National Institute on Aging.
Report.

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Overview of Epidemiology, Demography, and Biometry Program
National Institute on Aging

Dr. Jacob A. Brody, Director of the Epidemiology, Demography, and Biometry Program, since its origin in 1978, retired from an illustrious career in the Public Health Service to become the Dean of the School of Public Health at the University of Illinois at Chicago.

Since 1978 the EDB Program has progressed from initially recognizing the lack of population estimates of prevalence and incidence of health problems and impairments of the elderly to meeting this deficiency by initiating several population studies of the elderly. These studies have now been established and are accumulating valuable prospective data. The direction and efforts of the EDB Program must now turn to the analysis of this vast amount of data to provide much needed information on the leading health problems of the elderly. These analyses should identify associated factors for further investigation. They should generate hypotheses to define the actual risk factors of developing the health problems. The ultimate goals of this research are the transfer of knowledge to the implementation of programs for prevention, and the provision of solutions for maintaining persons at their optimal ability for independent living and life satisfaction in the later years.

While the staff has turned its attention to analyses of the accumulated data, effort has also been focused on continuing the data collection on the major research projects, the Established Populations for Epidemiologic Studies of the Elderly (EPESE), the National Health and Nutrition Examination Survey (NHANES I) Epidemiologic Followup Survey, the Survey of the Last Days of Life, the various aspects of the Framingham Study, and initiation of a few new projects. Although this is a logical and potentially profitable direction for the Program to take, the ability to be successful is severely handicapped by the limited number of full-time permanent professional employees within the Program. An example is the NHANES Followup Project which was initiated by NIA, and for which NIA provided the major support. The other eight institutes which have participated in the NHANES Followup have initiated a large number of analytic investigations, whereas the EDB/NIA may not be able to produce equivalent analyses, since there are so few people to do them. The Program has dedicated a considerable effort to the NHANES Followup and would like to have the visability derivable from the publication of results, but the current staffing situation may prohibit that outcome.

The EPESE is proceeding with the analysis of data being collected prospectively. The major endpoints were defined as mortality, hospitalization, admission to nursing home, and disabilities. Analyses related to these endpoints have been labeled "core analyses." The definitions and responsibilities for studies of related demographic characteristics and exposure variables have been assigned during FY 1985. A fourth EPESE project has been initiated in Durham, North Carolina to study a predominantly black population of elderly persons. The first year, a planning year, included pretesting the baseline survey instruments and developing field procedures. The staff of this project has been integrated into the administrative scheme of the other three EPESE projects, a representative having been assigned to each of the major EPESE working committees.

The EPESE Resource Data Book is nearing completion and publication is anticipated during this fiscal year. A paper on the methodologic issues and preliminary findings on the epidemiology of disability in the oldest old was published in the Milbank Quarterly. This publication was developed from the collaboration of the researchers at the three original EPESE locations and EDB staff. The three original EPESE projects, which were to end on June 30, 1985, were awarded an extension of 3 years (to fiscal year 1988). The contracts included support for adding into the East Boston cohort all persons who have become 65 since the study began. This is the only site that is continuing to admit participants into the study population as they become 65 years of age. Also, the extension contract for the University of Iowa included continued followup of the nursing home population which the Iowa investigators interviewed at the time of the baseline survey.

Plans are being developed for specific research aimed at the oldest old participants of all four EPESE sites. These plans include indepth studies of nursing home admissions and clinical evaluation of specific health problems. The field work for the NHANES I Epidemiologic Followup was completed in 1984 and the final data tapes have become available to the participating institutes. A committee to organize publications from this data set has been functioning. Several writing committees with representation from multiple institutes are progressing on specific analyses. The EDB staff is involved with analyses in the areas of hypertension, disability, cognitive functioning, osteoarthritis, hearing, sleep complaints, height/weight, and other subjects. A major area of investigation is nutrition and dietary behavior. The EDB staff is working with experts through professional services contracts to describe eating patterns of the elderly and relate these to morbidity and mortality.

Studies of dementing diseases continue to be a major focus of activities during FY 1985. Preliminary data from the study in East Boston (The Natural History of Senile Dementia) suggests the rates of Alzheimer's disease are substantially higher than expected among the East Boston elderly population. Analyses of these data are in progress and are expected to be published in the final quarter of this fiscal year. Analysis of the data from the Framingham Dementia Study will be initiated early in FY 86. These analyses will include the clinical diagnosis of dementia.

Dr. Mary Farmer has completed an analysis of the Framingham data on the relationship of concurrent and prior blood pressure with levels of cognitive functioning which fails to confirm an association between elevated blood pressure and poor cognitive functioning.

The EDB staff has published several papers from the ongoing studies. Dr. Farmer and other investigators published an important paper in the American Journal of Public Health on the incidence of hip fractures by age, sex, and race. Papers are being developed by other members of the staff on the occurrence of digitalis use among the EPESE subjects, and studies of self assessment of hearing vs. pure

tone audiometry, the relationship between sleep problems and dementia, the relationship of hearing ability and bone density, and correlates, predictors, and prognostic significance of varicose veins in later life from the NHANES I Epidemiologic Followup Survey data.

The pretest of the Survey of the Last Days of Life was completed and the results analyzed. Revisions were made to the questionnaire and the main study went into the field in January 1985. Data collection is proceeding satisfactorily with a high degree of cooperation from respondents, physicians, and health facilities and low rates of item nonresponse and missing data. The Program has supported and assisted in the development of the National Mortality Followback Survey. This is an appropriate investment of time since the study is strongly related to the EDB project entitled, "Survey of the Last Days of Life" and will provide national norms to which we may compare our data.

The pretest results from the NCHS study of nursing home admissions in the National Nursing Home Survey (NNHS) have been received. The results of the study indicated that it was not feasible to include an admissions cohort in the NNHS. Instead, a sample of nursing home residents and a next of kin for each sample resident will be interviewed concerning the resident's history of nursing home admissions up to the time of the NNHS. This retrospective design is to replace the original prospective approach in describing paterns of admission, discharge, and length of stay of a representative sample of persons admitted to nursing homes. The EDB Program continues to work with NCHS on the planning and support of this study.

An important responsibility of the Biometry Office is the development of statistical methodology. A study completed through a professional services contract examined nonrandom item nonresponse for the Iowa EPESE baseline survey. The results showed that many of the CES-D depression scale questions had item nonresponse rates characterized by age, sex interactions and virtually all responses from females were affected by the age of the respondent. The nonrandom associations of other items were also reported. It is concluded that imputation for missing values is a viable technique for remedying the incomplete data due to item nonresponse in the Iowa study. These results may apply to the other locