain lipids. It can be used to determine transfer constants between brain and blood, and to calculate brain lipid turnover and synthesis from time-dependent changes in brain radioactivity following the i.v. injection of 14C-palmitate.

00 2. Aging and Jpalm. H. Tabata demonstrated that Jpalm is age-invariant in adult Fischer-344 rats. As the rate of incorporation of plasma palmitate into brain represents the lower limit for turnover of brain lipids, the results are consistent with the maintenance of brain structural integrity throughout aging of the rat.

00 3. Neuronal processes recovery following axotomy. The hypoglossal nerve was unilaterally severed in 3 month old Fischer 344 rats, and Jpalm was determined bilaterally in the hypoglossal nucleus at various times thereafter. From 1 day to 24 days after axotomy, Jpalm was increased by up to 20% in the nucleus ipsilateral to the lesion, indicative of increased lipid synthesis. This study again demonstrates the utility of the palmitate method for examining brain plasticity in response to lesions. It was conducted by S. Yamazaki and J. Noronha.

00 4. Incorporation of [9,10-3H] palmitate into metabolic compartments of the brain. It was shown that this tritiated palmitate has advantages over [14C]palmitate for studying brain structure and function, because the tritiated tracer provides higher resolution autoradiographs, and because the products of its beta-oxidation, mainly 3H20, are removed during drying for autoradiography. Following intravenous injection, this tracer is distributed (within 15 min to 4 h) mainly within brain phospholipids, particularly phosphatidyl choline, and thus can be used to mark turnover or synthesis of this phospholipid in vivo. This work was done by J. G. Noronha and colleagues.

00 5. Incorporation of [1-14C]arachidonate into brain phospholipids. Arachidonic acid, a C20 polyunsaturated essential fatty acid, is derived from dietary sources and is a major component of brain phosphoinositides. Following intravenous injection in rats, it is taken up by brain regions near maximally by 5 min, and is a marker particularly of phosphatidyl inositol. As such, it can be used to examine in vivo turnover and synthesis of this phospholipid. This work was done by J. DeGeorge and colleagues.

00 6. Fatty acid incorporation into brain following cholinergic stimulation. Arecoline, an M1 muscarinic agonist, when given to awake rats caused a 30% increase in [1-14C]arachidonate incorporation into brain, but did not alter [9,10-3H]palmitate incorporation. Increased arachidonate incorporation was blocked by atropine, a muscarinic receptor antagonist, and occurred in association with the distribution of M1 cholinergic receptors. Thus, [1-14C]arachidonate can be used to examine neurotransmitter-receptor coupling in vivo for transmitters using the phosphoinositide second messenger system. This work was done by J. DeGeorge and colleagues.

00 7. Palmitate uptake into central auditory structures following unilateral auditory deprivation. Destruction of the cochlea in 11 day-old rats reduced incorporation of [U-14C]palmitate into brain regions which subserve central auditory processing -- ipsilateral cochlear nucleus, contralateral inferior colliculus, medial geniculate and auditory cortex. Cells in these regions also showed evidence of atrophy. Thus, the method can be used to examine central effects on brain structure of disuse atrophy. This work was done by O. Tone and colleagues.

00 8. Palmitate incorporation into metastatic brain tumors in rats. Cerebrally implanted Walker 256 carcinosarcoma in rats accumulated intravenously injected [9,10-3H]palmitate 4-7 fold more than did surrounding brain, suggesting that radiolabeled fatty acids can be used for brain imaging of growing tumors in humans, in which new lipid is synthesized. This work was done by T. Nariai and colleagues.

000 F. MOLECULAR BIOLOGY OF BRAIN AGING AND DISEASE.

00 1. Localization of glucocorticoid receptor messenger mRNA in hippocampus of rat brain using in situ hybridization. The in situ hybridization procedure was applied to quantify glucocorticoid receptor (GR) mRNAs in the hippocampus of the rat brain, using a radiolabeled antisense probe complementary to the rat liver GR gene. The specificity of the method was confirmed. Within the hippocampus, a brain region known to preferentially concentrate steroid hormones, quantitative autoradiography indicated that neuronal silver grains were highest in number in pyramidal cell layers of CA2 and CA4, and lowest in CA1 and CA3. Thus, continuous but distinct cell fields in the hippocampus express different levels of GR transcripts, indicating differential regulation of GR expression. This work was done by G. Yang and colleagues.

00 2. Oncogene-related mRNA sequences and aging. Northern blot analysis showed that several s-src-related transcripts are age-invariant in the rat brain. RNA isolated from liver or brain showed that the transcript levels of c-myc, but not of c-sis or c-src-related genes, were elevated in the liver but not in the brain in relation to age, demonstrating organ specific differences in expression during aging. This work was directed by M. Matocha.

00 3. Regional gene expression in the primate brain. Subtraction hybridization of cDNA libraries obtained from various brain regions demonstrated a number of clones that differentially hybridized with given probes within the frontal pole, a region particularly vulnerable to Alzheimer's disease. Differences in gene expression may be related to regional vulnerability to the disease process. This work was done by K. Chandrasekaran and colleagues.

000 G. NEUROCHEMISTRY IN RELATION TO AGE AND DISEASE.

00 1. Nucleus basalis model for Alzheimer's disease. The nucleus basalis of Meynert, which provides cholinergic input to the neocortex, shows significant cell loss and pathology in the post-mortem Alzheimer brain. Based on this, a model was established by lesioning the rat nucleus basalis of Meynert bilaterally. M2 muscarinic receptors fell bilaterally in the neocortex at 1 week after lesioning but recovered by 3 months, whereas the M2 receptors were normal at 1 week but were reduced bilaterally in the neocortex at 3 months after lesioning. Thus, complex and nonuniform changes in cortical cholinergic receptors follow loss of input from the nucleus basalis. The study was performed by J. Atack.

00 2. Plasma proteins in normal human brain. Strong immunopositive staining was consistently seen in various regions of the normal postmortem human brain, using antibodies against albumin, acid glycoprotein and transferrin, particular in the cerebral cortex, thalamus, hypothalamus, and dentate nucleus of cerebellum. In the pons and medulla, cranial nerves were always strongly positive. These results demonstrate plasma protein in postmortem, formalin-fixed brain, possible in relation to retrograde transport from the periphery, and suggest that similar findings in Alzheimer's disease do not reflect breakdown of the blood-brain barrier, as has been suggested. This work was done by J. Atack and H. Liu.

00 3. Proliferation of extra-adrenal catecholamine-storing cells in the aged rat. Catecholamine-storing cells in paraganglia are increased in volume in the aged rat, but as they did not incorporate the mitotic blocker 5-bromo-2-deoxy-uridine, this increase was not associated with active proliferation. The age-changes may be regulated by a glucocorticoid receptor mechanism. This work was done by G. Yang and colleagues.

00 4. Nerve growth factor in Alzheimer brain. Quantitative receptor studies showed equal abundance of NGF in temporal, frontal, and motor neocortices of post-mortem human brain. There was no difference in binding of [125I]-NGF in the Alzheimer brain, however, suggested that the nerve growth factor trophic system is not involved in Alzheimer's disease. This work was done by J. Atack and colleagues.

000 H. BLOOD-BRAIN BARRIER AND CENTRAL NERVOUS SYSTEM FUNCTION.

00 1. Cerebrovascular permeability to lipophilic vinca alkaloids. The vinca alkaloids vincristine and vinblastine are important agents in the chemotherapy of cancer. It was shown in rats that, despite their high lipophilicity, their cerebrovascular permeability was quite low, even after correcting for plasma protein binding. It is likely that their large size (mol wts exceed 900 daltons) allows physical separation of charged and noncharged regions within the molecule, and that this factor, as well as overall lipophilicity, is an important determinant of blood-brain barrier permeability. This work was done by N. Greig and colleagues.

00 2. Chemical modification of water soluble drugs for enhancing brain uptake. The alkylating anticancer agent, chlorambucil, was made into a number of esters to increase its lipid solubility and brain uptake. The tertiary butyl ester of chlorambucil was found to have optimum properties, as its half-life in plasma was prolonged, it rapidly entered the brain as compared with chlorambucil, and it retained significant alkylating activity. Recently, this ester was shown to have significant activity against human tumors grown in vitro, and is entering into clinical testing. This work was conducted by N. Greig and colleagues.

00 3. Brain uptakes of anti-cancer, water-soluble drugs. The pharmacokinetics of melphalan and chlorambucil, two structurally related anticancer drugs, were described in rats. The brain uptake chlorambucil was low, but that of melphalan was greater than expected from its lipid solubility, due to its facilitated transport by the large neutral amino acid carrier at the blood-brain barrier. Brain uptakes of both drugs were nevertheless insufficient for treatment of central nervous system tumors. For these drugs to be centrally effective, their uptake must be enhanced by chemical modification. This work was done by N. Greig.

00 4. Osmotic modification of blood-brain barrier for central nervous system chemotherapy. It was shown that the inadequate delivery of essential chemotherapeutic drugs to the brain, due to an intact or partially intact blood-brain barrier, probably accounts for poor therapeutic responses of patients with brain tumors. Drug delivery in such patients can be enhanced by osmotic opening of the blood-brain barrier, following intracarotid infusion of a concentrated mannitol solution. A review of the literature shows that the procedure causes morbidity in less than 1% of cases, and significantly prolongs survival of patients with primary lymphoma or glioblastoma (Phase II studies). Phase III (controlled clinical trials) are now intended to evaluate the efficacy of the osmotic procedure. This work as done by S. Rapoport.

000 I. REGULATION OF NEURONAL DEVELOPMENT.

00 1. Human trisomy 21 (Down syndrome) dorsal root ganglion (DRG) neurons in culture. Experimental conditions were established to culture DRG neurons from fetal tissue of human abortuses, 14-17 weeks old, with and without the Down (trisomy 21) karyotype. Current and voltage clamp recordings were made in 4 to 21 day old primary cultures. The duration of the action potential was reduced in trisomic neurons, due to faster depolarization and repolarization phases. With voltage clamp, three different potassium currents were demonstrated. Trisomic neurons showed decreased activation time constants for these currents. There are distinct differences in the action potential, and in specific potassium conductances, between trisomy 21 and normal human DRG neurons. This work was done by K. Nieminen.

00 2. Sodium action currents in cultured trisomy 21 neurons. Using voltage clamp procedures, two inward sodium currents were identified in trisomy 21 human dorsal root ganglion neurons in culture, which had been replated to remove excessive dendrites and axonal connections and reduced interference of membrane capacitance. These were: a slow, tetrodotoxin-insensitive current (accounting for 90% of net) and a fast tetrodotoxin-sensitive current (accounting for 10% of net). Deactivation kinetics of the slow component were significantly reduced in the trisomic as compared to control neurons; furthermore, inactivation curves for both components had a 10 mV shift in the depolarizing direction in the trisomic neurons. Both changes in kinetics and in the inactivation curve can account for acceleration of the depolarization of the action potential in trisomy 21 neurons.

00 3. Membrane properties of neurons of trisomy 16 mice. Trisomy 16 in the mouse is a model for trisomy 21 (Down syndrome) in humans, as specific genes on murine chromosome 16 correspond to genes on human chromosome 21 which contribute to the Down phenotype. Experimental conditions were established to culture DRG and spinal cord neurons from fetal trisomy 16, trisomy 19 and control mice. Patch clamp electrodes were employed to measure electrical membrane properties. Trisomic neurons had a faster rate of rise of the action potential (depolarization), and a faster rate of fall of the action potential (repolarization), than controls, resulting in a shorter overall action potential. Over production of products of genes on chromosome 16 in the mouse results in abnormal electrical properties of neurons during development. Furthermore, the action potential abnormality in murine trisomy 16 neurons corresponds to the abnormality in human trisomy 21 neurons. It is absent in trisomy 19 mice, indicating its specificity. This work was done by B. Ault.

00 4. Electrical properties of transgenic mice with extra copies of human Cu/Zn superoxide dismutase. This gene, which resides on the human 21st chromosome and murine 16th chromosome, when replicated in transgenic mice, did not produce the abnormal action potential noted with both the human and murine trisomies; thus, this enzyme does not play a role in the abnormal action potential phenotype. This work was done by B. Ault and colleagues.

00 5. Voltage activated conductances in trisomy 16 neurons. Two sodium conductances, a fast tetrodotoxin (TTX)-sensitive and a slow TTX-resistant conductance, were demonstrated in trisomy 16 and control mouse DRG neurons in culture, using a whole cell patch clamp technique. The slow TTX-resistant conductance was 3-4 times higher than the fast TTX-sensitive conductance, indicating that the action potential of fetal DRG neurons is sustained by the slow conductance. Both conductances were about 50% higher in trisomy 16 than in control neurons, accounting for the higher rate of depolarization of the action potential in trisomic neurons. This work was conducted by C. Orozco.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 AG 00120-12 LN

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Bloob-Brain Barrier and Central Nervous System Function

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	N.H. Greig	Guest Researcher	LN, NIA
	S.I. Rapoport	Chief	LN, NIA
	S. Genka	Guest Researcher	LN, NIA
	P. Robinson	Senior Staff Fellow	LN, NIA
	H. Shetty	Guest Researcher	LN, NIA
Other:	I. Lieberburg	Senior Scientist	Athena Neurosciences
	T. Soncrant	Senior Staff Fellow	LN, NIA

COOPERATING UNITS *(if any)*

Athena Neurosciences, Inc., San Francisco, CA

LAB/BRANCH

Laboratory of Neurosciences

SECTION

Cerebral Physiology and Metabolism

INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.0	3.0	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

A model was developed to interpret the binding of drugs and physiological substances to plasma proteins, and was applied to examine binding of bilirubin, tryptophan, phenobarbital and palmitate.

The blood brain barrier could be opened in rats, mice and humans by intracarotid infusion of a hypertonic solution of mannitol or arabinose. The rate of reclosure was related to the size of the intravascular tracer, indicating that tight junctions between cerebrovascular endothelial cells were modified. This technique has been used to deliver water-soluble agents of potential clinical value, such as interferons, to the brain. A mathematical model describing drug uptake into brain tumors, directly from blood and indirectly from neighboring tissue, was developed and used to quantitate the effectiveness of the osmotic method for drug delivery to tumors.

Analysis of the pathology, development, host responses and state of the blood-brain barrier within malignant brain tumors was undertaken to design more effective drugs and rationales for the treatment of primary and metastatic brain tumors.

IKH-LN-1

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 AG 00121-12 LN

PERIOD COVERED: October 1, 1988 to September 30, 1989

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Function and Structure of Peripheral Nerve

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

P.I.:	K.C. Wadhwani	Staff Fellow	LN, NIA
	Q.R. Smith	Section Chief	LN, NIA
Others:	S.I. Rapoport	Laboratory Chief	LN, NIA
	J. Koistinaho	Visiting Fellow	LN, NIA
	E. Rechthand	Senior Staff Fellow	LN, NIA
	C. Latker	Senior Staff Fellow	LN, NIA

COOPERATING UNITS (if any)

University of Maryland; US Uniformed Health Services, MD; University of Tampere, Finland

LAB/BRANCH

Laboratory of Neurosciences

SECTION

Neurochemistry and Brain Transport

INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.5	1.5	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Blood-nerve barrier permeability to ions and nonelectrolytes is very low, indicating limited exchange between plasma and nerve endoneurium. The nerve barrier, unlike the brain barrier, does not have regulatory transport systems for potassium and calcium. Nerve concentrations of these ions can change under chronic alterations in plasma concentrations.

Glucose and amino acids are transported across the blood-nerve barrier by facilitated systems that are stereospecific, saturable and sodium independent. The transport systems accelerate the nerve uptake of these critical nutrients, over that expected for passive diffusion, and allow matching of transport and metabolic demand.

Permeabilities of both nerve capillaries and perineurium increase during the first few weeks of Wallerian degeneration. Nerve capillary permeability eventually returns to normal, but perineurial permeability remains elevated, suggesting that nerve fibers are required to maintain blood-nerve barrier integrity.

A pharmacokinetic model was developed that incorporates solute transfer across nerve capillaries, epineural blood vessels and perineurial sheath, and allows prediction of endoneural drug concentrations from barrier transfer constants and the time course of plasma drug concentration.

Blood-nerve barrier permeability and nerve water content were found to increase in rats fed high galactose diets for 11 months. Both changes could be prevented by treatment with aldose reductase inhibitors, such as Statil and Alconil, consistent with the "polyol" hypothesis of galactose neuropathy.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00123-08 LN

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Neuronal Development in Tissue Culture

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	B. Ault	Senior Staff Fellow	LN, NIA
	P. Caviedes	Visiting Fellow	LN, NIA
	J. Koistinaho	Visiting Fellow	LN, NIA
Others:	J. Hidalgo	Visiting Fellow	LN, NIA
	K. Nieminen	Visiting Fellow	LN, NIA
	D. Gambal	Guest Researcher	LN, NIA

COOPERATING UNITS *(if any)*

Department of Pediatrics, University of California at San Francisco;
University of Lubeeck, W. Germany

LAB/BRANCH

Laboratory of Neurosciences

SECTION

Cerebral Physiology and Metabolism

INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.1	2.1	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Dorsal root ganglion (DRG) neurons from fetal trisomy 16 mice, a model for trisomy 21 (Down syndrome) in humans, were shown in tissue culture to have altered electrical properties compared to control neurons. Trisomy 16 neurons displayed action potentials with elevated rates of depolarization and repolarization, resulting in reduced spike duration. These differences were essentially identical to abnormalities observed in fetal trisomy 21 neurons. Trisomy 19 DRG neurons showed no differences in passive or active membrane properties compared to normal cells. DRG neurons transgenic for the human gene for superoxide dismutase showed no significant differences in action potential parameters compared to control cells, indicating that excess dosage of this gene alone does not underlie abnormalities identified in trisomy 16 or trisomy 21 neurons.

In trisomy 21 fetal neurons, voltage clamp studies revealed decreased activation time constants for outward potassium currents. Additionally, fast TTX-sensitive and slow TTX-insensitive sodium currents could be identified, the latter accounting for 90% of the total charge moving across the membrane. No alterations in maximal conductances were observed. The slow sodium component had slowed deactivation kinetics. Inactivation curves for both fast and slow currents were shifted 10 mV in the depolarizing direction in trisomy 21 neurons, resulting in a greater number of sodium channels available for activation.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00125-11 LN

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Cerebral Metabolism, Relation to Brain Function and Aging

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	T. Soncrant	Senior Staff Fellow	LN, NIA
	U. Freo	Visiting Fellow	LN, NIA
	J. Atack	Visiting Associate	LN, NIA
	Y. Lamour	Guest Researcher	INSERM, Paris
Others:	H. Holloway	Biologist	LN, NIA
	D. Larson	Biologist	LN, NIA
	N. Greig	Visiting Associate	LN, NIA

COOPERATING UNITS *(if any)*

Department of Neuropathology, Univ. Western Ontario
Laboratory of Clinical Sciences, NIMH
Laboratory of Analytical Chemistry, NIDDK

LAB/BRANCH

Laboratory of Neurosciences

SECTION

Cerebral Physiology and Metabolism

INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
5.0	3.0	2.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The regional cerebral metabolic rate for glucose was measured with the [14C]2-deoxy-D-glucose technique in young and aged male Fischer-344 rats, following administration of cholinergic (arecoline), dopaminergic (haloperidol, bromocriptine), and serotonergic (m-chlorophenylpiperazine) drugs. For arecoline, the absence of age differences in most brain areas indicated that muscarinic receptor mechanisms are intact in the rat brain during aging. Responses to bromocriptine and haloperidol were reduced in senescent as compared to younger rats, suggesting reduced central dopaminergic function, and an imbalance between cholinergic and dopaminergic systems. Aged rats displayed reduced responsivity to m-chlorophenylpiperazine, indicating an age-dependent functional defect in serotonergic neurotransmission.

Structural analogs of physostigmine, a cholinesterase inhibitor, were synthesized. Some were shown to have longer half-lives and greater selectivity for acetylcholinesterase than does physostigmine.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 AG 00126-10 LN

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Brain Function in Aging and Dementia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: M. Schapiro	Senior Staff Fellow	LN, NIA
C. Grady	Research Psychologist	LN, NIA
B. Horwitz	Senior Staff Fellow	LN, NIA
A. Kumar	Medical Staff Fellow	LN, NIA
J. Haxby	Senior Staff Fellow	LN, NIA
Others:		
S.I. Rapoport	Chief	LN, NIA
R. Friedland	Chief, SBAD	LN, NIA

COOPERATING UNITS *(if any)*
Child Psychiatry Branch, NIMH; Department of Nuclear Medicine, CC

LAB/BRANCH
Laboratory of Neurosciences

SECTION
Brain Aging and Dementia

INSTITUTE AND LOCATION
NIA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.6	1.6	0

CHECK APPROPRIATE BOX(ES)

- [x] (a) Human subjects
- [ ] (b) Human tissues
- [ ] (c) Neither
- [ ] (a1) Minors
- [ ] (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Using a high resolution PC1024 positron emission tomograph (PET), whole brain glucose utilization was found to decrease by 12% between the ages of 20 to 90 years in healthy subjects. No effect of gender on metabolism was found in young subjects.

Analysis of high resolution PET data in Alzheimer's disease replicated our earlier findings of metabolic deficits in association neocortex. Four subgroups of Alzheimer patients were identified by their brain metabolic patterns and correlated cognitive profiles. Longitudinal analysis of mildly demented Alzheimer patients demonstrated progressive neocortically mediated cognitive deficits which were preceded by metabolic abnormalities. Analysis of metabolic asymmetries showed that disproportionate left hemisphere hypometabolism predicted later declines in language functions. Regional cerebral blood flow was increased in the parietal cortex during visuospatial stimulation, in the temporal-occipital cortex during object identification, in young and old healthy subjects. Patients with obsessive-compulsive disorder had high cerebral metabolic rates in frontal cortical regions, but those patients who responded favorably to drug therapy had metabolic rates that were closer to normal.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 AG 00127-09 LN

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Neurochemistry of the Nervous System in Aging and Neurodegenerative Disorders

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	J. Atack	Visiting Associate	LN, NIA
	G. Yang	Visiting Fellow	LN, NIA
Other:	M. Matocha	Staff Fellow	LN, NIA
	M. Iyo	Guest Worker	LN, NIA
	G. Wenk	Neurochemist	Johns Hopkins
	D. Katz	Pathologist	CC, NIH
	M. Ball	Neuropathologist	Univ. W. Ontario

COOPERATING UNITS *(if any)*

Department of Behavioral Sciences, Johns Hopkins Medical School, Baltimore
Department of Neuropathology, University Western Ontario, Canada
Department of Pathology, Clinical Center, NIH

LAB/BRANCH

Laboratory of Neurosciences

SECTION

Cerebral Physiology and Metabolism

INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.5	2.5	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Following a unilateral lesion of the rat nucleus basalis of Meynert, there was an acute (1 week) increase in the number of neocortical M2 muscarinic binding sites which returned to normal after 3 months. Neocortical M1 muscarinic binding sites were normal at 1 week but decreased at 3 months. These changes were bilateral and suggest that bilateral changes in cortical cholinergic receptors follow unilateral degeneration of cholinergic input.

Differentiation of adrenergic derivatives of the rat neural crest was examined using the glucocorticoid receptor (GR) as a molecular marker. Both adrenal and extra-adrenal chromaffin cells had similar temporal patterns of GR localization and responsiveness to dexamethasone during postnatal development, whereas these same characteristics were not found in sympathetic neurons. The numerial increase in extra-adrenal chromaffin cells in the aging rat was not accompanied by a cellular proliferation mechanism.

Nerve growth factor (NGF) receptors were identified in the human cerebral cortex and had a dissociation constant (Kd) of 150-300 pM. The binding of [125I]-NGF to membranes prepared from Alzheimer's disease brains did not differ significantly from binding in normal brains. Receptor binding did not reflect the laminar distribution of cortical cholinergic markers, suggesting that the NGF receptors are not cholinergic-specific.

Intro

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 AG 00128-09 LN

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Analytical Drug Methods

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	T. Soncrant	Senior Staff Fellow	LN, NIA
	N. Greig	Guest Researcher	LN, NIA
	J. Deutsch	Visiting Scientist	LN, NIA
	H.U. Shetty	Guest Researcher	LN, NIA
Others:	E. Daly	Chemist	LN, NIA
	G. Phelan	IRTA Fellow	LN, NIA
	S.I. Rapoport	Chief	LN, NIA

COOPERATING UNITS *(if any)*

Athena Neurosciences, Inc., San Francisco, CA

LAB/BRANCH

Laboratory of Neurosciences

SECTION

Cerebral Physiology and Metabolism

INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

An analytical method using high performance liquid chromatography (HPLC) with ultraviolet detection was developed for the measurement of bromocriptine, a dopaminergic agonist, in plasma and brain of rats. HPLC assays for chlorambucil and lipophilic derivatives were developed. Gas chromatographic/mass spectrometric assays for arecoline and scopolamine in rat plasma and brain in human plasma were developed.

GPO 914-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 AG 00129-09 LN

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Distribution of Nutrients, Metals and Toxins within Central Nervous System

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Q.R. Smith	Section Chief	LN, NIA
	V. Murphy	Senior Staff Fellow	LN, NIA
	S. Fukui	Visiting Fellow	LN, NIA
	J. Rosenberg	NRC Fellow	LN, NIA
Others:	S.I. Rapoport	Laboratory Chief	LN, NIA
	S. Kaufman	Laboratory Chief	LNC, NIMH

COOPERATING UNITS *(if any)*
Laboratory of Neurochemistry, NIMH; Unit on Neurotoxicology, INSERM, Paris, France; Neuroscience Laboratory, Maryland Psychiatric Research Center; Tokyo Medical and Dental University, Tokyo, Japan.

LAB/BRANCH
Laboratory of Neurosciences

SECTION
Neurochemistry and Brain Transport

INSTITUTE AND LOCATION
NIA, NIA, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.0	4.0	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

An electron beam X-ray microanalysis method was developed to examine the cellular and regional distribution of metals in unfixed, unstained, fresh-frozen human brain tissue. Analysis of samples from patients with Alzheimer's disease demonstrated that neither aluminum, calcium or silicon is accumulated significantly in senile plaques as compared to surrounding brain tissue or brain tissue from aged-matched controls.

Rates of entry of selected metals into the central nervous system were determined in awake, unanesthetized rats following intravenous administration. Values were found to differ among metals by at least two-orders of magnitude with lead > calcium = cadmium > gallium for uptake into brain. Calcium influx into cerebrospinal fluid is maintained constant during chronic hypocalcemia by a saturable, vitamin D-independent transport mechanism at the choroid plexus epithelium.

Essential nutrients that are required for brain metabolism are transported into brain from plasma by specific, saturable transport mechanisms at the blood-brain barrier. A brain perfusion technique was used to characterize the transport systems for glucose and amino acids and to evaluate the structural specificity of the neutral amino acid transport system. The availability of albumin-bound tryptophan for uptake into brain was found to be dependent on the cerebral perfusion rate.

IRP-LN-1

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 AG 00130-07 LN

PERIOD COVERED: October 1, 1988 to September 30, 1989

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Neuropsychological Function in Aging and Dementia

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

P.I.:	J.V. Haxby	Unit Chief, Neuropsychology	LN, NIA
	C.L. Grady	Research Psychologist	LN, NIA
Others:	B. Sonies	Speech Pathologist	RM, CC
	R. Parasuraman	Cognitive Psychologist	Catholic Univ.
	J. Gillette	Psychology Technician	LN, NIA
	A. Berardi	Guest Researcher	LN, NIA

COOPERATING UNITS (if any)

Rehabilitation Medicine Department, Clinical Center; Department of Psychology, Catholic University

LAB/BRANCH

Laboratory of Neurosciences

SECTION

Brain Aging and Dementia

INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.0	2.0	0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Neuropsychologically relevant mental abilities are studied in healthy men at different ages, in patients with clinically-diagnosed Alzheimer's disease, and in adults with Down syndrome at different ages. Tests are administered to evaluate intelligence, memory, language, visual attention, visuoperceptive and visuoconstructive ability, and perceptual-motor speed. The presence and neuroanatomical location of separate visual pathways for spatial vision and object vision were investigated in healthy young men by measuring regional cerebral blood flow (rCBF) with positron tomography (PET) and H-2-15-O. The results demonstrated two distinct visual pathways at work in humans. Age-related differences in general intelligence, verbal memory and visual memory in our sample of healthy men, ranging in age from 20 to 83 years, were found to be smaller than the differences reported in normative studies of non-health-screened adults. No significant age-related difference on verbal processing and memory was found. Age-related differences on visuospatial processing and memory were statistically significant. In healthy adults, visual memory and the discrepancy between verbal and visuospatial ability were not correlated with regional cerebral metabolic rates for glucose (rCMRglc) as measured by PET and 18-Fluorodeoxyglucose, but the discrepancy between visual and verbal memory was correlated with right-left parietal rCMRglc asymmetry. Neuropsychological patterns were correlated with neocortical rCMRglc patterns in patients with moderate Alzheimer's disease, but not in patients with mild Alzheimer's disease. Longitudinal study of mildly impaired patients, however, demonstrated that the development of neocortically-mediated neuropsychological impairments follows the appearance of significant

IKP-LN-1

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 AG 00131-07 LN

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Neurological Function in Aging and Dementia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	C. Grady	Research Psychologist	LN, NIA
Other:	A. Grimes	Audiologist	CC
	A. Pikus	Audiologist	CC
	J. Kaye	Medical Staff Fellow	LN, NIA
	M. Schapiro	Senior Staff Fellow	LN, NIA
	R. Friedland	Chief, SBAD	LN, NIA
	O. Devinsky	Medical Staff Fellow	CNB, NINDS
	S. Sato	Chief, EEG Lab	CNB, NINDS

COOPERATING UNITS *(if any)*

Audiology Section, CC
Clinical Neurosciences Branch, NINDS

LAB/BRANCH

Laboratory of Neurosciences

SECTION

Brain Aging and Dementia Section

INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.8	.5	.3

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

In patients with Alzheimer's disease, studies of central auditory function using both dichotic and degraded monotic tests showed that performance on the dichotic test was more difficult for the patients, compared to healthy controls. Only dichotic performance was related to measures of cerebral atrophy and glucose metabolism in the temporal lobes.

Basal metabolic rate (BMR) was measured in young subjects with Down Syndrome (DS) and healthy controls to see if extra genomic material affects basal metabolism. No difference was found between DS subjects and controls, suggesting that chromosome 21 does not control BMR.

The occurrence of motor vehicle accidents was assessed in patients with Alzheimer's disease to determine the effect of cognitive deterioration on the complex motor behavior of driving. Patients were found to have more accidents than elderly controls (47% vs. 10%), but these were not related to disease severity or duration.

The relation of EEG alpha background to cognitive function and cerebral metabolism was assessed in young and old DS subjects. Old DS subjects with decreased alpha backgrounds had dementia, reduced cognitive function, larger ventricles, and a global decrease in cerebral glucose utilization compared to age-matched subjects with normal alpha backgrounds. In contrast, the EEG background did not correlate with psychometric or PET data in the younger DS subjects.

IRP-LN-1

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 AG 00132-05 LN

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Brain Anatomy in Aging and Dementia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	C. DeCarli	Senior Staff Fellow	LN, NIA
	B. Horwitz	Senior Staff Fellow	LN, NIA
	W. Kozachuk	Medical Staff Fellow	LN, NIA
Others:	J. Kaye	Medical Staff Fellow	LN, NIA
	R. Friedland	Chief BADS	LN, NIA
	J. Luxenberg	Medical Staff Fellow	LN, NIA
	S.I. Rapoport	Chief	LN, NIA

COOPERATING UNITS *(if any)*
Laboratory of Neurochemistry, NIMH; NIS, NINDS; Department of Radiology, CC; Division of Cancer Treatment, Pediatric Branch, NCI

LAB/BRANCH
Laboratory of Neurosciences

SECTION
Brain Aging and Dementia

INSTITUTE AND LOCATION
NIA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.0	1.0	

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The transverse computer assisted tomography (CT) method of calculating ventricular volumes of the human brain in vivo, using TRACE image analysis procedure was found to be highly reliable, and suitable for longitudinal studies of aging and dementia.

Quantitative CT analyses in healthy aging men and women demonstrated significant sex differences in ventricular volume and in age of onset of ventricular enlargement. Structural brain changes, as measured by ventricular enlargement, and decline in cognitivie performance on the WAIS appear to be relatively independent processes correlated more to the age of the subject.

Three sets of monozygotic twins discordant for dementia of the Alzheimer type were studied and found to have significant differences in ventricular volumes. The Alzheimer patients also had faster rates of left ventricular enlargement than did normal controls, whereas their unaffected twins were within the normal range.

Eight children with AIDS encephalopathy were studied and found to have significant reductions in the ventricular brain ratio accompanied by significant improvement of cognitive function when treated with chronic infusion AZT.

IRP-LN-1

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 AG 00133-07 LN

PERIOD COVERED: October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*: Clinical Pharmacokinetics, Pharmacodynamics and Therapeutics

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	T. Soncrant	Senior Staff Fellow	LN, NIA
	P. Morris	Visiting Associate	LN, NIA
	K. Raffaele	Staff Fellow	LN, NIA
	A. Kumar	Medical Staff Fellow	LN, NIA
	J. Haxby	Senior Staff Fellow	LN, NIA
Others:	J. Atack	Visiting Associate	LN, NIA
	N. Greig	Guest Researcher	Athena Neurosciences

COOPERATING UNITS *(if any)*: Laboratory of Neurochemistry, NIHM; Section of Clinical Psychopharmacology, NIMH; Human Motor Control Section, NINDS; College of Pharmacy, University of Saskatchewan; Athena Neurosciences, Inc., San Francisco, CA

LAB/BRANCH: Laboratory of Neurosciences

SECTION: Cerebral Physiology and Metabolism

INSTITUTE AND LOCATION: NIA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1	1	

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Biopterin administration to some subjects with Alzheimer's disease elevated cerebrospinal fluid biopterin values to age-matched normal values. Biopterin appeared also to increase dopamine turnover in these subjects, suggesting that biopterin deficiency may lead to impaired dopaminergic neurotransmission in a subset of Alzheimer's subjects. Administration of haloperidol, a dopamine antagonist, to normal subjects produced greater cognitive and motor effects in young than in aged men. These results suggest that the responsivity of the brain dopamine system may be reduced with age in humans. Arecoline, a cholinergic agonist, can be administered safely to humans and has favorable pharmacokinetic properties for clinical studies in Alzheimer's disease. Brain dopamine turnover, as measured with the debrisoquin method, is reduced in aged compared to young healthy adult males.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 AG 00134-06 LN

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Brain Lipid Metabolism, Related to Function and Aging

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	J. Gnaedinger Noronha	Senior Staff Fellow	LN, NIA
	J. J. DeGeorge	Senior Staff Fellow	LN, NIA
	P. J. Robinson	Visiting Scientist	LN, NIA
Others:	T. Nariai	Visiting Fellow	LN, NIA
	S. Yamazaki	Visiting Fellow	LN, NIA
	J. C. Miller	Staff Fellow	LN, NIA
	O. Tone	Visiting Fellow	LN, NIA

COOPERATING UNITS *(if any)*
Department of Nuclear Medicine, Clinical Center
Athena Pharmaceutical, San Francisco, CA

LAB/BRANCH
Laboratory of Neurosciences

SECTION
Cerebral Physiology and Metabolism

INSTITUTE AND LOCATION
NIA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.75	3.50	1.25

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

A method was developed to measure the rates of incorporation of palmitate and arachidonate, from plasma into different brain regions in the awake rat. A theoretical model was developed to calculate incorporation rates, J_{palm} and J_{arach}, and transfer constants, k_{palm} and k_{arach}, from data.

The distribution of radiolabelled fatty acid in brain lipids was predominantly within phospholipid classes. Palmitate derived label was found primarily in phosphatidyl choline while arachidonate became incorporated into phosphatidyl inositol.

The incorporation of arachidonate into brain lipids was increased 30% in rats given a cholinergic agonist, arecoline. This increase is likely the result of the stimulation of the phosphoinositide second messenger cascade, by the activation of the M1 muscarinic receptor by arecoline.

[9,10-^{3}H]Palmitate incorporation was increased 4-7 fold in tumors that were implanted in rat caudate nuclei and allowed to develop for seven days.

[U-^{14}C]Palmitate incorporation into the hypoglossal nucleus increased maximally 24 days after hypoglossal nerve axotomy. This increase correlated with nerve regeneration. Following axotomies in which regeneration was prevented, palmitate incorporation remained decreased between 24 and 35 days.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 AG 00135-06 LN

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Molecular Biology of Brain Aging and Disease

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	M. F. Matocha	Senior Staff Fellow	LN, NIA
	K. Chandrasekaran	Visting Scientist	LN, NIA
Others:	J.R. Atack	Visiting Associate	LN, NIA
	S.P. Wise	Chief	LNP, NIMH
	G. Yang	Visiting Fellow	LN, NIA

COOPERATING UNITS *(if any)*

Laboratory of Neurophysiology, National Institute of Mental Health

LAB/BRANCH

Laboratory of Neurosciences

SECTION

Cerebral Physiology and Metabolism

INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.75	2.75	

CHECK APPROPRIATE BOX(ES)

- [X] (a) Human subjects
  - [ ] (a1) Minors
  - [ ] (a2) Interviews
- [X] (b) Human tissues
- [ ] (c) Neither

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The activity of the protein product (tyrosine protein kinase) of the src oncogene was measured in whole brain of Fischer-344 rats, by an in vitro immune complex kinase assay. There was no significant difference in the pp60c-src specific kinase activity as a function of age.

In situ hybridization methods were developed to measure cellular levels of genes involved in cell signaling mechanisms. High levels of expression of the glucocorticoid receptor gene were found in rat brain. Quantitative analysis indicated significant differences in expression between the pyramidal cell layers of the rat hippocampus.

cDNA libraries were prepared using mRNAs isolated from specific regions of nonhuman primate brain. Subtractive and differential hybridizations were carried out to identify cDNA clones corresponding to genes predominantly expressed in either the association or primary sensory neocortices, or the primary sensory areas.

Total RNA was prepared from control and Down syndrome human fetal brain tissue. The polyadenylated fraction was isolated intact and used for Northern blot hybridization analysis of genes mapped to chromosome 21.

IRP-LN-1

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 AG 00140-04 LN

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Cerebrospinal Fluid Chemistry in Aging and Dementia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	J.R. Atack	Visiting Associate	LN, NIA
	S.I. Rapoport	Chief	LN, NIA
Others:	J. DeGeorge	Senior Staff Fellow	LN, NIA
	C. May	Medical Staff Fellow	LN, NIA
	J.A. Kaye	Medical Staff Fellow	LN, NIA
	T. Soncrant	Senior Staff Fellow	LN, NIA
	I. Rainero	Guest Researcher	LN, NIA

COOPERATING UNITS *(if any)* Laboratory of Neurochemistry, NIMH; Department of Pharmacology and Experimental Therapeutics, Loyola University; Department of Neurology, Massachusetts General Hospital, Boston, MA

LAB/BRANCH
Laboratory of Neurosciences

SECTION
Brain Aging and Dementia/Cerebral Physiology and Metabolism

INSTITUTE AND LOCATION
NIA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.4	1.4	

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Subtypes of dementia of the Alzheimer type (DAT) - DAT with motor abnormalities, such as extrapyramidal signs (EDAT) and myoclonus (MDAT), were studied using neurochemical measurements in the cerebrospinal fluid (CSF). Reductions in somatostatin-like immunoreactivity (SLI) and acetylcholinesterase (AChE) activity were found in DAT, EDAT and MDAT. The latter two groups had deficits in the monoaminergic neurotransmitter systems, seen as reduced CSF homovanillic acid (HVA) and the hydroxylation cofactor, biopterin. MDAT patients also had reduced CSF 5-hydroxyindoleacetic acid (5-HIAA). Compared to age-matched control subjects, early-onset DAT patients have reductions in CSF AChE activity, and late-onset DAT patients have reductions in CSF alpha-melanocyte stimulating hormone-like immunoreactivity (alpha-MSH-LI).

An inverse relation between CSF HVA and alpha-MSH-LI was found in DAT patients. Furthermore, in patients with Parkinson's disease, CSF alpha-MSH-LI was elevated. Young adult Down syndrome subjects had elevated levels of CSF choline, but AChE activity and somatostatin and neuropeptide Y concentrations did not differ from control values in either young or old Down patients. In healthy control subjects, age-related increases were found in CSF total protein, choline, the polyols erythritol and myoinositol, and AChE activity.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 AG 00403-04 LN

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Genetics of Alzheimer's Disease

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	Carol Fuchs, MSW	Social Worker	LN, NIA
	Mark Schapiro	Senior Staff Fellow	LN, NIA
	Anand Kumar	Medical Staff Fellow	LN, NIA
Others:	Beverly White	Medical Res. Officer	LCB, NIDDK
	Angela Moore, MSW	Social Worker	LN, NIA
	Katherine K. Sanford	Chief, In Vitro Carcinogenic Section	LCMB, NCI

COOPERATING UNITS *(if any)*
Department of Psychiatry, University of Pittsburgh School of Medicine; LCMB, National Cancer Institute; Dept. of Pathology, Howard University School of Medicine; LCB, National Institute of Diabetes and Digestive and Kidney Diseases

LAB/BRANCH
Laboratory of Neurosciences

SECTION
Brain Aging and Dementia

INSTITUTE AND LOCATION
NIA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.5	.3	.2

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Pedigrees were constructed from the family histories of all patients participating in the dementia program in order to examine the genetic basis of Alzheimer's disease.

Collaborative studies were established to examine the ability of peripheral blood lymphocytes of probands with Down syndrome and familial Alzheimer's disease to repair X-irradiation induced damage during the G2 period of the cell cycle, and for the Down syndrome subjects, to see if the parents' lymphocytes show chromosomal instability.

Efforts continue to evaluate genetic aspects of presenile dementia. Specifically, secondary sex chromosomal variation, alpha-1-antitrypsin (PI) phenotyping, and cytological analysis of variations in the Nucleolus Organizing Regions (NOR) were analyzed.

Hind III digests of southern blots of genomic DNA from 4 sets of identical twins were obtained. Analysis with the polymorphic DNA marker D21S52 showed that all sets of twins were identical.

Blood samples have been collected from patients with dementia of the Alzheimer type. Total cellular DNA will be isolated to test for the presence of retroviral sequences using the polymerase chain reaction method.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 AG 00404-03 LN

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Functional Interactions Among Brain Regions in Aging and Dementia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	B. Horwitz	Senior Staff Fellow	LN, NIA
Others:	T. Soncrant	Senior Staff Fellow	LN, NIA
	C.L. Grady	Psychologist	LN, NIA
	M.B. Schapiro	Medical Staff Fellow	LN, NIA
	J.V. Haxby	Senior Staff Fellow	LN, NIA
	S. Sato	Visiting Fellow	LN, NIA
	S.I. Rapoport	Chief	LN, NIA

COOPERATING UNITS *(if any)*

LAB/BRANCH
Laboratory of Neurosciences

SECTION
Cerebral Physiology and Metabolism

INSTITUTE AND LOCATION
NIA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.75	.75	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

A matrix method was developed to examine functional interactions between brain regions, by correlating regional cerebral metabolic rates for glucose as determined by positron emission tomography in humans. The method was applied to regional metabolic data from 14 young adult patients with Down Syndrome and 24 matched control subjects. Compared with controls, the Down Syndrome group had many correlations within and between the frontal and parietal lobes with lower values, as well as many correlations between the thalamus and cortex with reduced values. These results indicate a disruption of neural systems associated with attention in Down Syndrome.

The matrix method was applied to analyze glucose metabolism in awake Fischer-344 rats. Reduced correlations between left and right hemispheric brain regions were found in rats that had undergone corpus callosotomies, suggesting that interhemispheric interactions are mediated in part by callosal fibers.

A computer simulation model was developed for the purpose of giving a partial validation for correlational analysis as applied to metabolic data. Because the underlying pattern of functional couplings in the model is known, these simulations demonstrate that the correlation coefficient between normalized metabolic rates is proportional to the strength of the functional coupling constant, and that correlational analysis yields information on regional involvement in neural systems not evident in the pattern of absolute metabolic values.

IRP_NN 1-1

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 AG 00405-03 LN

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

New Investigations in Aging and Dementia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	M. Schapiro	Senior Staff Fellow	LN, NIA
	A. Kumar	Medical Staff Fellow	LN, NIA
	C. DeCarli	Senior Staff Fellow	LN, NIA
	W. Kozachuk	Medical Staff Fellow	LN, NIA
	J. Salerno	Senior Staff Fellow	LN, NIA
Others:	M. Folstein	Professor of Psychiatry	J. Hopkins University
	P. Rabins	Assoc. Professor	J. Hopkins University
	R. Friedland	Chief, BADS	LN, NIA

COOPERATING UNITS *(if any)*

Department of Psychiatry, Johns Hopkins University, Baltimore, MD; Laboratory of Central Nervous System Studies, NINCDS; Office of Director, NINCDS; School of Medicine, University of Colorado, Denver, CO; Laboratory of Chemical Biol, NIDDK; Div. of Neurology, Dept. of Medicine, Duke University

LAB/BRANCH

Laboratory of Neurosciences

SECTION

Brain Aging and Dementia

INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.0	2.0	0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

A number of new protocols were introduced to examine brain aging and cerebral metabolism. In using the isotope fluoro-18-deoxyglucose with positron emission tomography, we found that cerebral glucose utilization does not change with advancing age in healthy males, but changes are found in patients with Alzheimer's disease and Down syndrome. Four new protocols allow us to evaluate these findings and determine their specificity. Studies are underway in multi-infarct dementia, the second leading cause of dementia; a major depressive disorder both with and without cognitive impairment; and fragile-X syndrome to evaluate PET alterations uncovered in our laboratory in subjects with Down syndrome. We also are studying healthy adult subjects with hypertension who have no symptomatic cognitive impairment.

Blood has been collected from healthy controls, patients with Alzheimer's disease, and unaffected first degree relatives of patients with Alzheimer's disease. The buffy coat of this blood will be intracerebrally inoculated into hamsters to determine if Alzheimer's disease is transmissible. The role of the dopaminergic system in normal aging, Alzheimer's disease with and without extrapyramidal signs, and familial inverted chorea will be explored with 6-[18-F]-fluoro-L-Dopa (6-FD) and positron emission tomography (PET).

ANNUAL REPORT OF THE LABORATORY OF PERSONALITY AND COGNITION, NATIONAL INSTITUTE ON AGING

Overview

The fundamental scientific paradigm which guides research in the Laboratory of Personality and Cognition (LPC) is the analysis of individual differences. Few phenomena are more basic than the fact that human beings differ--in health, in rates of aging, in cognitive ability, in personality, in happiness and life satisfaction. The mission of the LPC is threefold: (1) to conduct basic and clinical research on individual differences in cognitive and personality processes and traits; (2) to investigate the influence of age on these variables and their reciprocal influence on health, well-being, and adaptation; and (3) to employ longitudinal, experimental, and epidemiological methods in the analysis of psychological and psychosocial issues of aging, including health and illness, predictors of intellectual competence and decline, models of adult personality, and correlates of disease risk factors.

Cognition and Neuropsychology

The retirement this year of Dr. David Arenberg, Chief, Cognition Section, marks the end of an illustrious career at the Gerontology Research Center. In the past 30 years, Dr. Arenberg has set the standard for longitudinal research on cognitive processes, contributing several classic studies that document the nature and rate of decline of fundamental processes of reasoning, learning, and memory. His careful, patient work has established much of what we now know about cognitive change in aging men and women, and his retirement is a loss to the Laboratory and to the field of Gerontology.

However, research on cognition will continue in this Laboratory, with a new emphasis on neuropsychological testing and the detection of early signs of Alzheimer's disease. In collaboration with an FSKMC neurologist and with other GRC investigators, LPC scientists have begun a prospective study of the natural history of dementia in the Baltimore Longitudinal Study of Aging. This study will capitalize on archival data on cognitive performance and personality traits which can be used as long-term predictors of Alzheimer's disease in participants who subsequently develop this disease. A sophisticated battery of neuropsychological tests is presently being administered to BLSA participants over age 70; future enhancements of this project may include collaborative research on brain metabolism and autopsy reports in the same sample.

One major finding has already emerged from this project. In a paper presented at the American Academy of Neurology Meetings in Chicago, Personality, Stress and Coping Section (PSCS) investigators reported that, in the absence of neurological evidence of impairment, memory complaints were not predictive of poorer neurological test performance. Instead, such complaints appeared to be related to psychological distress and neuroticism. This finding, which has received considerable attention, has important implications for research and

clinical practice. For example, it suggests that memory complaints themselves are probably not useful as a screen for early dementia.

The necessity for prospective studies of dementia was underscored by another analysis reported this year by the Cognition Section (CS). Several papers in the literature refer to 27 men in the BLSA as "probable Senile Dementia--Alzheimer's Type." The method used to identify those presumed cases was based on a retrospective review of archival medical records. However, an examination of the cognitive performance data of the 27 men indicated that many were misclassified: The cognitive data were inconsistent with the diagnosis of SDAT. Even with very careful evaluation of historical medical records, the identification of SDAT cases is fraught with difficulty. Prospective studies using state-of-the-art neuropsychological evaluations are essential.

Predictors of Physical and Mental Health

This Laboratory has been in the forefront of research on personality and health, emphasizing the need to employ a conceptual model of personality in assessing its effects. The hypothesis that the personality dimension of Agreeableness vs. Antagonism is relevant to the prediction of coronary disease, especially in younger men, was supported in analyses of the MRFIT data set which will shortly appear in Psychosomatic Medicine. The hypothesis that traits related to Neuroticism, such as depression, are not related to cancer mortality and morbidity was supported in analyses of the NHANES sample, as will be reported in a forthcoming article in JAMA.

By contrast, there is reason to believe that Neuroticism is related to psychiatric morbidity. A prospective study of a nationally representative subsample of the NHANES study suggested that both age and Neuroticism were associated with increased risk for diagnoses of neuroses and non-organic psychoses. Closer examination, however, showed that the apparent association with age was probably artifactual: Higher rates of physical illness in older subjects led to higher rates of hospitalization, and thus of diagnosis; and some diagnoses of psychotic conditions appeared to be effects of acute medical (especially cerebrovascular) conditions. These data show that age does not bring an increased risk for psychiatric conditions. Individuals high in Neuroticism, regardless of age, are at greater risk of receiving a psychiatric diagnosis.

The close link between dimensions of personality and psychopathology was also demonstrated in studies of the personality disorders. In presentations at the meetings of the Society for Personality Assessment and the American Psychological Association, researchers in PSCS showed that the DSM-III-R Axis II Personality Disorders, as assessed by three different instruments, could be organized in terms of the five-factor model of personality. Studies of BLSA participants using both self-reports and observer ratings were supplemented by studies of two other samples, one adult and one student. Although additional research is needed to determine whether the same pattern of findings holds up in clinical samples, results to date present an encouraging picture: Psychiatric conceptions of personality disorder and factor analytic

conceptions of personality structure are not worlds apart; in fact, they share the same five basic dimensions. Such findings lay the groundwork for future research by PSCS investigators on clinical applications of the five-factor model.

Aging, Stress, and Coping

Researchers in PSCS have long been recognized as leaders in the longitudinal analysis of personality. Last year, the Chief, LPC, was invited to present a Master Lecture for the American Psychological Association on "Personality Continuity and the Changes of Adult Life"; this year, Section investigators were asked to write a chapter on personality in adulthood for a new Handbook on Personality Psychology; next year, they will contribute an article on longitudinal studies of personality to a Special Issue of European Journal of Personality. Research in the past year has confirmed earlier studies which suggested that there is continued change in personality dispositions until around age 30; thereafter, stability is the rule. Documentation of stability in late life for healthy adults lays the groundwork for studies suggesting personality changes associated with disease processes. Indeed, changes in personality may be among the earliest markers of dementia.

PSCS researchers have also contributed to advances in our understanding of the stress and coping process. The first long-term longitudinal study of age changes in the use of coping mechanisms was recently completed. It showed that while there are generational differences in the use of some coping mechanisms, there do not appear to be maturational changes in ways of coping. Over a seven-year interval, there is modest to moderate stability in the ways individuals cope. In both these regards, coping variables appear to resemble personality variables, to which they are in fact known to be related. Individuals appear to carry with them throughout adult life relatively constant ways of dealing with stressful events.

But the events themselves also have a major impact on the ways in which individuals cope, as previous research on losses, threats, and challenges showed. In current analyses, PSCS investigators are turning their attention to other features of the stressor, including controllability, chronicity, and severity, which may affect the choice of coping mechanisms. Both person and environment interact in determining the ways in which individuals respond to stress.

Basic Research on Personality Structure

The five-factor model of personality has become the cornerstone of research for the PSCS. A recent chapter reviews the evidence for this model and shows why it is an appropriate, even essential, basis for conceptualizing individual differences. The five factors are stable over time, show agreement between self-reports and raters, and capture the basic dimensions underlying such prominent personality instruments as the Guilford-Zimmerman Temperament Survey, the Eysenck Personality Questionnaire, the Myers-Briggs Type Indicator, and the California Psychological Inventory. In the past year, investigators have refined their conceptions of the factors and broadened

their applications.

The five-factor model originated in studies of natural language trait adjectives culled from the dictionary. Although this has proven to be a fruitful source of hypotheses about personality structure, Section researchers have shown that natural languages are deficient in terms which describe the dimension of Openness to Experience. Many terms reflect Openness to Ideas (e.g., curious, reflective, perceptive), but Openness to Fantasy, Aesthetics, and Feelings are rarely conveyed by single adjectives in English. Personality questionnaires, which utilize full sentences, are thus a better basis for the assessment of personality. These conceptualizations of Openness were presented at an Invited Workshop on Personality Language in Groningen, The Netherlands; they were elaborated in a chapter in the Handbook of Personality Psychology. Here Openness was distinguished from the related constructs of culture and intellect, and data were reviewed which suggested that Openness must be viewed in both structural and motivational terms.

Several years ago, Section researchers proposed that psychological well-being was determined in large part by the two temperamental dimensions of Neuroticism and Extraversion. Extraverts are by nature cheerful and optimistic; Neurotics are gloomy and distress-prone. Studies here and elsewhere have confirmed this temperamental model of well-being. This year, two additional mechanisms were hypothesized which relate the remaining dimensions of personality to well-being. Openness is an experiential dimension, and Open individuals experience both positive and negative emotions more forcefully. Most importantly, Agreeableness and Conscientiousness appear to have instrumental effects on well-being: The interpersonal bonds that Agreeableness fosters and the achievements and accomplishments that Conscientiousness promotes may contribute to greater quality of life and higher life satisfaction. Data from both self-reports and spouse ratings of personality supported these hypotheses. Instrumental mechanisms in well-being are of particular interest because they suggest possible interventions. For example, pets may increase morale because they allow the expression of affection and other forms of Agreeableness; interventions aimed at giving older individuals more control of their environment may be helpful because they allow satisfaction of needs for achievement. The five-factor model can provide a scientific rationale for techniques of increasing well-being.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00062-16 LPC

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Aging Influences on Sustained Attention and Task-Unrelated Images and Thoughts

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	L. M. Giambra, Ph.D.	Senior Investigator	LPC, GRC, NIA
Others:	A. Grodsky, Ph.D.	Psychologist	LPC, GRC, NIA
	E. Rosenberg, B.S.	Psychologist	LPC, GRC, NIA

COOPERATING UNITS *(if any)*

Cognitive Sciences Lab., Catholic University, Washington, D.C. (R. Parasuraman), Psychology Department, University of Cincinnati, Cinn., Ohio (J. Warm).

LAB/BRANCH

Laboratory of Personality and Cognition

SECTION

Cognition Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.40	1.8	0.6

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This work attempts to determine the nature of sustained attention and to determine the parameters of task-unrelated images and thoughts (TUITs) as well as related mental activity such as insight, attention and sustained attention as phenomena, their relationships amongst one another, and their susceptibility to the influence of aging in adulthood. These goals are accomplished through the use of controlled laboratory studies and retrospective questionnaires. This year's findings were that (a) extended practice on a vigilance task, with typical exposure times, is best fit by a hyperbolic functional relationship derived from an accumulation model of learning in which age significantly affects final asymptotic performance but which does not affect learning rate; (b) TUIT likelihood is inversely related to performance on a vigilance task and reflects the capacity demands of the vigilance task.

The study of task-unrelated images and thoughts in adults, along with variables which may moderate their occurrence, e.g., age, intelligence, task structure, etc., may aid us in understanding the fundamental processes which underlie all thinking. Sustained attention as a skill involves both alertness and concentration over long periods of time. This skill plays an important role in both daily living and in the job market place, e.g., jobs requiring inspection. This research provides us with information on how age influences the use and acquisition of that skill as well as how alertness and concentration are susceptible to aging influences.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

PROJECT NUMBER

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00064-28 LPC

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Problem Solving and Aging

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	D. Arenberg	Chief, Cognition Section	LPC, NIA
Others:	L. M. Giambra	Senior Investigator	LPC, NIA

COOPERATING UNITS *(if any)*

LAB/BRANCH
Laboratory of Personality and Cognition

SECTION
Cognition Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.0	.2	.8

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Among the goals of this project are to describe age differences and changes in reasoning performance and to investigate processes underlying such age-related performance. Previous analyses demonstrated cross-sectional age differences in concept problem solving for both men and women in the Baltimore Longitudinal Study of Aging (BLSA). Furthermore, magnitude of individual change over six years was age related; younger men tended to improve both in effectiveness of solutions and in number of problems solved correctly, whereas older men tended to decline. Although a large proportion of both the men and the women in the BLSA are educated, it is possible that some part of the age differences and age changes found in problem solving is attributable to those participants with lower education. When the data were analyzed for only those individuals with a college degree, the results were the same. For all three types of problem, the age correlation cross-sectionally was at least as high for the educated men as for all the men; and the results were the same for the women as well. Furthermore, the men initially in their sixties and seventies with a college degree showed at least as much decline as all the men in those two age groups. Education does not account for the age differences and changes with age in problem solving performance found in the BLSA.

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00065-29 LPC

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Verbal Learning and Age

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	D. Arenberg	Chief, Cognition Section	LPC, NIA
Others:	L. M. Giambra	Senior Investigator	LPC, NIA
	P. Mullin	IRTA Fellow	LPC, NIA

COOPERATING UNITS *(if any)*

Department of Human Development, University of Maryland, College Park

LAB/BRANCH

Laboratory of Personality and Cognition

SECTION

Cognition Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.9	1.5	1.4

CHECK APPROPRIATE BOX(ES)

☑ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Among the goals of this project are to describe adult age differences and changes in memory and learning performance and to investigate processes underlying such age-related performance. Two recent studies of sentence retention in this laboratory demonstrated that amount of information forgotten over 24 hours was the same for young adult and old groups. In addition to comparing amounts of information forgotten, it is of interest to compare rates of forgetting for different age groups. In order to compare forgetting rates when two groups differ in amount of information learned (as is usually the case in age studies), however, it is necessary to determine the forgetting function. Then the parameters of the function can be compared. Hyperbolic functions over time provided the best fit of all four of the forgetting curves for cued recall performance in the two studies of sentence retention. There is a renewed interest in forgetting models among cognitive theorists, and a hyperbolic function is consistent with models of forgetting that include two or more components of performance that decline exponentially and are additive. These data are evidence supporting those models of forgetting that include additive components that decline exponentially.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00066-28 LPC

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Perceptual Retention and Age

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: D. Arenberg Chief, Cognition Section LPC, NIA

COOPERATING UNITS *(if any)*

Department of Human Development, University of Maryland, College Park
Department of Psychology, University of Calgary, Calgary, Alberta, Canada

LAB/BRANCH

Laboratory of Personality and Cognition

SECTION

Cognition Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.6	.3	.3

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

A primary goal of this project is to describe adult age differences and age changes in nonverbal memory performance. Nonverbal memory is measured in the Baltimore Longitudinal Study of Aging with the Benton Visual Retention Test (BVRT), a test of memory for designs involving spatial memory. This year, we analyzed the BVRT data for 277 men who had three measures spanning at least 12 years to address the question of whether cognitive declines are smaller for those who are initially better endowed. Although this question has been addressed in the literature on intelligence and aging, all of those studies share a common methodological problem. It is known that when there are errors of measurement, initial level and measures of change are artifactually negatively related. In the current analyses, initial measures were adjusted for errors of measurement, and maximum likelihood procedures were applied to relate these adjusted scores to individual regression measures of change. We found a small positive correlation between initial level and change for the BVRT in the two groups over age 55 at first test. Men with high error scores initially tended to increase their errors more than men with lower initial scores. When this procedure was applied to the Vocabulary subtest of the Wechsler Adult Intelligence Scale for the same 277 men, the results were quite different. Men with high vocabulary scores tended to decline more than men with lower initial levels. When the methodological bias is avoided, it appears that the answer to the question about the relationship of initial level and change is specific for the kind of cognitive performance measured.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00080-4 LPC

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Age Effects On Automatic and Effortful Information Processing

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: L. M. Giambra, Ph.D. Senior Investigator LPC, GRC, NIA

COOPERATING UNITS *(if any)*

Human Factors Laboratory, School of Psychology, Georgia Institute of Technology

LAB/BRANCH

Laboratory of Personality and Cognition

SECTION

Cognition Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.3	.1	.2

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of this research is to examine the influence of aging upon the development and enactment of automatic and effortful attentional processes. The purpose is accomplished through controlled laboratory studies. Previous research in this laboratory, investigating the development of automatic visual detection in young, middle-aged, and old adults, found old adults unable to attain automatic detection after extensive practice. An additional series of experiments established that the older adults' failure to develop automatic detection was not due to the nature of the items to be detected, insufficient practice, the practice schedule, or response competition. Automatic detection is viewed as the result of a second level of learning, "priority" learning. The future course of this project will be an examination of the extent to which old adults can go beyond the first level of learning, i.e., "associative" learning, to priority learning which establishes a direct and immediate response of the attentional system to the item to be detected.

The significance of this project lies in mapping out and accounting for maturational changes in the development of automatic visual detection which plays such an important part in our daily lives.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 AG 00180-04 LPC

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Stress, Coping and Personality in Aging Men and Women

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Robert R.McCrae	Research Psychologist	LPC, NIA
Others:	Paul T. Costa, Jr.	Chief, LPC	LPC, NIA
	Alan B. Zonderman	Senior Staff Fellow	LPC, NIA

COOPERATING UNITS *(if any)*
Longitudinal Studies Branch

LAB/BRANCH
Laboratory of Personality & Cognition

SECTION
Personality, Stress & Coping

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Md 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.5	1.0	1.5

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

As part of a program of research on adult personality, the stresses faced by aging adults, the methods and strategies used by them to cope, and the effectiveness of their coping efforts, a seven-year longitudinal study of age changes in the use of coping mechanisms was conducted. In 1980, Section investigators conducted two parallel cross-sectional studies of coping. In the first, 255 men and women completed a 118-item Coping Questionnaire (CQ) concerning the ways in which they had dealt with a single event they had previously reported on a checklist of life events. In the second study, 150 men and women completed a shortened version of the CQ for each of the three events. Subjects were participants in the Baltimore Longitudinal Study of Aging and their spouses. In 1987 the full CQ was administered to 398 subjects aged 20 to 93. Of these, 191 had participated in the original study; on data from these subjects, repeated measures analyses and retest correlations were conducted. The remaining 207 subjects were first tested in 1987; their responses were compared with the 1980 data in cross-sequential analyses. The CQ was scored for 28 specific ways of coping and 2 broad coping factors, neurotic coping and mature coping. Repeated measures analyses of the full CQ showed only a few significant changes, and only one of these--a small decline in self-adaptation --was replicated in repeated measures analyses of the short version of the CQ. Cross-sequential and time-sequential analyses showed some changes that were probably due to time of measurement rather than aging. It appears from these analyses that there are few maturational changes in the ways in which individuals cope. Retest correlations for the two subsamples showed that 22 of the specific coping mechanisms had at least modest stability over the seven-year interval. Stability coefficients for the neurotic and mature coping factors, respectively, were $r = .51$ and .38, $N = 113$, $p < .001$, in the first subsample and $r = .55$ and .34, $N = 78$, $p < .01$, in the second subsample. These findings suggest that there are consistent individual differences in coping, attributable either to the enduring effects of personality traits or the retainment of learned ways of coping.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

PROJECT NUMBER

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00182-3 LPC

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Age Effects On Concentration During Information Processing

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	L. M. Giambra, Ph.D.	Senior Investigator	LPC, GRC, NIA
	R. Barr, Ph.D.	Expert	BSRP, NIA
	E. J. Metter, M.D.	Medical Officer	LSB, GRC, NIA

COOPERATING UNITS (if any)

Behavioral Science Research Program, NIA
Longitudinal Studies Branch, IRP, NIA

LAB/BRANCH
Laboratory of Personality and Cognition

SECTION
Cognition Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS.	PROFESSIONAL.	OTHER:
.4	.1	.3

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

A primary purpose of this work is to investigate the relationship between age and concentrative ability. Using laboratory studies of task-unrelated imagery and thought (TUIT) it was determined that old adults had fewer TUITs than young and middle-aged adults. One possible explanation for this result is that age and concentrative ability are directly related. Laboratory investigations are needed to confirm this apparent increased concentrative ability in the older population. An experimental procedure was developed where subjects are asked to repeat messages presented to one ear (shadowing) while ignoring simultaneous messages in the other ear. High concentrative ability is demonstrated by equivalent shadowing performance with and without simultaneous (and different) messages in the other ear. Last year it was reported that after controlling for differences in intelligence, hearing loss, and monaural shadowing performance that age and concentrative ability are inversely related. With increased age there was an increase in dichotic shadowing errors. The decrease in concentrative ability with increased age was especially prominent in old adults who had been hospitalized within the prior two years and were on prescription medication. This year a more precise investigation was begun into the moderating effect of health. Also begun was an investigation in the specific source of the apparent age-related loss of concentration, reduced ability to control attention or to discriminate among inputs.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00183-01 LPC

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Basic Research in Personality

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	P.T. Costa, Ph.D.	Chief, LPC	LPC, GRC, NIA
OTHER:	R.R. McCrae	Research Psychologist	LPC, GRC, NIA
	A.B. Zonderman	Senior Staff Fellow	LPC, GRC, NIA

COOPERATING UNITS *(if any)*

Department of Psychology; Duke University

LAB/BRANCH

Laboratory of Personality and Cognition

SECTION

Personality, Stress & Coping Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.0	1.0	1.0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Personality can be defined in terms of enduring individual differences in emotional, interpersonal, experiential, and motivational styles. The five factors of Neuroticism, Extraversion, Openness to Experience, Agreeableness, and Conscientiousness provide a comprehensive taxonomy of traits for the description of personality in aging men and women. As part of an ongoing series of studies on these basic dimensions of personality, section investigators tested that hypothesis that Openness can be viewed in both structural and motivational terms. Data were analyzed from 348 subjects (BLSA participants and their peers) aged 25 to 89 on the NEO Personality Inventory Openness Scale, Gough's Revised CPI scales of Social Presence, Empathy, Achievement via Independence and Flexibility, and Haan's four coping mechanism scales created from CPI items. The correlations of Openness with the Revised CPI scales ($\bar{r}$ = .40 to .55) suggest that open people are empathic, flexible, creative, and thoughtful, and have high needs for change and intellectual understanding. Openness was positively related to coping scales measuring Intellectuality ($\bar{r}$ = .45), Adaptive Regression ($\bar{r}$ = .34), and Logical Analysis ($\bar{r}$ = .48), and negatively related to Suppression ($\bar{r}$ = -.12, all ps < .05). Open individuals have access to more thoughts, feelings, and impulses in awareness and can maintain many of these simultaneously. For the closed individual, ideas, feelings, and perceptions are relatively isolated and must compete for full attention. For the open individual, all these elements may be simultaneously in awareness, providing a deeper and more intense experience.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00184-01 LPC

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Psychosocial Predictors of Mental & Physical Health

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Paul T. Costa, Jr.	Chief, LPC	LPC, NIA
Others:	Robert R. McCrae	Research Psychologist	LPC, NIA
	Alan B. Zonderman	Senior Staff Fellow	LPC, NIA
	William E. Whitehead	Guest Worker	FSKMC
	Chester A. Schmidt	Special Volunteer	FSKMC

COOPERATING UNITS *(if any)*

Dept. of Psychology, University of Maryland Baltimore County
Dept. of Psychiatry, Duke University Medical Center

LAB/BRANCH

Laboratory of Personality & Cognition

SECTION

Personality, Stress & Coping

INSTITUTE AND LOCATION

NIH, NIA, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.0	1.0	1.0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The National Health and Nutrition Examination Survey I (NHANES) Epidemiologic Follow-up Study was used to examine the incident risks associated with age and trait neuroticism for psychotic and neurotic psychiatric diagnoses. Medical outcome data on 6,410 subjects (93% of the original sample tested between 1971 and 1975) from hospitalization records were transformed into ICD-9 classifications by trained coders. 857 subjects, or 13% of subjects were eliminated from the proportional hazards analyses because of previous history of psychological problems or psychiatric disorders. The relative risks for the incidence of neurotic and psychotic diagnoses controlling for gender and race, for trait neuroticism were 2.3 for the Neurotic Diagnoses (ICD-9 300, 311) and 2.3 for the psychotic diagnoses (ICD-9 295-298). Age (over 50) conferred a 1.6 increased risk for neurotic diagnoses and a 2.4 risk for psychotic diagnoses. Closer examination, however, showed that the apparent association with age was probably artifactual: Higher rates of physical illness in older subjects led to higher rates of hospitalization, and thus of diagnosis; and some diagnoses of psychotic conditions, especially unspecified nonorganic psychoses, appeared to be the effects of acute medical (especially cerebrovascular) conditions. These data show that age does not bring an increased risk for psychiatric conditions. Individuals high in Neuroticism, regardless of age, are at greater risk of receiving a psychiatric diagnosis. Future analyses will investigate alternative psychiatric outcomes (alcohol and substance abuse; organic brain syndromes) and examine additional predictors including depression.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

PROJECT NUMBER

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00185-01 LPC

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Early Markers of Alzheimer's Disease in Longitudinal Participants

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.)* *(Name, title, laboratory, and institute affiliation)*

PI:	A.B. Zonderman	Senior Staff Fellow	LPC, NIA
Others:	D.L. Arenberg	Chief, Cognition	LPC, NIA
	P.T. Costa	Chief, LPC	LPC, NIA
	C.H. Kawas	Staff Neurologist	FSKMC
	R.R. McCrae	Research Psychologist	LPC, NIA
	E.M. Metter	Medical Officer	LSB, NIA

COOPERATING UNITS *(if any)*

Longitudinal Studies Branch, GRC; Department of Neurology, FSKMC

LAB/BRANCH

Laboratory of Personality & Cognition

SECTION

Personality, Stress & Coping Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Md 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
		1.0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Participants in the Baltimore Longitudinal Study of Aging aged 56 and older were examined to detect changes in psychological, neurological, and neurophsychological tests related to early sings of Alzheimer's disease. For an analysis of memory complaints and memory problems, data were available on 173 participants. As part of a neurological examination, subjects were asked whether they had experienced any memory loss, and the neurologist probed for the conviction behind these reports. Of the 151 subjects with no signs of neurological deficits, only the 45 subjects who maintained their conviction about their self-perceived memory loss were assigned to the memory complaint group. The remaining 106 subjects were assigned to the no memory complaint group. With the exception of intrusions in the free recall memory test, there were no significant differences between the memory complaint groups on any of the neuropsychological tests. Despite subjects' convictions about their inability to remember, no objective evidence for differences in memory abilities was found in the neuropsychological test results. No differences were found between subjects making memory complaints and subjects without such complaints on a vocabulary test and memory tests administered 6 years prior and concurrently with the neurological examination. Repeated measures analyses of the four memory tests showed that memory abilities declined over six years at the same rate in both memory complaint groups. Subjects with memory complaints had significantly more neurological and total physical complaints than subjects without memory complaints. Subjects with memory complaints were also significantly more depressed and had significantly greater emotional distress than subjects without memory complaints. These results suggest that subjective memory complaints are poor indicators of memory problems in the absence of objective memory tests. Individuals who are convinced that they are suffering from memory problems may be influenced as much by characteristic personality traits such as neuroticism and inadequacy as by disease processes.

Endocrinology Section

The objective of the research program of the Endocrinology Section, LCP is to study the effects of aging on regulation of endocrine systems, particularly those under the control of the anterior pituitary gland. It has the dual aims of: (a) elucidating the mechanisms by which aging alters hormone secretion and action and; (b) the extent to which hormone changes produce the effects on metabolism and body composition associated with aging.

Our studies in animal models investigate whether previously observed age-related alterations in LH and PRL production result from intrinsic changes in pituitary gonadotropic and lactotropic cells and attempt to clarify the mechanisms of these changes. The *in vitro* secretion of luteinizing hormone (LH) and prolactin (PRL) by isolated cells and tissues from anterior pituitary glands of old vs. mature male and female rats has been studied in both static monolayer and dynamic perifusion culture systems. We have found that age-related alterations in basal and modulated hormone secretion by pituitary cells from old rats result (in part) from multiple changes in intrinsic pituitary gonadotropic and lactotropic cell functions. These appear to include:

1. Decreased GnRH- and dopamine-mediated membrane signal transduction.
2. Decreased transcription of LH-b, and presumably a-subunit, genes.
3. Altered post-transcriptional regulation of PRL secretion

Additional studies have examined the interaction of age and moderate caloric reduction on thyroid and testes function in male Rhesus an Squirrel monkeys. After 15 months of observation, there were age-related alterations in hormone function in both species, which were independent of diet.

Normal aging in man is associated with various alterations in hormone secretory physiology and in body composition. However, the interactions among aging, changes in bone, muscle, and fat, and hormonal alterations remain to be clarified. In particular, aging is associated with: (a) decreases in the anabolic hormones, growth hormone (GH) and its "second messenger", somatomedin-C (Sm-C); (b) increases in the catabolic hormone, cortisol; and (c) in women, deficiency of ovarian estrogen, a hormone with important beneficial effects on bone and and other metabolic functions.

We have completed the clinical phase of a study of the interaction of age and transdermal estradiol replacement at 3 different doses in 28 postmenopausal women, investigating effects of estrogen with and without progestogen on basal growth hormone (GH), GH responses to GHRH, and calciotropic hormone regulation. Preliminary analysis of data from the first 15 women studied shows that: (a) Older women remain responsive to the bone-conserving influence of estrogen; and (b) Estrogen's action to preserve bone mass is independent of any modulation of GH secretion. Studies of the interrelationship of sex hormones, glucose metabolism, and body fat distribution have revealed that age and body compostion variables (WHR, BMI), but not sex hormone levels or phase of the menstrual cycle, were independent determinants of glucose response to oral GTT. A new study to quantitate the effects of aging on the regulation of the hypothalamic-pituitary-adrenal axis has been initiated. This study, to be conducted in 12 young and 12 older men, requires overnight monitoring of adrenal function with every 10-minute blood samples followed by CRH stimulation tests, The protocol is carried out under basal conditions and during ACTH suppression with each of 3 doses of dexamethasone. Four subjects have completed the protocol to date.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00013-14 LCP

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Hormones, Hormone Receptors, and Aging. III. Aging and Human Endocrine Regulation

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*
S. M. Harman, M.D., Senior Investigator, LCP, NIA
Other:
Marc R. Blackman, M.D. Guest Scientist, LCP, NIA
Michele Bellantoni, M.D., Medical Staff Fellow LCP, NIA
Claire Waltman, M.D., Medical Staff Fellow LCP, NIA
Reubin Andres, M.D., Chief, LCP
Janis Busby, M.D., Asst. Prof., Medicine, Johns Hopkins University

COOPERATING UNITS *(if any)*
Depts. of Medicine, Francis Scott Key Med. Center and J.H.U. Medical School

LAB/BRANCH
Gerontology Research Center, Laboratory of Clinical Physiology

SECTION
Metabolism Section, LCP

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.0	3.0	

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Summary of Work

Continuation of this project in FY-89 has included completion of the clinical phase of a study of the interaction of age and transdermal estradiol replacement at 3 different doses in 28 postmenopausal women, investigating effects of estrogen with and without progestogen on basal growth hormone (GH), GH responses to GHRH, and calciotropic and reproductive hormone regulation. Preliminary analysis of data from the first 15 women studied shows that: (1) Older women remain responsive to the bone-conserving action of estrogen; and (2)Estrogens' action to preserve bone mass is independent of any modulation of GH secretion. Studies of the interrelationship of age, sex hormones, glucose metabolism, and body fat distribution in healthy women have revealed glucose homeostasis to be influenced by age, body mass and fat distribution, but not by sex hormones. A new study to quantitate the effects of aging on the regulation of the hypothalamic-pituitary-adrenal axis has been initiated. This study, to be conducted in 12 young and 12 older men, requires overnight monitoring of pituitary-adrenal function with every 10-minute blood samples followed by CRH stimulation test, The protocol is carried out under basal conditions and during ACTH suppression with each of 3 doses of dexamethasone. Four subjects have completed the protocol to date.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

ZO1 AG 00023-13 LCP

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Hormones and Aging. Hypothalamic-Pituitary Function in Experimental Animals

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory and institute affiliation)*

S. M. Harman, M.D., Ph.D., Senior Investigator, LCP, NIA

Other:

M. R. Blackman, M.D. Guest Scientist, LCP, NIA

Robin Roberson, B.S., Chemist, LCP, NIA

George S. Roth, Ph.D., Section Chief, MPGS, LCMB, NIA

Donald K. Ingram, Ph.D.Senior Investigator, MPGS, LCMB, NIA

Mary Ann Kowatch, B.S., Chemist, MPGS, LCMB, NIA

K. Kochman, Ph.D., Visiting Scientist MPGS, LCMB, NIA

David Danner, M.D., Ph.D. Section Chief LMG, NIA

T. Maki, Ph.D. Visiting Scientist MPGS, LCMB, NIA

David Stewart, M.S. LMG, NIA

COOPERATING UNITS *(if any)*

Dept. of Medicine, F.S.K. Med. Center and J.H.U. Medical School

Molecular Physiology and Genetics Section, LCMB, GRC

Laboratory of Molecular Genetics, GRC

LAB/BRANCH

Gerontology Research Center, Laboratory of Clinical Physiology

SECTION

Endocrinology Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.0	1.0	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Summary:

The *in vitro* secretion of luteinizing hormone (LH) and prolactin (PRL) by isolated cells and tissues from anterior pituitary glands of old vs. mature male and female rats has been studied in both static monolayer and dynamic perifusion culture systems. We found that age-related alterations in basal and modulated hormone secretion by pituitary cells from old rats result in part from multiple changes in intrinsic pituitary gonadotropic and lactotropic cell functions. These appear to include:

1. Decreased GnRH- and dopamine-mediated membrane signal transduction.
2. Decreased transcription of LH-b, and presumably a-subunit, genes.
3. Altered post-transcriptional regulation of PRL secretion

In addition, we have studied the interactive effects of age and prolonged moderate (30%) caloric reduction on testis and thyroid function in male Old World (Rhesus) and New World (Squirrel) monkeys. After 15 months of observation, there were dissimilar age-related alterations in plasma levels of testosterone, T_4 and T_3 in Rhesus versus Squirrel monkeys, but no apparent effect of caloric reduction on these hormone levels in either species.

Applied Physiology Section

The Applied Physiology Section is concerned with studying the relationship of levels, and rates of changes in levels, of performance of physiologic and non physiologic variables in health and disease. The two major areas are the study of bone, both osteoporosis and osteoarthritis. Other areas of interest in the section include ongoing studies on glucose physiology, dermatoglyphics (genetics) and Amyotrophic Lateral Sclerosis/Parkinsonism-Dementia.

In the area of osteoporosis a new effort has been started that investigates the biochemical and hormonal contributions to bone mineral homeostasis in normal men and women across the age span. This study has demonstrated that normal aged men and women have an adequate level of Vitamin D metabolites and that a fall in 25 (OH)D is not a normal or necessary concomitant of aging. This result is in contrast to a second study in sunlight-deprived elderly patients in a nursing home or under home care. As many as 50% of these elderly patients have 25 (OH)D levels below the accepted limit of normality and represent a treatable age related deficiency. While women have greater bone loss than men across the age span, the serum levels of the D vitamins, parathyroid hormone, ionized calcium, and creatinine clearance were not significantly different between the normal men and women. Only serum phosphorus, which declined markedly in men and remained constant in women showed a sex difference.

The measurement of bone density and bone content was examined cross-culturally in the men and women of the BLSA, and in a well characterized rural population in Yugoslavia. The percent cortical area of these two populations followed the same pattern of bone loss across the age span despite their markedly different life styles.

The effort in osteoarthritis has resulted in the development of new scales of grading radiographic osteoarthritis of the hand that have been proven reliable in both cross-sectional and longitudinal studies. These new scales were used to investigate the natural history of osteoarthritis in a 20 year longitudinal study of men from the BLSA. Both joint narrowing and a small osteophyte were predictive of progression of the disease which was shown to be age related and at the same time to demonstrate a slowing down of progression at the later stages, a phenomenon consistent with burn out of the disease.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00021-26 LCP

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Study of Normal Human Variability and Cross Cultural Aging

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Principal Investigators:

C.C. Plato, Ph.D. Sr. Research Geneticist, LCP NIA

J.D. Tobin, M.D. Chief, Applied Physiology, LCP NIA

Other Investigators:

J. White Biologist, LMG NIA

COOPERATING UNITS *(if any)*

CNS NINDS; CPSB NCI; University of Maryland; University of Zagreb, Yugoslavia.

LAB/BRANCH

Gerontology Research Center, Laboratory of Clinical Physiology

SECTION

Applied Physiology Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.25	.20	.05

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project represents an ongoing collaborative effort, involving WHO and other national and international laboratories to coordinate the collection , evaluation and interpretation of normal genetic markers in order to study the cross-cultural patterns of genetic and extraneous factors as they relate to normative aging and to diseases with late onset, including Alzheimer's disease, breast cancer, Amyotrophic Lateral Sclerosis, and Parkinsonism Dementia. Specifically, the objectives of this study are: A) To study the cross cultural patterns of genetic and non-genetic factors in an effort to better understand the process of normative aging. B) To study the genetic segregation of these markers in families with late onset diseases, such as Alzheimer's disease, breast cancer, ALS and others, in an effort to establish genetic linkages and eventual identification of the factors responsible for these diseases. C) To study the distribution of DNA minisatellites, dermatoglyphics, lateral dominance and other genetic variables in BLSA participants and other control samples, as well as in patients with late onset diseases.

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00022-13 LCP

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Bone Loss with Age: Epidemiological, Familial and Cross-Cultural Considerations

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Principal Investigators:

C.C. Plato, Ph.D. Sr. Research Geneticist, LCP NIA
J.D. Tobin, M.D. Chief, Applied Physiology Section, LCP NIA

Other Investigators:
T.A. Roy, M.A. Biologist, LCP NIA
S.S. Sherman, Ph.D. IRTA Fellow, LCP NIA

COOPERATING UNITS *(if any)*

University Zagreb, Yugoslavia; Nihon University, Tokyo; University of Maryland; Francis Scott Key Medical Ctr.; Johns Hopkins University; CNS, NINDS

LAB/BRANCH

Gerontology Research Center, Laboratory of Clinical Physiology

SECTION

Applied Physiology Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL.	OTHER:
2.10	1.00	1.10

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

At some time during the fourth decade of life, the human skeleton begins to lose bone. That is, bone mass decreases in relation to bone volume. Menopause and the associated estrogen deficiency will enhance bone loss in females. It has also been suspected that bone loss is familial, mainly because of the increased prevalence of osteoporosis in relatives, although there are no satisfactory scientific data to support either a familial or a genetic control of bone loss. In long bones, cortical bone is resorbed from the endosteal surface. Because of the thinning of the cortical bone shell, bones lose their mechanical integrity and fracture more readily. The trabecular bone mass of the vertebral column also decreases with age. The vertebral plates decrease in density, lose resistance to vertical compression stress and become more vulnerable to vertebral collapse. Vertebral compression fractures and fractures of the femoral neck are the most serious consequences of bone loss.

This project deals with the epidemiological, genetic, cross-sectional, longitudinal, and biomechanical aspects of bone loss (1) among the participants of the Baltimore Longitudinal Study of Aging (BLSA), (2) in genetic isolates of the Croatian Islands of Yugoslavia and the island of Guam in Micronesia, (3) senior athlete population, (4) in long distance runners and relatively inactive normal controls, and, (5) in rats and other animals.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00028-13 LCP

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Epidemiological and Genetics Studies of ALS/PD Complex of Guam

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Principal Investigators:

C.C. Plato, Ph.D. Sr. Research Geneticist, LCP NIA
J.D. Tobin, M.D. Chief, Applied Physiology Section, LCP NIA
Other Investigators:
R.C. Elston Louisiana State University
J. Bailey-Wilson Louisiana State University

COOPERATING UNITS *(if any)*

D.C. Gajdusek, Chief, CNS NINDS
R.M. Garruto, Sr. Staff Associate, CNS NINDS
R.T. Yanagihara, Research Associate, CNS NINDS

LAB/BRANCH

Gerontology Research Center, Laboratory of Clinical Physiology

SECTION

Applied Physiology Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.15	.10	0.05

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project represents further efforts to elucidate the etiology of high incidence of Amyotrophic Lateral Sclerosis (ALS) and Parkinsonism Dementia (PD) on the island of Guam. A patient-control prospective study (Registry) was established in 1958. The initial analysis of the Registry data published in 1967 and the follow-up analysis published in 1986 showed that these diseases as found on Guam are highly familial. That is, relatives of patients have a higher risk for developing the disease than those of controls. The next question to be answered is whether this familial occurrence is due to genetic or environmental factors. The specific objectives of this study are:

A) To ascertain the extent of genetic involvement in the high incidence of Amyotrophic Lateral Sclerosis and Parkinsonism Dementia through: (1) segregation analysis of the pedigrees of all patients diagnosed since 1958 and, (2) through segregation analysis of sibships where both parents, one parent or neither of the parents (controls) are affected with ALS and PD.

B) To study the distribution of various established genetic and anthropological markers among the normal Guamanian populations and compare them with those of the ALS and PD patients.

C) To ascertain the effects of immobilization due to paralysis on bone density.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00290-04 LCP

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Osteoarthritis and Aging

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Principal Investigators:

J.D. Tobin, M.D. — Chief, Applied Physiology Section, LCP NIA

D.A. Kallman, M.D. — IRTA Fellow, LCP NIA

Others:

C.C. Plato, Ph.D. — Senior Research Geneticist, LCP NIA

COOPERATING UNITS *(if any)*

Francis Scott Key Medical Center; Johns Hopkins Hospital; Laboratory of Personality & Cognition, NIA

LAB/BRANCH

Gerontology Research Center, Laboratory of Clinical Physiology

SECTION

Applied Physiology Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.05	0.95	0.10

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Osteoarthritis (OA) is the most common rheumatic disease of the elderly, with 40 million Americans estimated to have radiological evidence of OA. A controversy exists regarding the accuracy of the established radiographic OA grading scale (Kellgren, Lawrence 1957) because it assumes a natural history of osteoarthritis which has never been validated by longitudinal studies. The most notable shortcoming of the Kellgren/Lawrence scale is that the OA status of many joints doesn't fit easily into the grading system. In this project we developed grading scales for the individual radiographic features of hand osteoarthritis (osteophytes, joint space narrowing, subchondral sclerosis, lateral deformity, and cortical collapse). We use the new scales to individually examine each of the radiographic features of hand osteoarthritis, in a prospective study of normally aging men. This methodology allows us to establish both the initial findings and the progression -- in short, the natural history of hand OA. This has demonstrated that: a) The incidence of hand OA increases with age -- men who have escaped developing OA into their later years of life are still at an increased risk. b) Hand OA progresses faster in older subjects. c) Joint space narrowing is a common early finding of hand osteoarthritis. Lone osteophytes, even very small ones, are also an early predictor of the later development of OA.

A project which utilized magnetic resonance imaging was designed to establish whether MRI can visualize joint abnormalities in subjects with knee pain and normal radiographs, however our MRI was unable to distinguish early changes in OA.

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00291-04 LCP

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Physiology of Aging

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Principal Investigator:
J.D. Tobin — Chief, Applied Physiology Section, LCP NIA
Other Investigators:
D. Kallman — IRTA Fellow, Applied Physiology Section, LCP NIA
S. S. Sherman — IRTA Fellow, Applied Physiology Section, LCP NIA
C.C. Plato — Geneticist, Applied Physiology Section, LCP NIA

COOPERATING UNITS *(if any)*

J. Fleg — Laboratory of Cardiovascular Sciences, NIA

LAB/BRANCH
Gerontology Research Center, Laboratory of Clinical Physiology

SECTION
Applied Physiology Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.90	0.65	0.25

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Studies on age changes in physiologic systems have related performance in exercise (peak VO2), and kidney function (creatinine clearance) to parameters of bone mineral homeostasis (ionized calcium, phosphorous, vitamin D metabolites, and PTH) and to measures of bone mineral density (BMD) (single and dual photon absorptiometry). There were no independent effects of level of performance on exercise testing on either the biochemical parameters or on the level of BMD in the hip, spine or forearm, beyond that due to age. This was demonstrated by multiple regression analysis and by comparing mean values for the parameters and BMD in two parts of the normal population, the third of the population that had the best age-adjusted performance on peak VO2 and the third of the population with the worst age-adjusted performance. Similar analyses for performance on kidney function showed the same results. Any biochemical or BMD variable related to creatinine clearance was also related to age. The effect of kidney function was not demonstrable once the age effect was taken into account.

Cross-sectional and longitudinal analyses agree that grip strength declines at an accelerating rate after age 40. With advancing age, grip strength deteriorates more than is predicted by the age-related decline in muscle mass.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00293-01 LCP

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Biochemical Parameters of Bone Metabolism: Age and Sex Contrasts

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Principal Investigators:

J.D. Tobin M.D. Chief, Applied Physiology Section, LCP NIA
S.S. Sherman Ph.D. IRTA Fellow, LCP NIA

Other Investigators:
C.C. Plato Ph.D. Sr. Research Geneticist, LCP NIA
M.Gloth, MD Guest Researcher, JHU

COOPERATING UNITS *(if any)*

Francis Scott Key Medical Ctr.; Johns Hopkins University

LAB/BRANCH

Gerontology Research Center, Laboratory of Clinical Physiology

SECTION

Applied Physiology Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.90	0.85	1.05

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Age-related alterations within the vitamin D endocrine system have been implicated in the pathogenesis of bone loss and osteoporosis. Compromises in vitamin D status and/or metabolism of vitamin D to the hormonal form, 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) are thought to be responsible for a decline in calcium absorption which in turn leads to compensatory hypersecretion of parathyroid hormone (PTH) and enhanced osteolysis in order to maintain normocalcemia. It has been hypothesized that compromised vitamin D status and/or circulating levels of the active, hormonal form of the vitamin are a concomitant of aging and are responsible for part of the bone loss seen in the elderly. To test this hypothesis normal men and women from the BLSA and elderly patients who have not been exposed to sunlight for 6 months have been studied.

There were no differences across the age span in 25-OHD or $1,25(OH)_2D$ levels in men or women. Both men and women had an age associated increase in PTH levels that was not independently correlated with creatinine clearance. While women had no change with age in ionized calcium or phosphorus levels men had a slight (4%) decline in ionized calcium and a marked (25%) decline in phosphorus. In both sexes there was a seasonal variation in vitamin D and in females a variation in $1,25(OH)_2D$.

The sunlight deprived patients had significantly lower vitamin D levels than controls, and 43 % had levels <15 ng/ml with 30% <10. None of the control population were <10.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 AG 00208-5 LCP

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Obesity, Physical Inactivity, and Functional Capacity in Obese Older Men

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.)* *(Name, title, laboratory, and institute affiliation)*

Principal Investigators:

Reubin Andres	Chief, Metabolism Section, LCP, NIA

Other Investigators:

Richard Pratley	Medical Staff Fellow, LCP, NIA
Leslie Katzel	Medical Staff Fellow, LCP, NIA
Howard Baldwin	Chemist, Metabolism Section, LCP, NIA
Mary E. Bannon	Biologist, Metabolism Section, LCP, NIA
Denis Muller	Chemist, Metabolism Section, LCP, NIA

COOPERATING UNITS *(if any)*
Francis Scott Key Medical Center, The Johns Hopkins, A.P. Goldberg, P.Coon, M.J. Busby, E. Rogus, J. Hagberg, E. Bleecker, L. Lakatta, M. Lumpkin, B. Wingrad, J. Oriani, B. Crawley, J. Lee, E. Cottrell, T. Toter

LAB/BRANCH
Gerontology Research Center, Laboratory of Clinical Physiology

SECTION
Metabolism Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS: 1.1	PROFESSIONAL: 0.4	OTHER: 0.7

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Obesity, physical inactivity and aging are associated with declines in glucose, lipid and adipose tissue metabolism and altered sympathoadrenal responses. To distinguish the age-related declines in cardiovascular and endocrine-metabolic function from those due to obesity and physical inactivity, healthy obese sedentary men, aged 45-80 yrs old were evaluated at entry into the study and after interventions of weight loss (WL) or exercise training (ET). Metabolic evaluations included glucose tolerance, insulin secretion and sensitivity by euglycemic clamps, lipoprotein lipid profiles, HDL_2 cholesterol and sympathoadrenal responses to upright posture. Norepinephrine responses to upright posture decreased to a greater degree with ET than WL and were associated with reductions in systolic and diastolic blood pressure as well as heart rate. Furthermore, HDl-C levels rose and plasma triglyceride levels decreased and insulin sensitivity rose to a greater extent with WL than ET. Thus, interventions of exercise training and weight loss have the potential to reduce metabolism risk factors for coronary artery disease (CAD) and blood pressure in obese older men. This suggests that changes in lifestyle even at older ages have the potential to reduce risk for morbidity and mortality from CAD. This has implications with regard to improving the cardiovascular status of older individuals and reducing the risk of chronic morbidity and mortality from chronic cardiovascular complications. Studies in this project are supported by collaborative investigations with scientists in the Laboratory of Clinical Physiology, Metabolism Section, GRC, NIA with investigators at Johns Hopkins University and Francis Scott Key Medical Center funded by The Johns Hopkins Academic Teaching Nursing Home Award from the NIA.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00209-5 LCP

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Aging and Insulin Resistance

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Principal Investigators:

Reubin Andres	Chief, Metabolism Section, LCP, NIA
Other Investigators:	
Richard Pratley	Medical Staff Fellow, LCP, NIA
Denis Muller	Chemist, Metabolism Section, LCP, NIA
Mary E. Bannon	Biologist, Metabolism Section, LCP, NIA
Howard Baldwin	Chemist, Metabolism Section, LCP, NIA
Faye Barrack	Lab Tech, Metabolism Section, LCP, NIA

COOPERATING UNITS *(if any)*

Francis Scott Key Medical Center, The Johns Hopkins University, Patricia Coon Andrew Goldberg, Ellen Rogus, Loretta Lakatta, Helene Pokrawka, Joan Lee

LAB/BRANCH

Gerontology Research Center, Laboratory of Clinical Physiology

SECTION

Metabolism Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.7	0.7	1.0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This research was designed to clarify the roles of obesity and physical inactivity in the pathogenesis of the deterioration in insulin sensitivity and reductions in HDL-C and glucose tolerance which occur in obese older men. Oral glucose tolerance tests (OGTT) and hyperinsulinemic euglycemic clamps at 100 $mU/m^2 \cdot min$ insulin infusion rates were performed and lipoprotein lipids measured in 36 healthy older 45-75 yr old and 13 younger (19-36 yr) men with wide ranges of obesity (% body fat: 5-39%), body fat distribution (WHR: 0.79-1.07) and maximal aerobic capacity (VO_2max: 15-58 ml/kg·min). To control for obesity and steady state plasma insulin levels during clamps (I), glucose metabolized (M) was normalized for both fat free mass (FFM) and I [mg/kg FFM·min·$(uU/ml)^{-1}$] and designated M/I. Insulin sensitivity declined with age, and correlated negatively with % body fat and WHR and positively with VO_2max; in multiple regression analyses, the only significant independent predictor of insulin sensitivity was VO_2max. In older and younger men matched for VO_2max, WHR, or % body fat, there were no significant differences in M/I. In contrast, M/I was significantly lower in the older men with either a lower VO_2max, higher WHR, or greater % body fat. Plasma HDL-C levels correlated negatively with % body fat and directly with insulin sensitivity; in multiple regression analyses insulin sensitivity and % body fat were the only independent predictors of HDL-C levels. Weight loss (WL) and exercise training (ET) reversed the decline in insulin sensitivity and low HDL-C levels in obese older men; WL in 6 and ET in 4 men improved M/I and HDL-C levels. Thus, the declines in insulin sensitivity, glucose tolerance and HDL-C which occur in obese older men seem modifiable by interventions which increase physical fitness and reduce body weight. This research is collaborative effort of scientists in the Metabolism Section, LCP, NIA and the Division of Geriatric Medicine, Department of Medicine, Johns Hopkins University at Francis Scott Key Medical Center.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 AG 00211-01 LCP

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Adipose Tissue Metabolism and Lipoprotein Lipids in Obese Older Men

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Principal Investigators:

Reubin Andres	Chief, Metabolism Section, LCP, NIA
Other Investigators:	
Richard Pratley	Medical Staff Fellow, LCP, NIA
Leslie I. Katzel	Medical Staff Fellow, LCP, NIA
Mary E. Bannon	Biologist, Metabolism Section, LCP, NIA
Howard Baldwin	Chemist, Metabolism Section, LCP, NIA

COOPERATING UNITS *(if any)*

Francis Scott Key Medical Center, The Johns Hopkins University, Andrew Goldberg Patricia Coon, Ellen Rogus, Jan Busby, Joan Lee, Marilyn Lumpkin, Helen Pokrywka

LAB/BRANCH

Gerontology Research Center, Laboratory of Clinical Physiology

SECTION

Metabolism Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.0	0.7	0.3

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

During aging, there is an increase in body fat, especially in upper body sites, and maximal aerobic capacity (VO_2max) declines; these changes cause glucose tolerance, insulin sensitivity and lipoprotein lipid profiles to deteriorate. This study examines the mechanisms responsible for upper body distribution of fat and its relationship to lipoprotein lipid profiles and insulin sensitivity in obese older men. Metabolic testing revealed hyperinsulinemia with normal glucose tolerance, and reduced glucose disposal rates (euglycemic clamp), indicative of an insulin resistant state. HDL-C levels were also low. Adipose tissue biopsies at abdominal and gluteal sites demonstrated fasting adipose tissue lipoprotein lipase (LPL) activity correlated directly with % body fat and inversely with insulin sensitivity. LPL activity increased in abdominal fat during euglycemic clamps but did not change in buttock fat. Basal lipolysis correlated negatively with VO_2max in abdominal and directly with % body fat in buttock fat. There were significant declines in WHR, adipose tissue LPL activity, fat cell size and basal lipolysis in abdominal fat, no change in buttock fat metabolism and increases in HDL-C levels and insulin sensitivity with weight loss (WL). In men with an upper body fat distribution, there was less of an increase in beta stimulated lipolysis in abdominal fat after WL than in gluteal fat; similar results occurred in men with a lower body fat distribution. Thus there are regional differences in adipose tissue responses to beta agonists which appear specific to fat distributed in upper or lower body sites suggesting that selective differences in mobilization of triglyceride from adipose depots may be one mechanism by which body fat is deposited preferentially in a body site with age and increasing obesity. This is important since upper body fat distribution increases morbidity and mortality from cardiovascular events.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 AG 00212-01 LCP

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

HDL-Metabolism in Older Men with Silent Myocardial Ischemia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Principal Investigators:
Reubin Andres — Chief, Metabolism Section, LCP, NIA
Other Investigators:
Leslie Katzel — Medical Staff Fellow, LCP, NIA

COOPERATING UNITS *(if any)*

LCS, NIA, J. Fleg, E. Lakatta; Francis Scott Key Medical Center, The Johns Hopkins, A.P. Goldberg, P.Coon, M.J. Busby, S. Gottlieb, G. Gerstenblith; Lawrence T. Donner Labs, R. Krauss, Squibb Pharm, R. Gregg; NHLBI, B. Brewer

LAB/BRANCH

Gerontology Research Center, Laboratory of Clinical Physiology

SECTION

Metabolism Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.0	0.6	0.4

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Older men screened for the presence of cardiovascular and metabolic disease prior to entry into exercise training and/or weight loss intervention were found to have a 25% incidence of silent myocardial ischemia (SI). A reduction in HDL-C and HDL_2 subspecies was found, independent of the % body fat or VO_2max of the subjects. An equivalent percentage of athletes and obese sedentary individuals were found to have SI, and the metabolic abnormalities in both groups were comparable except for a greater reduction in HDL-C in the obese sedentary individuals. Plasma HDL-C and the HDL_2 subspecies were low in the individuals with SI. Gradient gel electrophoresis revealed an increase in the HDL_{3a} and 3c subspecies and reciprocal declines in the HDL2b subspecies which correlated inversely with hepatic lipase activity. Individuals with low HDL_2-C levels had high hepatic activity, independent of body composition or VO_2max. Individuals with SI consistently had higher hepatic lipase and lower HDL_2 subspecies levels than their nonischemic controls. An ApoE 4,3 phenotype was more prevalent in the individuals with SI than in the normal controls. Whether or not the ApoE 4,3 phenotype represents a genetic form of dyslipoproteinemia is unclear, and family studies are planned to test this possibility. In addition, the individuals with SI tended to have a higher WHR than the nonischemic controls, suggesting that the regional distribution of body fat may be an important determinant of risk for silent myocardial ischemia and low HDL-C. Studies are in progress to examine the relationship of a high waist to hip ratio to HDL-C, hepatic lipase activity and plasma lipoprotein lipid levels. Sex hormone binding globulin levels will be measured and related to levels of insulin sensitivity, VO_2max, and WHR in these subjects. These studies represent collaborative efforts of scientists in the Metabolism Section, LCP, GRC, NIA and members of the Geriatrics Division, Johns Hopkins University at the Francis Scott Key Medical Center.

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

PROJECT NUMBER

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01-AG-00093-17-LCP

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Cellular Basis of Regulation of the Humoral Immune Response

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	A. A. Nordin	Research Chemist	LCP, NIA
Others:	J. J. Proust	NIH Special Volunteer	LCP, NIA
	M. A. Buchholz	Biologist	LCP, NIA
	F. J. Chrest	Biologist	LCP, NIA

COOPERATING UNITS *(If any)*

C. Filburn, LBC, NIA, D. Kittur, Dept. Surgery, Johns Hopkins University, J. Shaper, Oncology, Johns Hopkins University, Baltimore, MD.

LAB/BRANCH
Gerontology Research Center, Laboratory of Clinical Physiology

SECTION
Clinical Immunology Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.2	2	1.2

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The presence of IL-2 during the induction of high affinity IL-2 receptors determines if the receptors will acquire the capacity to transmit a proliferative signal. High affinity receptors expressed in the absence of IL-2 early in the induction phase are unable to transmit a proliferative signal unless exceptionally high concentrations of rIL-2 are used. Low levels of extracellular or intracellular IL-2 suffice to establish functional high affinity IL-2 receptors. These studies suggest that IL-2 regulates a restriction point early in the G_1 phase of the cell cycle that determines the functionality of the IL-2 receptor.

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

PROJECT NUMBER

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01-AG-00095-16-LCP

PERIOD COVERED
October 1, 1988 - September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
The Role of Cell Membrane Structures on Cellular Recognition

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	W. H. Adler	Medical Officer, PHS	LCP, NIA	
Others:	+J. E. Nagel	Medical Officer, PHS	LCP, NIA	
	R. K. Chopra	Visiting Associate	LCP, NIA	June 89
	W. O. Boto	NRC Fellow	LCP, NIA	left 3/89
	S. D. Kittur	Medical Staff Fellow	LCP, NIA	
	J. J. K. Hoh	Medical Staff Fellfow	LCP, NIA	left 7/89
	D. C. Powers	Medical Staff Fellow	LCP, NIA	

COOPERATING UNITS *(if any)*

Drs. R. Winchurch, D. Kittur and S. Xu - Dept. of Surgery, FSK Medical Center, Johns Hopkins University, Baltimore, MD.

LAB/BRANCH
Gerontology Research Center, Laboratory of Clinical Physiology

SECTION
Clinical Immunology Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.45	2.45	1

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Activation of cells proceeds through signals generated by phosphorylation of certain cellular proteins. Inhibition of the phosphorylation disrupts activation through specific signals. The ability to generate T lymphocytes is an age related function which can be seen to decline in the third decade of life. Vaccine development must take these changes into account in order to provide an effective level of protection for the elderly individual. The transcription of the neurofibrillar L and M genes is decreased in brain tissue from Alzheimer's Disease patients. However, Lamenin in the CSF increases with age. The action of neuroactive lymphocytes and interleukins may modulate neuronal protein synthesis and induce pathology. Certain lymphocyte factors such as IL-6 and IL-2R are excellent markers for the presence of infection and/or inflammation. In an immune rejection of a graft, the foreign tissue cells provide activation signals to the host lymphocytes. Recognition of tissue proceeds through alternations of the expression of membrane markers by the tissue in response to an immune reaction.

Others:	+F. J. Chrest	Biologist	LCP, NIA
	R. S. Pyle	Bio. Lab Tech.	LCP, NIA
	B. A. Dorsey	Bio. Lab Tech.	LCP, NIA
	G. D. Collins	Biologist	LCP, NIA

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

PROJECT NUMBER

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01-AG-00096-16-LCP

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Lymphocyte Activation and Function in Aging Individuals

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	M. A. Brock	Research Biologist	LCP, NIA
Others:	W. H. Adler	Medical Officer, PHS	LCP, NIA
	F. J. Chrest	Biologist	LCP, NIA

COOPERATING UNITS *(if any)*

H. J. Hoffman, D. W. Denman III, Biometry Branch, NICHD

LAB/BRANCH
Gerontology Research Center, Laboratory Clinical Physiology

SECTION
Clinical Immunology Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.3	1.1	.2

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Cytoskeletal function influences activation events and ultimately the proliferative potential of T lymphocytes and also contributes to the age related decline in their physiological function. Concentrations of cytochalasin E (CE) that bind to F-actin synergized with Concanavalin A (Con A) in the presence of rIL-2 to increase the rate of entry into cell cycle and the proliferative capacity of G_0 T cells from spleens of aged (24 mo old) but not young C57Bl/6 mice. Resting (G_0) T cells were cultured with either Con A and rIL-2 or Con A and CE and rIL-2 and fluorescence intensities were determined with flow cytometry by using biotinylated PC61 monoclonal antibody to the p55 chain of the IL-2 receptor. CE in combination with Con A and rIL-2 potentiated the early expression (16 hr) of p55 chains by cells from both young and aged mice but to a greater degree for young mice. To assess the functional properties of the IL-2 receptors, G_0 T cells were activated with Con A or Con A and CE for 16 hrs, washed and then incubated with rIL-2. Cells from both young and aged mice responded to the same concentration (5×10^{-11}M) of rIL-2. These data show that functional high affinity receptors are expressed by cells from both young and old mice, and that their expression is augmented by CE. This suggests that the age-related differential effects of CE on the activation and proliferation of resting T cells are unlikely to be related to IL-2 receptor expression but to other signals dependent on microfilament functions.

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01-AG-00104-13-LCP

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Clinical Immune Survey of the Longitudinal Project Participants*

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	W. H. Adler	Medical Officer	LCP, NIA	
Others:	+J. E. Nagel	Medical Officer	LCP, NIA	
	R. K. Chopra	Visiting Associate	LCP, NIA	June 89
	F. J. Chrest	Biologist	LCP, NIA	
	R. S. Pyle	Bio. Lab Tech.	LCP, NIA	
	D. C. Powers	Medical Staff Fellow	LCP, NIA	
	G. D. Collins	Biologist	LCP, NIA	

COOPERATING UNITS *(if any)*

LAB/BRANCH
Gerontology Research Center, Laboratory of Clinical Physiology

SECTION
Clinical Immunology Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.2	2.2	1

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

These studies utilize participants in the Baltimore Longitudinal Study of Aging to gain insight into the genetic, biochemical and molecular mechanisms underlying age-associated changes in immune function. The projects are directed toward distinguishing and characterizing the origins of defective T cell activation and proliferation.

Others:	+B. A. Dorsey	Bio. Lab Tech.	LCP, NIA
	N. E. Kendig	Medical Staff Fellow	LCP, EOD 11/88

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

PROJECT NUMBER

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01-AG-00261-02-LCP

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Host Factors Relating to HIV Infections

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	W. H. Adler	Medical Officer, PHS	LCP, NIA	
Others:	+J. E. Nagel	Medical Officer, PHS	LCP, NIA	
	S. D. Kittur	Medical Staff Fellow	LCP, NIA	
	M. M. Bagdon	Biologist	LCP, NIA	Left Jan. 89
	F. J. Chrest	Biologist	LCP, NIA	
	G. D. Collins	Biologist	LCP, NIA	

COOPERATING UNITS *(if any)*

Dr. Clements, Vaccine Center, Johns Hopkins University, Dr. John Bartlet, Dept. Medicine, Johns Hopkins Univ., Drs. E. Dax and R. Lange, NIDA.

LAB/BRANCH
Gerontology Research Center, Laboratory Clinical Physiology

SECTION
Clinical Immunology Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.15	2.3	1.85

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

One hundred fifty individuals have been screened for the first two HIV vaccine trials. Evaluations of immune function on individuals admitted to the trial are proceeding. The investigation of the effects of drugs on immune function has been expanded to study the effects of multiple exposure to a amyl nitrite as is seen in society, and to study the effects of THC. The Interleukin-2 receptor in serum from individuals undergoing AZT therapy provides a measure of the extent of the inflammatory process. The detection of viral genome in tissues and cells is able to be accomplished even if the concentration of virus is very low. The PCR technique is useful for detecting a nucleic acid sequence even if low levels of DNA are present.

Others:	+R. K. Chopra	Visiting Associate	LCP, NIA	June 89
	N. E. Kendig	Medical Staff Fellow	LCP, NIA	Nov. 88
	R. S. Pyle	Bio. Lab Tech.	LCP, NIA	
	B. A. Dorsey	Bio. Lab Tech.	LCP, NIA	

Fiscal Year 1989

Annual Report of the Epidemiology, Demography, and Biometry Program

National Institute on Aging

ANNUAL REPORT OF THE EPIDEMIOLOGY, DEMOGRAPHY, AND BIOMETRY PROGRAM

NATIONAL INSTITUTE ON AGING

At the October 1988 Epidemiology, Demography, and Biometry Program Ad Hoc Scientific Advisory Committee Meeting, the Demography and Economics Office was reviewed and achievements and priorities were highlighted. Past research achievements of the Demography and Economics Office were identified as follows: The U.S. Wealth Distribution, 1979; The NIA Macroeconomic-Demographic Model (MDM); Cost of Caring for Dementia Patients; National Cost Estimate of Dementia for 1985; Health Insurance and Health Expenditures, and Life Cycle Wealth Accumulation Studies. Demography and Economics Office's future research priorities include Health Insurance - Coinsurance and Deductibles; Development of publications on the NIA MDM e.g., Health Expenditures, Retirement Income System, and Household Formation and Housing; and Long-Term Care i.e., insurance, demand for long-term care services, and nursing home expenditures.

In his annual report to the National Advisory Council on Aging (February 1989), Dr. J. David Curb, Associate Director for Epidemiology, Demography, and Biometry (EDB) Program outlined the current research agenda. He identified current Program priorities as follows: to broaden the research agenda for a more complete picture of aging (social, economic, biomedical); to focus on hypothesis-based research; to evaluate cross-cultural and international opportunities; to broaden EDB staff participation to use team approach in project management, analysis, and decision-making; to increase emphasis on training program; to increase information flow via EDBP Seminars on Aging; and to increase the peer review scientific publications produced by the Program.

As of July 26, 1989, Dr. Samuel P. Korper was designated Acting Associate Director for the EDB Program. Dr. J. David Curb returned to the University of Hawaii where he is Professor of Medicine and Director of Research of the Division of Geriatric Medicine in the Department of Medicine at the John A. Burns School of Medicine. He is also Principal Investigator of the Honolulu Heart Program.

Analytic activities continue with data sets from the National Health and Nutrition Examination Survey Epidemiologic Follow-up Survey (NHEFS), Framingham Dementia Study, Natural History of Senile Dementia Study, Survey of the Last Days of Life, Mortality Follow-Back Survey, NIA MDM, Health Insurance in the Elderly, National Medical Care Expenditure Utilization Survey, and the Established Populations for Epidemiologic Studies of the Elderly (EPESE).

The EDB Program Seminar Series on Aging continued in FY89. The series coordinated by Dr. LaCroix with the assistance of Drs. Guralnik, White and Curb was designed to bring experts in to discuss specialties of interest to the EDB Program researchers to help plan future studies and enhance our knowledge base in content areas that are relatively new or persistently challenging.

Fall Program

Dr. Suzanne C. Ho, The Chinese University of Hong Kong, Department of Community Medicine, discussed predictors of mortality among Hong Kong elderly.

Dr. William A. Satariano, Michigan Cancer Foundation, Division of Epidemiology, discussed co-morbidity and the study of cancer in the elderly.

Dr. Alex F. Roche, School of Medicine, Wright State University, discussed equations to predict percent body fat in the NHEFS.

Winter Program

Mr. Robert A. Wright, Chief, Utilization and Expenditures Statistics Branch, DHIS, NCHS, discussed linking the NHIS supplement on aging to the National Death Index and the HCFA Medicare data files.

Dr. J. Michael McGinnis, Deputy Assistant Secretary for Health, and Director, Office of Disease Prevention and Health Promotion, DHHS, discussed strategies for prevention in aging populations.

Dr. Hideo Sasaki a Cardiologist/Epidemiologist and Staff Member at the Radiation Effects Research Foundation, Hiroshima, Japan and Post Doctoral Fellow at the Epidemiology Research Center, The University of Texas Health Science Center at the Houston School of Public Health, discussed epidemiologic research on aging at the RERF.

Spring Program

Dr. Walter C. Willett, Professor of Epidemiology and Nutrition, Harvard School of Public Health, discussed the assessment of energy intake effects in epidemiologic studies.

Dr. Robert M. Schmidt, Professor of Clinical Science - Hematology, and Director, Center for Preventive Medicine and Health Research, San Francisco State University, School of Science, San Francisco, California, discussed a longitudinal study of healthy aging in 2200 men and women.

Dr. Gary G. Koch with assistance from Ms. Sandra Stinnett of the University of North Carolina Department of Biostatistics provided a short course in multivariate methods for the analysis of categorical data. Selected students had an opportunity to practice techniques in a laboratory setting.

Dr. David M. Buchner, Professor, Department of Health Services, University of Washington, Seattle, Washington, discussed strength as a risk factor for impaired health and fall-related injuries.

Epidemiology Office

Epidemiology Office staff members work with the Associate Director, other EDB Program staff members, other members of the NIA, other investigators at the NIH, Government contractors, the NCHS, and other agencies on a variety of analytic, developmental, methodologic, and administrative projects.

Most of the achievements of the Epidemiology Office involved new and continuing analyses of data from established EDB Program projects, including:

1. Established Populations for Epidemiologic Studies of the Elderly (EPESE)

   The three original community populations enrolled in the Established Populations for Epidemiologic Studies of the Elderly (EPESE) are located in East Boston, Massachusetts; Iowa and Washington Counties, Iowa; and New Haven, Connecticut. Baseline data collection began in December 1981, and annual interviews have been conducted either in-person (third and sixth years of follow-up) or by telephone (first, second, fourth and fifth years of follow-up) for 6 years following the baseline. At present 4 years of follow-up data are available for analysis.

   Data collection is now complete in Iowa and New Haven for the sixth year of follow-up in-person interview. During this contact, a brief physical assessment was also performed including several measures of physical performance and venipuncture (the only attempt to collect blood specimens in this study). Among survivors in these communities, participation rates to the sixth follow-up remained high (94 percent in Iowa and 92 percent in New Haven). Response rates to blood drawing were somewhat lower; approximately 75 to 80 percent in both communities. Data collection is still ongoing in East Boston where the data collection period for a single interview contact has been 18 months since the study's inception.

   A 5-year extension contract was awarded to each of the three original EPESE cohorts in February 1989. The extension places major emphasis on data clean-up during the first 2 years of the performance period. Deadlines for delivery of finalized data files are specified in the extension contract with the first of such deadlines occurring on December 1, 1989. The last 3 years of the contract give priority to continued monitoring of mortality through the National Death Index and to monitoring hospital utilization through linkage to Medicare records. The ability to link to Medicare records successfully and the

utility of the information obtained remain unproven in this study; therefore, year 3 of the renewal contract is devoted to a pilot test.

Another priority for the EPESE project as a whole is continued analysis and publication of the data collected so far. To this end, a tracking system for ongoing analyses has been established. The EPESE Publications Committee (composed of the EDBP Associate Director and the four EPESE Principal Investigators) reviews progress on each project at quarterly meetings and sets goals for continued progress. It is expected that research productivity associated with the EPESE database will grow substantially in the next few years.

2. Community Laboratory for Epidemiologic Studies of Aging (CLESA)

This project was developed with the goal of using a community-based epidemiologic study to examine a number of important issues in aging epidemiology. Compared to past EDBP research, it is conceived as more detailed, more biomedically oriented research to be done on smaller, more intensively studied yet representative samples of older persons. The project is seen as the second generation in the major epidemiologic studies of the EDBP with an emphasis on hypothesis based research which is more focused than the EPESE. This general approach was in response to recommendations from the EDB Program Ad Hoc Scientific Advisory Committee. The CLESA solicitation, which was released December 16, 1988, called for research in two areas: (1) the underlying causes and progression of disability and (2) infectious diseases of the respiratory system (pneumonia and influenza) and the urinary tract. Only one proposal was received, which was judged to be unacceptable by an Ad Hoc Technical Review Committee on April 26, 1989. The extremely ambitious goals of the solicitation, which demanded expertise in several broad areas, may have led to the absence of any acceptable proposals. Decisions are now being made as to where to proceed with the study. The disability component of the study may be issued as a separate study and it is likely that there will be a high level of competition for this work.

3. Development of research projects in the Pacific and Asia.

An RFC for a study of Aging and Dementia among Honolulu Heart Study Participants was developed with the NIH Research Contracts Branch, with the final document being delivered for their approval on August 14. The target date for funding is December 1989. Dr. Korper and Dr. White visited Hawaii in July for extensive talks with representatives of a number of a number of Hawaiian institutions.

4. NHANES III: Health of Older Americans (Baseline Survey)

The EDB Program made a decision to provide scientific and financial support to the NCHS Third National Health and Nutrition Examination Survey (NHANES III). Data from that study will provide insights into important biomedical and social conditions in a representative sample of older Americans. EDB Program scientists will provide consultation with NCHS on matters relating to the examination of older individuals in that study in the data collection period over the next few years. The first data analysis will not cocur, however, until after the first 3 years of the projected 6-year data collection period.

5. Natural History of Senile Dementia

This study, conducted at East Boston (Contract No. N01-AG-1-2106) was completed during FY88. In July the contractor supplied the EDBP with a final data tape and documentation.

6. Studies of Dementia in Framingham

Contract support for the Framingham Dementia Study (Agreement No. Y01-AG-2-0040) ended in FY88.

7. Analytic and developmental accomplishments by Epidemiology Office staff.

Dr. Jack Guralnik has played an active role in promoting the use of objective performance measures of physical functioning in both U.S. and international studies. This has occurred through personal consultations with numerous investigators, by distribution of the training videotape produced to instruct interviewers in the 1988 EPESE study in the standard administration of these measures, and through presentations at scientific meetings, including the XIV International Congress of Gerontology in Mexico. Consultations and distribution of the videotapes have involved scientists in the U.S. and the following foreign countries: China, Taiwan, Hong Kong, Japan, Australia, Belgium, and Italy. We anticipate future collaborative research efforts with several of these investigators.

Dr. Guralnik has provided consultation on aging research to researchers in Italy and Spain. Consultation on the development of a survey instrument was provided to Stefania Maggie, M.D., the principal investigator of a population study in the Veneto region of Italy. During a trip to Madrid and Granada, Spain, Dr. Guralnik presented scientific findings of EDB research and consulted with researchers in Spain who are

developing population studies of aging in that country. It is anticipated that collaborative studies will result from these projects.

Dr. Guralnik collaborated with Dr. Edward Schneider, Dean, Andrus School of Gerontology, University of Southern California on research assessing the impact on morbidity and health care costs of the increasing numbers of older people and the change in age distribution of the population age 65 and older. The manuscript resulting from this research will be submitted shortly.

Dr. Jack Guralnik and Dr. Andrea LaCroix have initiated research on factors which predict the maintenance of mobility in older populations using baseline and 4-year followup data from the original three EPESE sites. Impaired mobility has been found to be associated with increased numbers of chronic conditions and to be predictive of nursing home utilization and mortality. Investigations are now underway to evaluate specific factors which discriminate, in those with no mobility impairment at baseline, who will maintain mobility and who will lose mobility.

Dr. Guralnik has recently completed methodologic work which improves the assessment of active life expectancy. Applying methods used by the Bureau of Labor to evaluate total work life, increment-decrement life tables were created which allow for the transitions from both the non-disabled to the disabled and the disabled to the non-disabled state. This approach is important in that it takes into account previous observations that a large percentage of disabled individuals report making the transition back to the non-disabled state. The method was applied to the original three EPESE populations and results have been incorporated into a paper co-authored with Dr. Laurence Branch, Daniel Foley of EDB and other outside EPESE investigators.

Dr. Andrea LaCroix and Dr. Jan Wienpahl completed an investigation of the relation of thiazide diuretic use to incidence of hip fracture in the three original EPESE cohorts. This paper has been submitted for publication. Incidence rates of hip fracture were found to be lower among thiazide users than non-users in each community. The protective effect of thiazide use was independent of sex, age, impaired mobility, body mass index, and current and former smoking. Further, the protective effect was specific to thiazide diuretics as there was no association between use of anti-hypertensive medications other than thiazides and risk of hip fracture. This is the first prospective study, to our knowledge, to demonstrate a protective effect of thiazide diuretics consistent with a reduction of approximately one-third in risk of hip fracture.

The results of this investigation were presented by Dr. LaCroix at the Society for Epidemiologic Research meeting in Birmingham, Alabama.

Dr. Andrea LaCroix worked with Drs. Dwayne Reed and Katsuhiko Yano of the Honolulu Heart Program to perform a nested case-control study of the relation of dehydroepiandrosterone sulfate (DHEAS) levels to risk of coronary heart disease and extent of atherosclerosis. DHEAS values decline dramatically with age in both sexes, and a previous report in the New England Journal of Medicine has suggested that this hormone may play a role in, or be a biological marker of, the progression of atherosclerosis. Dr. LaCroix initiated this investigation, and EDBP funds were used to obtain DHEAS determinations on frozen sera from the Honolulu Heart Program cohort. The results of this investigation show no relationship between DHEAS levels and extent of atherosclerosis in autopsied men. DHEAS levels were not related to higher risk of non-fatal coronary heart disease events. This study did replicate the finding of an inverse relation between DHEAS levels and risk of fatal coronary heart disease. These apparently paradoxical findings appear to reflect a relationship of DHEAS levels with risk of death that does not operate through the progression of atherosclerosis. A manuscript for publication is now in preparation. This paper will be submitted for presentation at the 30th Annual Conference on Cardiovascular Disease Epidemiology.

Dr. Andrea LaCroix completed an investigation of uncomplicated chest pain symptomatology and risk of coronary heart disease death during three years of follow-up in the EPESE. This paper has been submitted for publication. Co-authors include Drs. Guralnik and Curb of EDB. Exertional chest pain was a strong, independent predictor of coronary heart disease death within three years for older men and women. There were no differences in the prognostic implications of this symptom between the sexes; the relative risks being 2.4 in men and 2.7 in women. The association between exertional chest pain and coronary heart disease mortality was independent of other coronary risk factors. The relation was specific for deaths from coronary heart disease, as there was no association between exertional chest pain and non-coronary causes of death. The results of this investigation were presented by Dr. LaCroix at the 2nd International Conference on Preventive Cardiology in Washington, D.C.

Dr. Ingrid Liu completed a study of the relationship of cognitive impairment and mortality in the Framingham Heart Study subjects. A document entitled, "Cognitive impairment and mortality: A study of possible confounders" has been submitted for publication. Coauthors include Drs. LaCroix and White.

Dr. Jan Wienpahl, finishing the first year of her PHS Epidemiology Traineeship with the EDB Program, has been investigating risk factors for hip fracture. Analyses were done of relationships among body mass index, race, sex, and the prevalence of hip fracture in the Duke EPESE; a manuscript is in preparation with Drs. LaCroix and White as coauthors. In collaboration with Dr. LaCroix, analyses are in progress of relationships among body mass index, cigarette smoking, alcohol use and incidence of hip fracture in the East Boston, New Haven, and Iowa EPESE. Dr. Wienpahl is also collaborating with Drs. Huntley and Wallace on studies of body size and morbidity and mortality in the EPESE.

Research Highlights for FY89

- Mortality and hospitalization rates for pneumonia have increased among older Americans during recent years (1979-1986), despite national commitment to reduction of premature deaths from pneumonia. We conducted a prospective investigation of pneumonia deaths and hospitalizations among 5474 subjects aged 55 and older who participated in the NHEFS. Prevalent chronic conditions, health behaviors, and nutritional status indicators, measured at baseline, were examined in relation to pneumonia hospitalization and death during 12 years of follow-up.

  Mortality and hospitalization rates for pneumonia were higher among men than women, and higher among older ($\geq$ 65) than younger (55-64) subjects of both sexes. Risk of pneumonia death was higher among subjects with a history of congestive heart failure, stroke, cancer or diabetes. Risk of pneumonia hospitalization was higher among subjects with a history of chronic obstructive pulmonary disease and among men who were current smokers. Daily alcohol consumption did not increase risk of pneumonia in this study population.

  Four measures of nutritional status were examined taking age, prevalent chronic conditions, and cigarette smoking into account: body mass index, arm muscle area, serum albumin and hemoglobin. Risk of pneumonia death was 2.6 and 4.5 times higher among men in the lowest (compared to the highest) quartile of body mass index and arm muscle area, respectively. Risk of pneumonia death was 3.6 times higher among women in the lowest quartile of serum albumin compared to women in the highest quartile. Relative risks for these nutritional status indicators remained elevated after adjusting for age and the medical history risk factors. These risk factors should be taken into account when designing and evaluating pneumonia vaccination trials and community prevention programs. (LaCroix et al. Public Health Rep, 1989;104(4):350-360.)

- The prevalence of Rose Questionnaire angina and its association with coronary heart disease risk factors and manifestations were investigated in representative samples of the US population. The study populations included 1,135 black and 8,323 white subjects aged 25-74 years examined in the NHANES II, 1976-1980 and 2,775 Mexican-American subjects aged 25-74 years examined in the Hispanic HANES, 1982-1983. Age-adjusted prevalence rates of Rose angina were similar among black, white and Mexican-American women (6.8%, 6.3%, and 5.4%, respectively). Compared to men, an excess among women in the prevalence of Rose angina was observed among white and Mexican-American persons under age 55, but not over age 55.

  Electrocardiographic evidence of myocardial infarction and self-reported heart attack were strongly associated with prevalent Rose angina among white men and women ages 55 and over, but not among those below age 55. Serum cholesterol, body mass index, current cigarette smoking and dyspnea were independently associated with an increased risk of prevalent angina in multivariate logistic models for white women, excluding those with a prior heart attack. Because many younger women with chest pain who may consult with physicians are likely to have elevations in cardiovascular risk factors, their self-reported chest pain can be used as an opportunity to intervene and reduce future risk of cardiovascular disease. (LaCroix et al. Am J Epidemiol, 1989;129: 669-686.)

- Hypertension was evaluated longitudinally in a nationally representative sample of the U.S.population. This study, based on the data from the NHEFS, analyzed changes in blood pressure and frequency of treatment, hypertension incidence, and ten year survival of the cohort relative to hypertension status at baseline. Higher prevalence rates for each older age group, especially in women, as previously reported on data from community studies were confirmed. However, this analysis found minimal differences in the incidence of hypertension between men and women for all age groups. Incidence rates for blacks were at least twice the rates for whites for almost every age-sex group. Decreased survival in older hypertensive men probably explained the higher prevalence in older women. Treatment and location of measurement in clinic or household must be major considerations in the calculation of incident cases. (Cornoni-Huntley et al., Arch Intern Med 1989; 149:780-788.)

- The NHEFS, an investigation of a cohort originally examined during the period 1971-1975, provided an opportunity to assess the frequency of antihypertensive drug therapy in the United States during the period 1982-1984. For most age-sex-race subgroups, the frequency of the medication use during the period 1982-1984 was higher than that observed during 1976-1980 based on the NHANES II. In the interval 1982-1984, diuretic agents were the most frequent medications prescribed (47% of drugs prescribed), and B-blockers were second (17%). At the

time of the initial survey in 1971-1975, participants had their blood pressures measured and a history of diagnosis and treatment of hypertension ascertained. Follow-up for interval status was 93% complete by 1984 (average length of follow-up, 9 years). In white men and women aged 50 years and older, the relative risk of death increased steadily, from those with elevated blood pressure (systolic blood pressure ≥160 mm Hg or diastolic blood pressure was ≥ 95 mm Hg) but no history of hypertension to those treated for hypertension but whose blood pressure was still elevated. Regardless of history or treatment, those with an elevated blood pressure had about 25-30% excess risk of death. Evidence from these national studies shows a high frequency of antihypertensive drug therapy in 1982-1984 and suggests the importance of adequate blood pressure control for optimal survival (Havlik et al., Hypertension 1989;13 (suppl I):I-28--I-32).

- Data from 3,087 persons age 45 or older in the NHANES, 1971-74, showed that subjects with lens opacifying disease had an increase in odds for age-related macular degeneration (AMD) compared to those who had no lens opacities. The crude odds ratio for aphakic patients was 4.6 (95% CI= 2.5,8.6). The association remained after controlling for age, sex, and systolic blood pressure (a common risk factor) in a logistic regression model. These data are consistent with the hypothesis that light-induced damage may contribute to both lens and retinal disease and suggest that cataract extraction without implantation of ultra-violet/ blue light absorbing intraocular lens may place subjects at increased risk of AMD. (Liu et al., Am J Public Health 1989; 79:765-769.)

- The relation of job psychologic demands and decision latitude to four coronary heart disease risk factors (cholesterol, smoking, and systolic and diastolic blood pressures) was tested among 12,555 men in five investigations conducted in the United States during the period 1959-1980 (NHANES I and II, National Health Examination Survey, Western Collaborative Group Study, and Exercise Heart Survey). Using an imputation strategy, the authors attached measures of the two job characteristics above to persons in each data base by occupation. In 19 possible tests, decision latitude was related ($p<0.05$)to cholesterol and smoking in two instances in the predicted direction in the Exercise Heart Survey, when controlling for Type I error rate. Psychologic demands were not related to anyof the risk factors. When a meta-analysis was performed across data bases, all relations were in the predicted direction except for the the relation to psychologic demands tosystolic pressure, and two of these were statistically significant ($p<0.05$): the relation of job decision latitude to smoking and to systolic pressure. The interaction of psychologic demands and decision latitude was not related to any of the risk factors when two common forms of an interaction were tested. These results indicate

that psychosocial aspects of work, in particular the decision latitude of the job, may be related to some cardiovascular risk factors. (Pieper et al., Am J Epidemiol 1989; 129:483-494.)

- The occurrence of pressure sores during a follow-up period of approximately 10 years is documented for a US nationwide cohort aged 55 to 75 years at baseline. Using data from NHEFS, those who developed pressure sores were identified through death certificates, hospital discharge summaries and self-report or proxy-report. During the follow-up period, pressure sores were identified in 113 of the 5,193 respondents (2.2%) for whom follow-up information was available. Incidence over the follow-up period was 1.7% for those aged 55 to 69 at baseline and rose to 3.3% for those 70 to 75 years old. Risk factors for pressure sore development were evaluated using data collected in NHANES I at baseline. Those with identified pressure sores were compared with the remainder of their cohort and also with a control group matched on age and length of longest hospitalization or nursing home admission. Significantly increased risk for pressure sore development was found for those who at baseline were current smokers, reported being relatively inactive, had poor self-assessed health status and who were found on physician's exam to have dry or scaling skin. Neurologic abnormality on the physician's exam and anemia at baseline were also associated with increased risk of pressure sores, although these associations were borderline statistical significance (Guralnik et al., J Am Geriatr Soc 36:807-812, 1988).

- Projections of future populations are fraught with uncertainties based on past fertility and immigration trends, assumptions about medical science and lifestyles. The U.S. Census Bureau and the Social Security Administration may be unduly cautious in their assumption that the mortality decline of the past two decades cannot continue; it may be sustained for the next half century. Alternative assumptions about rates of mortality and morbidity all indicate that the needs for health services, institutionalization, and home care of the disabled elderly--especially among the oldest old--will make ever greater relative and absolute demands on the nation's health care resources. (Guralnik et al., Milbank Memorial Quarterly 1988;66:283-308.)

- Between 1972 and 1982, Japan caught up to and then surpassed Sweden as the country with the longest life expectancy. The contributions of different causes of death and age groups to life expectancy changes in males during this time period are examined in detail for these two countries. Even though cerebrovascular disease mortality rates remained lower in Sweden over the entire interval, the rapid gain made by Japan relative to Sweden for this cause of death was a prime factor in Japan's ending the period with a higher life expectancy.

Important contributions to life expectancy improvement in Japan came from declining mortality rates in those aged 55 and older. (Yanagishita et al., Demography 1988;25:611-624.)

- Longitudinal data from the Alameda County Study are used to examine three health consequences of multiple or co-morbidity, defined as the coexistence of two or more chronic conditions and/or symptoms. Age-adjusted analyses of the consequences of baseline co-morbidity show significant associations in both age groups with 17-year mortality, and with the development of multiple new conditions and the occurrence of depression over a 9-year follow-up. After adjustments for sociodemographic characteristics and health behaviors, all associations with multiple new conditions remain significant. The association with depressive symptoms, however, remains significant for the younger age group only and the associations with mortality become nonsignificant in both age groups. (Seeman et al., Journal of Aging and Health 1989; 1:50-66.)

- Overall, the most useful measures of health status in the older population are those which reflect functioning, particularly in the domains of physical, cognitive and emotional functioning. Other areas of function, such as visual functioning and hearing, may also be components of comprehensive health status assessment instruments and are also of great importance for the maintenance of independence in older persons.

  In the standard medical model, an intensive effort is made to diagnose disease so that appropriate treatment can be prescribed. In both the clinical setting and in aging research, there is also much additional information to be gained by assessing overall health status or functional abilities. By doing this, the impact on the older person of one or multiple diseases as well as other intrinsic and extrinsic factors can be more broadly appreciated. (Guralnik, Quality of Life and Cardiovascular Care, 1988;4:151-155.)

- This report presents information on the prevalence and co-prevalence of nine common chronic conditions obtained in the Supplement on Aging to the 1984 National Health Interview Survey, a nationally representative sample of persons age 60 years and older. The impact of co-morbidity is then assessed by estimating the prevalence of disability in activities of daily living according to the number of conditions present.

  The percent of the population 60 years of age and older with two or more of the nine chronic conditions under consideration was higher at each older age and, for each age group, was higher for women than for men. The number of men and women having difficulty or receiving help with activities of daily living increased in proportion to the increasing number of chronic conditions present. A clear, graded increase also was seen in the proportion of individuals with disability from

those with none of the nine conditions to those individuals with disability having five or more of the conditions. (Guralnik et al., Advance data from vital and health statistics; no. 170. Hyattsville, Maryland: National Center for Health Statistics, 1989.)

- Long-term predictors of high levels of physical functioning were examined in a representative sample of Alameda County, California residents followed from 1965 through 1984. The cohort investigated in this study was born between 1895 and 1919, with survivors being age 65 to 89 at the time of followup. A scale of physical functioning was developed from a comprehensive set of questionnaire items which assessed the full spectrum of physical functioning, from severe disability through vigorous activities and exercise. Those scoring in the top 20% were functioning at high levels and were defined as having healthy aging. This group was compared to the remainder of the cohort, including those who died and those with lower levels of functioning at followup. After adjustment for age and functional status at baseline, the following variables were predictive of high functioning at followup 19 years later: race (non-black), higher family income level, absence of hypertension, absence of arthritis, absence of back pain, being a non-smoker, having normal weight and consuming moderate amounts of alcohol. Neither sex was more likely to have high function at followup. This was demonstrated to be the result of the counterbalancing effects of higher survival in females but greater likelihood of high functioning among surviving males. (Guralnik et al., Am J Public Health, 1989;79:703-708.)

- The authors examined national changes in socioeconomic differentials in mortality for middle-aged and older white men and women in the U.S. with the use of 1960 data from the Matched Records Study and 1971-1984 data from the NHEFS. In 1960, there was little difference in mortality by educational level among middle-aged and older men. Since 1960, death rates among men declined more rapidly for the more educated than the less educated, which resulted in substantial educational differentials in mortality in 1971-1984. In contrast, among women, death rates declined at about the same rate regardless of educational attainment, so that a strong inverse relation between education and mortality in 1960 remained about the same magnitude during 1971-1984. Trends in educational differentials for heart disease mortality are responsible for much of the change for all causes of death. Relative risk estimatew based on the NHEFS indicate that after taking into account selected baseline risk factors the least educated are still at substantially elevated risk of death from heart disease, ranging from a relative risk of 1.38 for men aged 65-74 years at baseline to 2.27 for men aged 45-64 years. Reasons for the observed educational differentials and their changes

over time are not easily explained and are likely to be multifactorial. (Feldman et al., Am J Epidemiol, 1989;129(5):919-933.)

- Information concerning bowel habits was gathered from a representative sample of 14,407 United States adults in the NHANES I in 1971-1975 and approximately 10 years later among the same individuals. The prevalence of self-reported constipation, diarrhea, infrequent defecation (three or fewer bowel movements per week), and frequent defecation (two or more bowel movements per day) increased with aging. Women were more likely than men ($P<0.05$) to report constipation (20.8% compared to 8.0%) and infrequent defecation (9.1% compared to 3.2%). Blacks were more likely than whites to report infrequent defecation ($P<0.05$). Older respondents reporting constipation were more likely to use laxatives or stool softeners than younger respondents reporting constipation, but they were also less likely to have infrequent defecation. To evaluate factors predictive of impaired bowel function, case definitions were created using information concerning complaint of constipation, laxative use, frequency of defecation, and stool consistency. Female gender, black race, fewer years of education, low physical activity, and symptoms, of depression were independent risk factors for impaired bowel function. This study provides national estimates of bowel complaints and their natural history and examines possible risk factors for constipation. (Everhart et al., Digestive Diseases and Sciences, 1989;34(8):1153-1162.)

- A cohort of 3,595 white women aged 40-77 years was followed for an average of 10 years during which 84 new cases of hip fracture were identified. Triceps skinfold thickness and arm muscle area measured at baseline were examined as possible risk factors for hip fracture controlling for physical activity, height, menopausal status, calcium consumption, and smoking. Of these variables only arm muscle area, triceps skinfold thickness, and activity in recreation were independent predictors of hip fracture incidence using the Cox proportional hazards model. After adjustment, the estimated relative risk of hip fracture was approximately two for an increment of each anthropometric indicator (adjusted for the other) equivalent to comparing those at the 25th percentile to those at the 75th percentile (maximum width of 95% confidence intervals, 1.2-2.9). Risk of hip fracture was approximately two-fold for persons who reported little recreational exercise compared to persons who reported much recreational exercise (95% confidence interval, 1.2-3.2).

  Our findings are the first evidence from a prospective study that anthropometric indicators besides body mass index may have an independent relationship to risk of hip fracture. (Farmer et al., J Am Geriatr Soc, 1989;37: 9-16.)

- The authors examined national changes in socioeconomic differentials in mortality for middle-aged and older white men and women in the United States with the use of 1960 data from the Matched Records Study and 1971-1984 data from the NHEFS. In 1960, there was little difference in mortality by educational level among middle-aged and older men. Since 1960, death rates among men declined more rapidly for the more educated than the less educated, which resulted in substantial educational differentials in mortality in 1971-1984. In contrast, among women, death rates declined at about the same rate regardless of educational attainment, so that a strong inverse relation between education and mortality in 1960 remained about the same magnitude during 1971-1984. Trends in educational differentials for heart disease mortality are responsible for much of the change for all cause of death. Relative risk estimates based on the NHEFS indicated that after taking in account selected baseline risk factors the least educated are still at substantially elevated risk of death from heart disease, ranging from a relative risk of 1.38 for men aged 65-74 years at baseline to 2.27 for men aged 45-64 years. Reasons for the observed educational differentials and their changes over time are not easily explained and are likely to be multifactorial. (Feldman et al., Am J Epidemiol, 1989;129(5): 919-33.)

CONTRACT

Name and Number: Duke University Medical Center (N01-AG-4-2110)

Title: Established Populations for Epidemiologic Studies of the Elderly (EPESE)

Date Contract Initiated: September 30, 1984

Current Annual Level: $988,270

Objectives: The purpose of this project is to conduct epidemiologic investigations in an elderly population, 65 years of age and older, and of which at least 50 percent is black. The population is stable with a wide range of socioeconomic status in both black and white groups. The influence of social, environmental, behavioral, and economic forces on the mortality, morbidity, and utilization of health services in the study population will be investigated.

Methods Employed: Descriptive and analytical epidemiologic studies of existing problems and surveillance of newly developing problems all with an emphasis upon future intervention and prevention have been conducted. Investigators conducted cross-sectional and prospective studies as well as more detailed problem-related studies in a carefully defined and accessible population using standard field and analytical techniques.

Significance to Biomedical Research: The NIA began funding three population studies of the elderly to determine the influences of social, environmental, behavioral, and economic forces on the mortality, morbidity, and utilization of health services in the elderly. These studies, however, were not fully representative of the U.S. elderly, specifically, they did not include a significant proportion of blacks. It is well known that distributions of certain risk factors and diseases differ between U.S. blacks and other racial groups. Therefore, the purpose of this contract is to conduct epidemiologic investigations in an elderly population of which at least 50 percent is black in order to develop new knowledge concerning the medical and social factors in health and diseases of the aging black population.

Proposed Course: From January 1986 to June 1987, 4,164 baseline interviews were conducted in Durham, Franklin, Granville, Vance, and Warren Counties in North Carolina. From January 1987 to June 1988, the first annual telephone follow-up was conducted and from January 1988 to June 1989, the second telephone follow-up was conducted. A second in-person follow-up of 3,746 respondents is being conducted from 1989 and will continue through June 1990. The third telephone follow-up will be conducted from January 1990 through June 1991.

CONTRACT

Name and Number: Peter Bent Brigham Hospital (N01-AG-0-2107)

Title: Established Populations for the Epidemiologic Studies of the Elderly (EPESE)

Date Contract Initialed: June 30, 1980

Current Annual Level: $690,290

Objectives: The purpose of this project is to conduct epidemiologic investigations in a community to develop new knowledge concerning the medical and social factors in health and disease of the aged.

Methods Employed: The project includes cross-sectional and prospective studies in a carefully defined and accessible population using standard field and analytical techniques. Yearly surveillance of the population is included.

Significance to Biomedical Research: The population over age 65 has been steadily increasing both in relative and absolute numbers. With this increase has come an awareness of a variety of health and social problems which are creating problems for our social and physical environment. To provide new knowledge it is important to have studies representing existing conditions in a community population.

Proposed Course: Continued surveillance during a 5-year period (1989-93) for two major endpoints of the EPESE: mortality and hospitalization. The additional data will be integrated with the previous data collected and the techniques shall be compatible with the techniques used in the previous EPESE contracts. During the 5-year period of the contract surveillance systems (involving no or minimal direct contact with study subjects) will be used to ascertain the occurence of hospitalization events including the time of these events, the admitting and discharge diagnosis, and the subject's discharge dispositions. Surveillance systems will also be used to monitor deaths among study participants including the time of these deaths, procurement of death certificates, and nosologist coding of causes of death.

Major Findings: A prospective study directly examines, in a defined community population, the extent to which a wide array of characteristics predict utilization of an important long-term care (LTC) service--medical home care--over a two-year interval among the cohort of 3,706 people aged 65 or older. The overall age-sex adjusted rate of two-year incident home care use was 3.2 per cent. For both men and women, the rates among the aged 85 or older group were approximately 12 times the rates of those aged 65-74. The multivariate predictors of incident home care, adjusted for age and sex, were five: receiving help with at least one activity of daily living (ADL), being dependent in Rosow-Breslau functional health

areas, being homebound, more errors in mental status items, and no involvement with social groups. The dominance of indicators of frailty in physical function and cognitive function are consistent with the predictors of another group of LTC clients, those who subsequently enter nursing homes. However, in the present study the ratios of medical home care use were similar for those living alone and for those living with others in the multivariate model, suggesting the possibility of differences between home care and institutional LTC clients (ref. 1).

In 1982 and 1983, brief, structured performance tests of selected areas of cognitive function were administered to 3,682 (82.1 per cent) of the residents aged 65 and older of the geographically defined community of East Boston, Massachusetts, a center of the Established Populations for Epidemiologic Studies of the Elderly program. There was a strong inverse relation between age and performance on all four cognitive tests in analyses adjusted for sex only as well as in those adjusted for effects of other variables. Similarly, fewer years of formal education, increasing level of disability on the modified Katz Activities of Daily Living Scale, and less prestigious occupations, as measured by the modified Duncan Socioeconomic Index, were each independently related to lower performance on all four tests (ref. 2).

The findings of a relation between smoking and Alzheimer's disease have been inconsistent in institutional-based case-control studies. Since only a small select proportion of cases come to medical attention, selection bias is difficult to avoid. To overcome this, the effects of smoking and alcohol use on cognitive function were examined in a defined population. A questionnaire containing a brief test of immediate story memory was administered in the home to 3,623 persons aged 65 or older in East Boston, Massachusetts in 1982-1983. Three years later, 90% of survivors were reinterviewed. Among 1,660 retested persons who performed well on the first test (0-2 errors of six possible), three-year change in memory score was not related to lifetime smoking habits or to moderate alcohol consumption, as reported at initial interview. Insignificant change in memory was associated with smoking one pack of cigarettes per day (0.004 score points, 95% confidence interval (CI) = -0.08 to 0.09) and with drinking 1 oz (29.6 ml) of alcohol per day (0.04 score, 95% CI= -0.03 to 0.11).
This study provides evidence that longitudinal change in an objective measure of cognitive function was not related to smoking or alcohol use (ref. 3).

A population survey was conducted in 1982-1983 among 3,812 persons aged 65 years and older residing in East Boston, Massachusetts, a geographically defined urban community. Three measurements of peak expiratory flow rate were obtained by using calibrated mini-Wright meters. Peak expiratory flow rate was strongly related to age, sex, smoking, and years smoked. After adjustment for these factors, low peak expiratory flow rate was associated with chronic respiratory symptoms (cough, wheeze, shortness of breath, exertional dyspnea, orthopnea, and paroxysmal nocturnal dyspnea;

p<0.0001) and with certain cardiovascular variables (history of stroke, p=0.0014; angina, p=0.05; and high pulse rate,p=0.004). No significant associations were found with history of myocardial infarction or systolic and diastolic blood pressures. Peak expiratory flow rate was positively related to education (p<0.0001) and income (p<0.0001). Peak expiratory flow rate also was strongly related (p<0.0001) to measures of functional ability and physical activity, self-assessment of health, and simple measures of cognitive function. The correlations of peak expiratory flow rate with pulmonary symptoms and other indices of chronic disease raise the possibility that peak expiratory flow rate will predict mortality in an elderly population (ref. 4).

Publications:

1. Branch LG, Wetle TT, Scherr PA, Cook NR, Evans DA, Hebert LE, Masland EN, Keough ME, Taylor JO. Prospective Study of incident comprehensive medical home care use among the elderly. Am J Public Health 1988;78:255-259.

2. Scherr PA, Albert MS, Funkenstein HH, Cook NR, Hennekens CH, Branch LG, White LR, Taylor JO, Evans DA. Correlates of cognitive function in an elderly community population. Am J Epidemiol 1988;128:1084-1101.

3. Hebert LE, Scherr PA, Smith LS, Albert MS, Funkenstein HH, Evans DA. Longitudinal study of the effects of smoking and alcohol use on memory. Am J Epidemiol 1988;128(Abstract):925.

4. Cook NR, Evans DA, Scherr PA, Speizer FE, Vedal S, Hennekens CH, Branch LG, Cornoni-Huntley J., and Taylor JO. Peak expiratory flow rate in an elderly population. Am J Epidemiol 1989;130:66-78.

CONTRACT

Name and Number: University of Iowa (N01-AG-0-2106)

Title: Established Populations for Epidemiologic Studies of the Elderly (EPESE)

Date Contract Initiated: June 30, 1980

Current Annual Level: $261,252

Objectives: The purpose of this project is to conduct epidemiologic investigations in a community to develop new knowledge concerning the medical and social factors in health and diseases of the aged.

Methods Employed: The project includes cross-sectional and prospective studies in a carefully defined and accessible population using standard field and analytical techniques. Yearly surveillance of the population is included.

Significance to Biomedical Research: The population over age 65 has been steadily increasing both in relative and absolute numbers. With this increase has come an awareness of a variety of health and social problems which are creating problems for our social and physical environment. To provide new knowledge, it is important to study representative community-dwelling populations. Within obvious logistical constraints populations will be available to the NIA scientific community for specific studies.

Proposed Course: Continued surveillance during a 5-year period (1989-93) for two major endpoints of the EPESE: mortality and hospitalization. The additional data will be integrated with the previous data collected and the techniques shall be compatible with the techniques used in the previous EPESE (involving no or minimal direct contact with study subjects). Linkage with HCFA medicare data will be used to ascertain the occurrence of hospitalization events including the time of these events, the admitting and discharge diagnosis, and the subjects' discharge dispositions. Surveillance systems will also be used to monitor deaths among study participants including the time of these deaths, procurement of death certificates, and nosologist coding of causes of death. From May to September 1989, a seventh year of follow-up interviews was conducted with additional information obtained on driving practices. The newly created database will be made available to staff at the National Highway Traffic Safety Administration for collaborative analyses of risks for driving accidents and pedestrian accidents.

Major Findings: Item nonresponse and inconsistent responses (IRs) and their health and psychobehavioral correlates in a population-based survey of adults 65 years and older were examined. An in-person questionnaire was administered concerning physical, social,

and psychological health to 1,155 men (mean age=73.7 years) and 1,942 women (mean age=74.8 years). Nonresponse rates varied with item topic, and "don't know" (DK) responses were more common than refusals. DKs increased with age of respondent, tended to be more common in women than men, and were associated with poorer physical, cognitive, and psychological functioning. Conversely, IRs increased with age among men but not women, but were also associated with poorer physical, cognitive, and psychological functioning. Results are discussed in terms of motivational and attentional factors, and their implications for survey research with the frail elderly and very old are noted (ref. 1).

Conjugal role organization in retired rural couples was investigated. Three major aspects of the conjugal relationship were examined: division of household tasks, decision-making patterns, and leisure activities shared by the couple. Interviews were conducted with 149 couples who participated in the retirement substudy of an 8-year epidemiological investigation of two rural counties in Iowa. Results showed that rural couples: (a) exhibited a traditional, gender-differentiated division of household tasks, but that household role segregation decreased significantly after retirement; (b) made a majority of decisions jointly during retirement, with joint decision making increasing significantly after retirement; (c) participated in a large number of joint leisure activities during retirement (ref. 2).

Prevalence of the use of medications that may affect dental health and dental treatment among 3,217 elderly Iowans was reported. Data were obtained from a large, ongoing epidemiological study of those aged 65 years or older in two rural Iowa counties. Nine categories of possible drug effects were created. Seventy-seven percent of the population reported taking at least one medication with potential importance for the dentist. Fifty-one percent reported being on medications known to cause xerostomia, 39% reported medications possibly affecting hemostasis, 28% were at risk of drug-induced soft tissue reactions, 22% reported medications which could interact with drugs used commonly in dentistry, 20% reported medications requiring that vasoconstrictor use be minimized, and 16% reported medications indicating reduced stress tolerance. Smaller percentages reported use of medications potentially altering host resistance, associated with orofacial movement disorders, or known to cause gingival overgrowth. Dentists must be knowledgeable about their patients' medications and their important side effects. This is especially important among the elderly who use more drugs per capita than do other age groups (ref. 3).

A thorough understanding of the relationship between ill health and retirement requires the investigation of specific illnesses and medications mechanisms. We examined the relationship between specific major and minor health conditions and work status (retired-health , RH; retired other, RO; or working, W) in a population-based (N=3097) study of rural elderly persons. Lifetime history rates of major conditions were typically highest among RH

persons, and differed little between RO and W persons. RH was associated with poorer self-perceived health, physical functional status, mood, and recall than were RO and W, which did not differ from each other. RH was also associated with increased prevalence and number major and minor condition among women but not men. Thus RH is preferentially associated with specified major medical conditions increased, increased number of major and minor health conditions, and quantitative functional and psychological decrements (ref. 4).

In a geographically-defined cohort of the rural elderly (N=3673), we obtained measures of physical, social and psychologic function at baseline and three years later in those with and without an interval myocardial infarction (MI) or (STR). MI events were associated with clear decrements in both basic and complex physical activities in women but not men. STR was associated with worsened physical function in both men and women. Both MI and STR were associated with decreased mental status scores, more depressive symptoms, and poorer life satisfaction. MI was associated with decreased memory performance in men. Those with MI or STR reported increased social network size and more social support after these events, not seen in control subjects. These findings help define resource and rehabilitative requirements for older MI and STR patients and have implications for clinical management and secondary prevention programs (ref. 5).

Publications

1. Colsher PL, and Wallace RB. Data quality and age: Health and psychobehavioral correlates of item nonresponse and inconsistent responses. J Gerontol: Psychological Sciences, 1989;44:45-52.

2. Dorfman LT, and Heckert DA. Egalitarian in retired rural couples: household tasks, decision making and leisure activities. Family Relations 1988;37(1): 73-78. Also published in, Families in Rural America: Stress, Adaptation and Revitalization, St. Paul, MN, National Council on Family Relations, February 1988.

3. Levy SM, Baker KA, Selma TP, and Kohout FJ. Use of medications with dental significance by a noninstitutionalized elderly population. Gerodontics 1988;4(3):119-125.

4. Colsher PL, Dorfman LT, and Wallace RB. Specific health conditions and work-retirement status among the elderly. J Appl Gerontol 1988;7(4):485-503.

5. Wallace RB, Colsher PL, Kohout, FJ, and Lemke J. Physical and psychological functional impact of heart attack and stroke in an elderly cohort. Poster Presentation at the 2nd International Conference on Preventive cardiology in Washington, D.C., June 1989.

CONTRACT

Name and Number: Yale University (N01-AGF-0-2105)

Title: Established Populations for Epidemiologic Studies of the Elderly (EPESE)

Date Contract Initialed: June 30, 1980

Current Annual Level: $444,029

Objectives: The purpose of this project is to conduct epidemiologic investigations in a community to develop new knowledge concerning the medical and social factors in health and disease of the aged.

Methods Employed: The project includes cross-sectional and prospective studies in a carefully defined and accessible population using standard field and analytical techniques. Yearly surveillance of the population is included.

Significance to Biomedical Research: The population over age 65 has been steadily increasing both in relative and absolute numbers. With this increase has come an awareness of a variety of health and social problems which are creating problems for our social and physical environment. To provide new knowledge it is important to have studies representing existing conditions in a community population. Within obvious logistical constraints populations will be available to the NIA scientific community for specific studies.

Proposed Course: Continued Surveillance during a 5-year period (1989-93) for two major endpoints of the EPESE: mortality and hospitalization. The additional data will be integrated with the previous data collected and the techniques shall be compatible with the techniques used in the previous EPESE contracts. During the 5-year period of the contract surveillance systems (involving no or minimal direct contact with study subjects) will be used to ascertain the occurrence of hospitalization events including the time of these events, the admitting and discharge diagnosis, and the subjects' discharge dispositions. Surveillance systems will also be used to monitor deaths among study participants including the time of these deaths, procurement of death certificates, and nosologist coding of causes of death. From May to September 1989, a seventh year of follow-up interviews was conducted with additional information obtained on driving practices. The newly created database will be made available to staff at the National Highway Safety Administration for collaborative analyses of risks for driving accidents and pedestrian accidents.

Major Findings: Relationships between structural characteristics of social networks and two types of support (instrumental and emotional support) were examined in a sample of community-dwelling individuals aged 65 and older. For each type of support, two dimensions are examined (1) the availability of such support and

(2) the perceived adequacy of that support. Regression models, adjusting for age, sex, race, and income show that structural characteristics such as total network size, number of face-to-face contacts and number of proximal ties are associated with greater availability of both instrumental and emotional support. The perceived adequacy of both types of support is most strongly related to the number of monthly face-to-face contacts. Comparisons of specific types of ties show that neither ones'spouse nor ones'children are primary sources of support. Rather the presence of a confidant is strongly associated with both dimensions of instrumental and emotional support; the presence of a spouse is not. And, while ties with children are most strongly related to aspects of instrumental support, ties with close friends and relatives are more strongly related to aspects of emotional support. Analyses of possible interactions show that for those without a spouse, confidants assume greater importance in providing emotional support. For those without children, ties with close friends and relatives assume a larger role relative to the perceived adequacy of both emotional and instrumental support (ref. 1).

The need to assess functions such as mobility in elderly patients is increasingly recognized. Lacking other methods, clinicians may rely on standard neuromuscular examination to evaluate mobility. Therefore, the sensitivity of the neuromuscular examination for identifying mobility problems were checked by comparing relevant neuromuscular findings with performance during four routine mobility maneuvers were checked: (1) getting up from a chair,(2) sitting down, (3) turning while walking, and (4) raising the feet while walking. The subjects investigated were 336 elderly persons living in the community. Many subjects who performed poorly during mobility maneuvers did not have the corresponding neuromuscular abnormalities. For example, although hip and knee flexion are needed to sit down safely, abnormal hip flexion was found in only 15% and abnormal knee flexion in only 30% of the subjects who had difficulty sitting down. The relationship between neuromuscular findings and functional mobility was not predictable enough to rely on neuromuscular findings for identifying mobility problems. Therefore, a simple assessment that reproduces routine daily mobility maneuvers should be developed for use in the clinical care of elderly patients (ref. 2).

The social and psychological consequences of living with a cognitively impaired spouse were assessed among community-dwelling elderly individuals. The study sample consisted of 318 spouse pairs drawn from a representative sample of noninstitutionalized eldelry individuals. Our principal findings were that: (a) Cognitive impairment in wives is significantly ($p<.05$) associated with depressive symptomatology in husbands, whereas cognitive impairment in husbands is only weakly ($p>.20$) associated with depressive symptomatology in wives; (b) Decreased participation in social/leisure activities is selectively related to spouses level of cognitive functioning among both men and women; (c) The relationship between wives cognitive impairment and husbands'

depressive symptoms is influenced by perceived availability of financial support from friends and relatives, but not by ADL limitations in wives, lack of emotional or instrumental support from wives, household responsibilities among husbands, or lack of participation in social/leisure activities in husbands (ref. 3).

A one-year prospective investigation was conducted to study risk factors for falling, using a sample of 336 persons at least 75 years of age who were living in the community. All subjects underwent detailed clinical evaluation, including standardized measures of mental status, strength, reflexes, and gait; in addition, an inspection of their homes was included to look for environmental hazards. Falls and their circumstances were identified during bimonthly telephone calls. During one year of follow-up, 108 subjects (32 percent) fell at least once; 24 percent of those who fell had serious injuries and 6 percent had fractures. Predisposing factors for falls were identified in linear-logistic models. The adjusted odds ratio for sedative use was 28.3; for cognitive impairment, 5.0; for disability of the lower extremities, 3.8; for palmomental reflex, 3.0; for abnormalities of balance and gait, 1.9; and for foot problems, 1.8; the lower bounds of the 95 percent confidence intervals were 1 or more for all variables. The risk of falling increased linearly with the number of risk factors from 8 percent with none to 78 percent with four or more risk factors ($P<0.0001$). About 10 percent of the falls occurred during acute illness, 5 percent occurred during hazardous activity, and 44 percent in the presence of environmental hazards. The findings suggest that falls among older persons living in the community are common and that a simple clinical assessment can identify the elderly persons who are at greatest risk of falling (ref. 4).

Publications

1. Seeman T, Berkman LF. Structural characteristics of social networks and their relationship with social support. Soc Sci and Med 1988;26(7):737-749.

2. Tinetti ME, Ginter SF. Identifying mobility dysfunction in elderly patients: standard neuromuscular examination or direct assessment? JAMA 1988;259:1190-1193.

3. Moritz D, Kasl S, Berkman L. The health impact of living with a cognitively impaired elderly spouse: Depressive symptoms and social functioning. J Gerontol: Social Sciences 1989;44(1):517-27.

4. Tinetti ME, Speechly M, Ginter SF. Risk factors for falls among elderly persons living in the community. N Engl J Med 1988;319:1701-7.

5. Kasl SV, Ostfeld AM, Berkman LF, Jacobs SC. Stress and alcohol consumption: The role of selected social and environmental facotrs. In E. Gottheil (ed.), Stress Addiction. New York: Brunner/ Mazel, 1987; 40-61.

6. Ostfeld A. Using epidemiologic data to plan services for the elderly. Public Health Rep 1988;103(5):520-522.

Demography and Economics Office

Three advisors met with Drs. T. Franklin Williams, Gene D. Cohen, Samuel P. Korper, J. David Curb, and William S. Cartwright to review the Demography and Economics Office. The advisors were Professor Dorothy Rice, Dr. Debra J. Chollet, and Dr. Pheobus Dhyrmes. This review was conducted as part of the Ad Hoc Scientific Advisory Committee Meeting of October 24-25, 1988. It was found that the Office properly focuses on social and behavioral implications of aging from the economic point of view, should not be eliminated at its current level, and is generally supportive of research efforts on long-term care and health insurance issues. It was considered desirable to do more studies with the Macroeconomic-Demographic Model (MDM) before additional funding be considered. The Office could benefit from expansion.

A paper will be published entitled "Demand for medigap insurance by the elderly: A micro-simulation analysis," in Applied Economics. Authors are Lien-fu Huang, William S. Cartwright, and Teh-wei Hu. This research was supported in part by the contract, Microeconomics of Aging, Health Status, and Conditions, and Health Expenditures (N01-AG-5-2107).

For the Western Economic Association International Conference of June 18-22, 1989, a paper was presented entitled, "The impact of varying medigap insurance coverage on the use of medical services of the elderly." The authors are William S. Cartwright, Teh-wei Hu and Lein-fu Huang. The paper was subsequently submitted for review.

For the Western Economic Association International Conference of June 18-22, 1989, a paper was presented entitled, "The impact of reducing Medicare expenditures on public and private payers: Simulations with a National Health Expenditures Model." Authors are Joseph M. Anderson and William S. Cartwright. This research is an illustration of the sensitivity of the MDM to estimating changes in Medicare benefits and the impact on the rest of the health care system.

A paper entitled, "The effect of chronic disease on work-status of aging males, 55-65," has been completed by William S. Cartwright and Joan Cornoni-Huntley. This paper estimates the impact of heart disease, arthritis, and respiratory disease on the work outcomes of a cohort of males who were initially working at the time of the NHANES I study and who were alive and interviewed at the NHANES Epidemiologic Follow-up Study (NHEFS). Additional work was completed on separate multivariate analysis for those reporting disease.

A draft for Chapter 7 of the Duke Resource Data Book was completed and entitled, "Self Reported Use of Dental, Hospital, and Nursing Home Service." William S. Cartwright, James Beck, Connie Service, Gordon H. DeFries, and Thomas R. Konrad are the authors.

A draft entitled, "Aging, health policy, and moral philosophy" was completed. The author is William S. Cartwright. The paper addresses the problems of individual's rights to health care, the moral functioning of the health care system, and the rationing of health care to the elderly at some predetermined age. Three postulates of policymaking are defined and used to conduct the moral analysis. The policy implications for reforming the U.S. health care system are derived for mandating of health insurance benefits.

The book entitled, The National Institute on Aging Macroeconomic-Demographic Model of Health Care and Consumer Expenditures, is being prepared for printing. The companion publication entitled, Future Health Care Expenditures and Consumer Expenditures has been reviewed and rejected as a separate publication. Instead, demographic scenarios have been extracted from the document and added as an appendix to the first document. The Medicare scenario has been prepared as a paper for the Western Economic Association International Conference.

The Lewin/ICF contracts "Updating and Revising the Macroeconomic-Demographic Model" (NO1-AG-2107) and "Household Formation and Housing" (NO1-AG-5-2106) are being modified to extend the delivery dates at no cost to the Government. The complete model demand system has been estimated by the sub-contractor, Dale Jorgenson of Harvard University and Daniel Sleznik of Texas University. The new base case is being prepared. The draft reports, "Alternative Futures for the Retirement Income System" and "Social Security Funding and Capital Accumulation: Implications of OASDI Trust Fund Build-up for the U.S. Economy" were delivered by the contractor.

A Professional Services Contract was awarded to Professor Lien-fu Huang of Howard University to review long-term care and to develop new theory with regards to insurance and deductibles in health insurance. This will expand theoretical work already completed on optimal coinsurance.

A Professional Services Contract has been awarded to Dr. Teh-wei Hu to deliver a SAS data base and cross-tabulations of the 1985 National Nursing Home Survey this fiscal year.

In a paper entitled, "The impact of varying Medigap insurance coverage on the use of medical services of the elderly," a three-equation, recursive model, is estimated for the demand for Medigap insurance coverage, the probability of medical service use, and the amount of expenses for physician and hospital medical care expenditures. A recursive structure was accepted since the simultaneous equation model was rejected after applying the Wu test. It is found that higher levels of coverage are associated with increased expenditures through higher probabilities of incurring a medical expense and increased levels of expenditures. Those with poor health had a smaller likelihood of having insurance than those with better health status, contrary to the notion of adverse selection. However, those in poor health status who had

obtained insurance tended to purchase more insurance coverage than those with better health status, consistent with adverse selection. Nonwhites were at a disadvantage in terms of the probability of having Medigap insurance and expected medical expenditures. This paper has been submitted for review.

In a paper entitled, "The effect of chronic disease on work-status of aging males, 55-65," a cohort of men aged 55 to 65 years in the National Health and Nutrition Examination Survey I, 1971-75 is studied. These men were re-interviewed in the NHANES I Epidemiologic Followup Survey, 1982-84 at which time work-status of the individual was ascertained. A comparison group of men without self-assessed arthritis, heart disease, or respiratory disease was established. The crude odds ratio indicated that all three chronic diseases were significant in depressing work-status, but after controlling for age, heart disease was no longer significant. In a multiple logistic regression, heart disease was not significant while arthritis and respiratory disease were significant in depressing work status. The interaction between arthritis and respiratory disease was insignificant, and other interactions were not ascertainable because of the small number of cases. It is concluded that chronic disease in late middle age men is associated with reduced work effort in the young-old years from 65 to 75. Reductions in the onset of these diseases could lead to an increase in the potential for work and enhancement of income in this cohort, as well as a reduction in lifetime dependency rates. This paper has been submitted for review.

Research Highlights for FY89

In a paper entitled, "Demand for medigap insurance by the elderly: A micro-simulation analysis," a micro-simulation model is developed to explain and estimate the optimum Medigap insurance coverage for elderly with different levels of insurance premium subsidy. The Medigap risk exposure is estimated from the 1977 National Medical Care Expenditure Utilization Survey, utilizing the Gamma distribution. The theory of expected utility maximization is assumed and the model for health insurance demand is operationalized for hypothetical parameters for risk aversion, the price elasticity of demand, the loading fee, and the subsidy. With the risk aversion parameter at 0.0005, the price elasticity of medical care demand at -0.5, loading costs at 9 percent, without any subsidy, the optimal Medigap coinsurance rate is 0.78; and with a premium subsidy of 60 percent, the coinsurance rate falls to 12 percent. The hypothetical price elasticity of demand is estimated to be between -.44 and -1.02. More than half of the increase in medical expenditure resulting from an increase in premium subsidy from 0.35 to 0.60 is a welfare loss. (Huang, Cartwright and Hu, Applied Economics, 1989, in press.)

CONTRACT

Name and Number: ICF, Incorporated (N01-AG-5-2106)

Title: Household Formation, Housing and the Aging Population

Date Contract Initiated: June 30, 1985

Total Cost of Contract: $252,180

Objectives: The purpose of this contract is to investigate household formation and the interactions with the aging United States population and the economy.

Methods Employed: This work shall involve analysis of appropriate data bases and econometric modeling. The NIA Macroeconomic Demographic Model (MDM) shall be augmented by the resulting behavioral relations developed in the analysis. Thus, a method of integrating household formation with the MDM is a key task in this project. Another particularly important aspect is the interaction of housing and household formation. Because housing and household formation are so closely related, a housing model will be constructed with the NIA MDM. The resultant household formation model and the housing model will permit an examination of the implications of an aging population in the United States.

Significance to Biomedical Research: The NIA supports the MDM which permits study of the relationship between the economic status of the elderly and the national economy. As population aging continues through the 20th century and into the 21st century, the complicated mechanisms of economic dependency and related health effects will be affected both by the evolution of the economy and the income security system. The MDM has recently been augmented by the development of health and consumer expenditure models.

Proposed Course: This work shall involve analysis of appropriate data bases and econometric modeling. The NIA MDM shall be augmented by the resulting behavioral relations developed in the analysis. Thus, a method of integrating household formation with the MDM shall be accomplished under this contract. Additionally, a housing model shall be constructed and integrated with the MDM. The resultant household formation model and the housing population model shall permit an examination of the implications of an aging population in the United States.

CONTRACT

Name and Number: ICF, Incorporated (N01-AG-4-2107)

Title: Updating and Revising the Macroeconomic-Demographic Model

Date Contract Initiated: September 26, 1984

Total Cost of Contract: $253,046

Objectives: The objective is to update and revise the MDM. This will involve both re-estimation and other revisions to the equations and structure of the model in order to update the model from newly available data and from institutional changes in Federal programs. The end result will be an updated new base case for the computer simulation model that can be used for analysis of policy change and population aging. This work shall be consistent with the ongoing modeling.

Methods Employed: The NIA MDM is a complex computer simulation model. It consists of a large FORTRAN program that is over 7,000 lines long and has 43 sub-routines and a main program. The equations that make up this computer simulation model come from mathematical relations of the actuarial and the demographic sciences, as well as behavioral relations from economic science. The behavioral relations are statistically based equations that are estimated from underlying data bases. The equations are conceptually grouped into various models depicting key aspects of the economy. These models are the Population Model, the Macroeconomic Growth Model, the Labor Market Model, the Social Security Model, the Private and Public Employee Models, the Supplemental Security Income Model, and the Medicare Models. Health and consumer expenditures models were recently added.

Significance to Biomedical Research: The demographic structure of the U.S. population is aging. This has profound implications for the nation as an increasing number of elderly survive into older and older ages. The NIA MDM projects a 150 percent increase in those 65 and older from 1980 to 2050. This will affect Federal programs for both health and income security. In particular, health information shall be enhanced through this updating process so that critical aspects of population aging and health policy may be examined with more immediate policy relevance. Further, there will be immediate near term requirements for analyses of the social security system and other private pension systems.

Proposed Course: A *new* base population and adjustment factors derived from the 1980 Census of the U.S. population will be incorporated. An alternative base population shall be developed that is consistent with the Social Security projections. A new set of projections will be constructed for the base case consistent with Census and Social Security projections. A report entitled "Alternative Futures for the Retirement Income System" is being edited.

Biometry Office

The Biometry Office performs a variety of functions involving the development and application of mathematical and statistical methods for EDB Program data on the epidemiology and demography of aging and health. The Office also provides statistical consulting, computing, graphics, and data management services to the other units within EDB as well as other Programs in NIA, other NIH Institutes, other Government agencies, and the private sector.

The developmental activities and achievements of the Office are summarized below by the projects to which they apply.

1. Established Populations for Epidemiologic Studies of the Elderly (EPESE).

   The EPESE projects, described in more detail in the Epidemiology Office Report, were the focus of numerous Biometry Office activities. Biometry Office staff serve as Project Officers for two of the four sites at which these studies are being conducted, New Haven (Yale University School of Medicine) and Duke University School of Medicine. In addition to the administrative duties performed by staff, a number of scientific and technical projects have been conducted.

   A paper by Dr. Brock and colleagues has been submitted for publication on mortality and physical functioning in the first three EPESE sites based on 3 years' follow-up of mortality. The results showed that the ADL, Rosow-Breslau and Nagi scales each separately provided significant prediction of mortality at 3 years' follow-up, but when all three scales were utilized simultaneously, only the Rosow-Breslau scale retained its statistical significance.

   A paper by Mr. Foley and co-authors is being completed currently on use of nursing homes at 3 years' follow-up in the first three EPESE sites. A variety of baseline variables appear to be related to the incidence of nursing home admission: among them, functional status, family status and living arrangements, mental functioning, income and other socioeconomic variables.

   The entire Biometry staff has been active in the production of the upcoming Duke EPESE Resource Data Book. The computing staff has contributed significantly to the production and review of the tables, using the Bureau of Labor Statistics' TPL language for producing tables. They have also produced computer-generated graphics for the book. Two staff members have written text for chapters on physical functioning and demographic characteristics. Another staff member is responsible for the production of the technical appendix on methods, which involves the estimation of standard errors for the survey which account for the complex design of the Duke sample and the fitting of models to smooth the estimates into

curves which are not only accurate representations of the standard errors but are also economical of space in the publication.

The Iowa and New Haven sites are in the field collecting data on driving practices as part of a seventh year telephone-followup contact. Data collection will be completed by the end of October or early part of November 1989. In May of 1989, the project officer for the Yale Health and Aging Project (Mr. Foley) as well as the principal investigator (Dr. Adrian Ostfeld), the project director (Ms. Joanne McGloin) and Dr. John Eberhard from the U.S. Department of Transportation met with Commissioner Lawrence F. DelPonte of the Connecticut Department of Motor Vehicles and successfully arranged for the linkage of DMV data including accident and injury records to the New Haven database. The Principal Investigator for the Iowa 65+ Rural Health Study (Dr. Robert Wallace) has already received a tape of the driving records for the participants in Iowa and will negotiate further with state officials for access to the accident and injury records.

HCFA and NIA have recently established an Interagency Agreement to study patterns of prescription and over-the-counter drug use among the elderly in partial response to HCFA's congressional mandate for prescription drug studies under the Medicare Catastrophic Coverage Act of 1988. Mr. Don Everett is the NIA Project Officer and Dr. Feather Davis, is the HCFA Project Officer. The drug data that have been collected as part of the EPESE contracts will be analyzed to investigate the interrelationships of medication use among the elderly with characteristics such as diagnosis, functional limitations, age, and components of health care services.

Work is continuing on a project to analyze data from the baseline and third follow-up interviews regarding patterns and correlates of performance on the brief mental status questionnaire administered to the EPESE respondents at these two interviews. This analysis addresses one of the important endpoints of the entire EPESE project, that is, change in cognitive function over time.

A team of Biometry Office computing staff led by Ms. Lafferty is conducting a massive data management operation on the EPESE database in preparation for public release of a portion of the data sometime in FY 1990. This activity involves not only editing and cleaning of the data but also preparation of standardized formats in which each EPESE center will provide common data for each of the seven interview files, the vital status file , and endpoint files including mortality, hospitalization and nursing home admissions. Coordination of this activity has consumed a great deal of staff resources to insure that the data are sufficiently accurate and well-documented for public release. It is expected that this activity will continue well into FY 1990 and perhaps beyond.

To alleviate the backlog of requests for computing support for data analysis of the EPESE, a professional services contract was awarded to University Research Corporation to create analytic files for EDB analysts to use in conducting analyses. This contract supported analyses on maintenance of mobility in three older community populations, part I, demographics and chronic conditions, and part II health habits and social networks. In addition, computing support was provided for analyses of weight and mortality and clustering of health conditions in the EPESE populations.

2. National Health and Nutrition Examination Survey (NHANES) and NHANES Epidemiologic Follow-up Survey (NHEFS)

Biometry staff have contributed significantly to several chapters of the forthcoming book on the NHEFS entitled Health Status and Well-Being of the Elderly to be published in 1990 by the Oxford University Press. The chapters on arthritis (Mr. Everett), physical functioning (Mr. Foley and Dr. Brock), stroke (Ms. Losonczy), and nutrition (Mr. Everett) were co-authored by Biometry staff. These chapters provided basic descriptive information and some detailed analyses on the respective conditions as measured in both the original NHANES in 1971-75 and the Follow-up, which was conducted in 1982-84.

Dr. Brock was a co-author on a paper on mortality among diabetics in a national sample, based on data from the NHEFS.

Mr. Everett was a co-author on a paper on the epidemiologic associations of pain in osteoarthritis of the knee, based on data from the NHANES I and the NHEFS. The paper presents results on factors associated with the presence of pain in persons with OA of the knee and the association of knee pain with subsequent mortality and morbidity, including disability, in persons with OA of the knee. (Hochberg, et al., Seminars in Arthritis and Rheumatism, 1989; 18(4)(Supp 2): 4-9.

Mr. Everett was a co-author on a paper on food group consumption reported by the elderly during the NHEFS. This paper provides a basic description of dietary intake patterns of older individuals in the NHEFS, constructed by the creation of common food groups from the NHANES I and NHEFS dietary intake data which used different methods of determining consumption. (Murphy, Dresser and Everett, Journal of Nutrition Education, 1989; in press.)

A paper was presented by Mr. Everett on osteoarthritis and mortality, comparing different analytic strategies, at the World Congress of Gerontology, the XIV Meeting of the International Association of Gerontology in Acapulco, Mexico in June of 1989.

Work is in progress on a number of other papers involving the NHANES and NHEFS studies. One such paper will examine the effects of dietary vitamin E intake in relation to the aging via disease (Ms. Losonczy). The hypothesis is that vitamin E is protective against a variety of conditions associated with aging. Data from the NHANES II are being used to predict various conditions from vitamin E intake, controlling for age and a variety of risk factors.

Other papers are underway on body weight and mortality (Mr. Everett), diet in relation to kidney disease (Mr. Everett), food consumption and functional health (Mr. Everett), and black-white differences in stroke (Ms. Losonczy).

3. Survey of the Last Days of Life

A paper by Dr. Brock and Mr. Foley was published on health status trends in the last year of life. The paper described the results of a series of questions asked of the next-of-kin of a sample of decedents whose deaths occurred in 1984-85 in Fairfield County, Connecticut. Trends in physical, cognitive and sensory function were established from the responses to the set of questions. For decedents with a history of stroke and Alzheimer's disease or other dementia, less desirable trends were associated with physical, mental and sensory functioning, but heart disease was associated with more desirable trends. (Brock and Foley, Proceedings of the American Statistical Association, Social Statistics Section, 1988; 418-423.)

A paper on transitions between residential and care settings in the last three months of life is currently being written by Dr. Brock and Mr. Foley in collaboration with Douglas and Monica Holmes who were responsible for the data collection in the field. These researchers are also collaborating on the writing of a chapter on methodological issues arising in the development of the survey. The latter is to be published in Methodological Issues in Epidemiologic Studies of the Elderly edited by Robert Wallace and Robert Woolson for Oxford University Press.

During FY89 Dr. Brock has participated in interviews and other press coverage of the basic descriptive data from the survey in a variety of settings, following a summary of the basic study data which was published by American Demographics.

Mr. Foley has initiated a series of analyses on long-term care, using data from several EDB studies and related data sources. The risk of institutionalization has been analyzed across five different studies including three of the EPESE sites, The Survey of the Last Days of Life, and the National Mortality Followback Survey. Results were presented last November to the NIA committee on LTC (Chairperson-Matilda Riley, BSR) and will be presented to the National Advisory Council on Aging this

September as part of the NIA report on LTC research and activities. Mr. Foley is currently preparing a manuscript of these findings and will submit the paper to a suitable journal in the near future.

4. Demographic and Epidemiologic Analysis

Dr. Brock made two presentations during FY89 on general demographic and epidemiologic characteristics of the United States older population. The first was at the fall conference of the American Speech-Language-Hearing Association in Washington. In June of 1989 Dr. Brock made the second presentation to the Aging Ear Conference sponsored by the Washington University Department of Otolaryngology in St. Louis, Missouri. In each presentation the latest available data on demographic and health characteristics of the U.S. older population were described in considerable detail, providing some projections to the twenty-first century and emphasizing data on hearing problems derived from the National Health Interview Survey Supplement on Aging (NHIS-SOA) and from the EPESE.

In other demographic analysis, Dr. Brock, Dr. Jack Guralnik of the Epidemiology Office and Dr. Jacob Brody of the University of Illinois collaborated on the writing of a chapter on the demography and epidemiology of aging for the third edition of the Handbook of the Biology of Aging, edited by Drs. Edward Schneider and John Rowe for Academic Press. As with other such efforts, the authors utilized the latest available data from the Census Bureau, the National Center for Health Statistics and EDB Program data for a variety of epidemiologic and demographic characteristics. The data showed continuing declining trends in mortality for the older population and rapid growth for the group age 85 and older, leading to projections into the twenty-first century of ever-increasing numbers of very old persons with declining function and increased use of health care services. (Brock et al., Handbook of the Biology of Aging, 1990, in press.)

5. Consultations and Collaborative Analyses from Other Data Sources

Mr. Everett participated as a co-author in an analysis of data from the NHIS-SOA on comorbidity and its association with disability (see detailed description of the analysis in the Epidemiology Office Report). (Guralnik et al., Advance Data, No. 170, NCHS, 1989.)

Mr. Everett is currently participating in a collaborative study of the epidemiology of the Spondyloarthropathies in Native Alaskan Populations, which involves consultation with NIAMS and the Indian Health Service and collaboration between the United States and the U.S.S.R. The purpose of the study is to

a) determine the prevalence of spondyloarthropathies in selected populations of Alaska and Siberia,

b) describe the spectrum of disease in these populations, and

c) establish groundwork for investigating the role of genetic and environmental factors in the pathogenesis and expression of spondyloarthropathies.

Dr. Brock served as a statistical sampling consultant to the Health Care Financing Administration on the review of proposals for the multi-year Medicare Current Beneficiary Survey to be conducted between 1990 and 1995. This survey seeks to collect a broad spectrum of information on the use of medical services by Medicare beneficiaries and the costs and sources of payment for those services. This is likely to be the first large-scale national survey to utilize computer-assisted personal interviews (CAPI) in a longitudinal study.

6. Statistical Methodology Activities

The Biometry Office, using 1 percent departmental evaluation funds, has developed a contract-supported project to conduct an evaluation study of statistical methodologies for the analysis of longitudinal data from epidemiologic studies. This project proposes to evaluate questions on statistical methodology concerning the analysis of change in variables measured over time in EDB Program longitudinal epidemiologic studies, taking into account measurement error, regression to the mean, use of change scores and the appropriateness of a variety of statistical models which currently exist and are under development. The evaluation shall consist of documentation of theoretical mathematical and statistical properties of the models, actual application of the techniques to EDB Program data on physical functioning of older persons, documentation of availability, appropriateness, and ease of use of software used, and recommendations as to the generalizability of the procedures evaluated. A contract award is anticipated at the end of FY89.

A project on the effect of missing data in the EPESE surveys is continuing. Previous results have shown that retention of survey respondents with item nonresponse provides more accurate estimates of many parameters than conducting analyses on cases with complete data only. A limited simulation study on two-variable regression models led to the above results. Current plans call for an extension of this study to examine simulation results on more complicated data structures and models.

Dr. Brock planned, arranged, and organized a 3-day course on modern statistical methods for categorical data analysis presented by Dr. Gary Koch and Ms. Sandra Stinnett of the University of North Carolina.

All of the data sets used as examples in the course were provided by the Biometry Office, most of them having been generated from EDB data sets.

The NIA EDB Program has jointly participated with other Public Health Service Agencies in the development of new software for the analysis of complex sample survey data which appropriately incorporates the complexities of the sample designs into the analysis of the data. This requires extensions of existing methodology, especially in logistic and proportional hazards regression models, to account for design parameters which do not allow for standard analysis assumptions of independent, identically distributed observations with homogeneous variance. The project seeks alternative methods that allow for computation of confidence intervals for survival and hazard estimates and makes handling time-dependent covariates feasible for large data sets. The project will also result in computer algorithms to carry out the methodology and will make recommendations for the implementation in newly-developed software.

The importance of these activities lies in their applicability to ongoing and future analytic research in the Program. Many of the analyses previously conducted on data taken from complex surveys--the NHANES, its epidemiologic follow-up study, the New Haven and Duke EPESE samples, the Survey of the Last Days of Life and others--have been limited by the availability of statistical techniques which met the assumptions required by the data. In the future, a much wider range of techniques will be available for application to EDB analyses.

7. Computing and Data Processing Activities

Ms. Lafferty developed and monitored a project performed under a professional services contract with the University of Texas Health Science Center at Houston to create an analytic data file for EDB personal computers to be used for analysis of the EPESE database using PC-SAS or SPSS-PC software. A prototype system called UTMOST was developed on a compact disk, write-once-read-many (CD-WORM) optical laser scanning device to store data with variable names and labels already assigned for easy retrieval from the CD-WORM on a personal computer. The data sets, so arranged, could then be analyzed directly on the PC without going through the time-consuming and expensive step of creating SAS data sets on the NIH mainframe computer. The additional value in the system lies in the cost savings attributed to the ability to perform the analysis on the PC at essentially no unit cost. A successful test of the prototype by Biometry staff (Mr. Foley and Ms. Losonczy) led to the creation of similar data sets for the first three EPESE sites for the baseline survey and the vital status files.

Future plans are to extend the UTMOST system to include common data from each follow-up personal interview data set and from the endpoint files of mortality, hospitalization and nursing home utilization.

The Biometry Office has developed a contract project for computer support services for epidemiologic research on aging. This project will provide a variety of computer support services for the EDB Program, primarily involving analytical activities in epidemiologic research on aging. Requirements vary from the development of on-line analysis systems to ad hoc requests utilizing existing statistical software. Additional areas of activity include assistance in the preparation and documentation of public use data tapes and in networking, installation and maintenance of personal computer (PC) systems. More sophisticated applications include the transfer of code for the NIA Macroeconomic-Demographic Model from the NIH mainframe to a PC, and the development of customized software for ongoing research in statistical methodology which requires mathematical computations and simulations. This project will provide substantial aid in alleviating the backlog of computing requests which have built up as the analysis phase of the EPESE projects has grown in intensity. An FY90 award is anticipated.

Members of the Biometry Office staff have developed a center of excellence in the production of high-quality computer graphics for presentations and publications prepared by EDB researchers. Virtually all graphics presentations are produced within the Office using the highly sophisticated Zenographics software and Ventura desktop publishing software. In addition, staff (in particular Ms. Cruz) have provided instruction to other interested EDB personnel in the uses of the various software programs available in this and some other graphics packages.

The computing staff provides valuable assistance to other EDB staff members in maintenance of computing equipment, installation of hardware and software and consultation on computing problems. Lyle Brenner, a summer student who worked during the summer of 1989, was particularly helpful in providing these services as well as computer support for a variety of data analysis activities involving several of the EDB data systems. His evaluation of the UTMOST system was particularly convincing to the analysts who were interested in learning its capabilities.

Research Highlights for Fiscal Year 1989

- Osteoarthritis (OA) is the most common joint disorder; however, it is clear from numerous population studies that many persons with radiographic changes of OA have no symptoms or resulting disability. The availability of national arthritis data, specifically the NHEFS, provide a unique opportunity for epidemiologic research in arthritis. Presented herein are results of analyses conducted by the authors to evaluate (1) factors associated with the presence of pain in persons with OA of the knee and (2) association of knee pain with subsequent mortality and morbidity, including disability, in persons with OA of the knee. (Hochberg et al., Seminars in Arthritis and Rheumatism, 1989;18(4):4-9.)

- Analysis of NHIS SOA data on comorbidity in the older U.S. population revealed that the percent of the population 60 years and older with two or more of the nine common chronic conditions obtained in the SOA was higher for women than men at each older age. Persons having difficulty or needing help with activities of daily living increased with increasing levels of chronic conditions. Likewise, a linear increase was observed in the proportion of persons experiencing none of the nine conditions as compared to those with five or more of them. (Guralnik et al., Advance data from Vital and Health Statistics, No. 170. Hyattsville, MD: National Center for Health Statistics, 1989.)

- Analysis of data from the Survey of the Last Days of Life has described the results of a series of questions asked of the next-of-kin of a sample of decedents whose deaths occurred in 1984-85 in Fairfield County, Connecticut. Trends in physical, cognitive and sensory function were established from the responses to the set of questions asked regarding the decedents' physical, mental and sensory functioning one year, one month and the day before the person died. Some 53 % of the decedents were reported to have been in good or excellent health a year before they died, and almost 60% were freely mobile. Approximately 87% were reported to have had no difficulty with orientation as to their whereabouts or recognizing family and friends and 88% were able to see well enough to watch television or read and hear well enough to carry on conversation. These percentages declined to 24% in good health, 30% freely mobile, 78% with good recognition and orientation, and 77% with good hearing and vision one month before death. The same percentages declined to 11%, 13%, 51%

and 43% for the day before death. For decedents with a history of stroke and Alzheimer's disease or other dementia, less desirable trends were associated with physical, mental and sensory functioning, but heart disease was associated with more desirable trends. (Brock and Foley, Proceedings of the American Statistical Association, Social Statistics Section, 1988; 418-423.)

- Analysis of NHEFS data on mortality among diabetics has shown that over the 9-year follow-up period, the age-adjusted death rates for diabetic men and women were twice the rates for nondiabetics. Some 75% of the excess mortality among diabetic men and 57% among diabetic women was due to cardiovascular disease deaths. After adjustment for age, systolic blood pressure, serum cholesterol, body mass index and smoking, the relative risk of death was 2.3 for diabetic men and 2.0 for diabetic women. The relative risk for diabetics was highest for ischemic heart disease mortality (2.8 for men and 2.5 for women) and lowest for noncardiovascular deaths (1.4 for men and 1.1 for women). When subjects who reported having had a heart attack prior to the baseline examination were excluded from the analysis, the relative risks for ischemic heart disease mortality among diabetics remained substantial (2.4 for men and 2.6 for women). (Kleinman et al., Am j Epidemiol, 1988;128(2): 389-401.)

- The development of a survey data analysis software package that is flexible enough to meet the needs of survey statisticians, as well as research scientists not necessarily schooled in survey sampling, has been developed by the Research Triangle Institute with funding from an EDB interagency agreement with NCHS. The system, designed to provide enhancements to existing software, is written in the 'C' language and provides greater flexibility and portability than previous software packages of this type. the procedures have been implemented on IBM PC's with expanded capacity and on VAX/VMS and IBM/OS computers. Variance estimation and data analysis techniques not previously available in software packages are among the many modifications incorporated into the new system. (LaVange et al., Proceedings of the American Statistical Association, Section on Survey Research Methods, 1988.)

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 07010 01 EDBP

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Driving Practices and Driving Records Related to EPESE Participants

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Daniel J. Foley, M.S.

COOPERATING UNITS *(if any)*

National Highway Traffic Safety Administration
Department of Transportation

LAB/BRANCH

Biometry Office

SECTION

Epidemiology, Demography, and Biometry Program

INSTITUTE AND LOCATION

NIA, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unraduced type. Do not exceed the space provided.)*

Investigators from the University of Iowa (Iowa 65+ Rural Health Study) and Yale University (Yale Health and Aging Project) will pretest a telephone questionnaire to gather data on driving and pedestrian practices among surviving participants in each of these two Established Populations for Epidemiologic Studies of the Elderly (EPESE) sites. In some cases, the driving practices will be ascertained from a next-of-kin on those recently deceased members and those unable to participate due to health or other reasons. After pretesting the instrument, investigators will conduct the full scale survey among the eligible participants and link this data to the existing database. The newly created database will be made available to staff at the National Highway Traffic Safety Administration for collaborative analyses of risks for driving accidents and pedestrian accidents. In addition, investigators will work with each state's Division of Motor Vehicles to link the DMV record data to the database at each site.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 AG 07020 01 EDBP

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Patterns of Drug Use Among the Elderly

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Donald F. Everett, Jr., Statistician, EDBP, NIA
Feather Ann Davis, Ph.D., Office of Research & Demonstrations, HCFA

COOPERATING UNITS *(if any)*

Health Care Financing Administration

LAB/BRANCH

Biometry Office

SECTION

Epidemiology, Demography, and Biometry Program

INSTITUTE AND LOCATION

NIA, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
	.10	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Analysis of prescription and over-the-counter drug data that have been collected by the four contracts that comprise the Established Populations for Epidemiologic Studies of the Elderly (EPESE) will be supported by an interagency transfer of funds. The existing contracts will be supplemented to focus on such analyses.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 06080 02 EDBP

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Complex Survey Analytical Software Development

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Dwight B. Brock, Ph.D., Chief, Biometry Office, EDBP, NIA
Lester R. Curtin, Chief, Statistical Methods Staff, ORM, NCHS

COOPERATING UNITS *(if any)*

National Center for Health Statistics

LAB/BRANCH

Biometry Office

SECTION

Epidemiology, Demography, and Biometry Program

INSTITUTE AND LOCATION

NIA, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
	.05	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of this project is to support the development of a comprehensive software package that will specifically address the statistical analyses of survey data for the type of sample designs used by NCHS and PHS. The Phase I procedures for (1) estimation of basic statistics and functions of those basic statistics, (2) generation of variances and covariances for those basic statistics and functions, and (3) variance components for each stage of sampling, have been installed on the NCHS computer, and documentation in the form of a user's manual has been delivered to NIA. In addition a version of the software for personal computers has been delivered to NCHS and NIA. Phase II involves software development for the general linear model, logistic regression and survival analysis using the Cox proportional hazards model.

Publications: LaVange LM, Shah BV, Barnwell BG, and Killinger JF. SUDAAN: A comprehensive software package for survey data analysis. In Proceedings of the American Statistical Association, Statistical Computing Section. Wash., D.C., 1988, in press.

PHS 6040 (Rev. 1/84) GPO 904-917

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 07030 01 EDBP

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

NHANES III: Health of Older Persons (Baseline Survey)

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Donald F. Everett, Jr., Statistician, EDBP, NIA
Robert Murphy, Division of Health Examination Statistics, NCHS

COOPERATING UNITS *(if any)*

National Center for Health Statistics

LAB/BRANCH

Biometry Office

SECTION

Epidemiology, Demography, and Biometry Program

INSTITUTE AND LOCATION

NIA, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
	.05	

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

NHANES III is planned as a multi-agency collaborative survey designed to estimate the prevalence of diseases and risk factors in some 40,000 Americans. Special efforts are being directed to collection of data from interviews and examinations for the population over age 60 and the oldest-old.

NCHS will conduct a dress rehearsal and carefully monitor survey operations, review response rates, review quality control materials and develop and institute corrective steps when necessary, and review preliminary distribution of results.

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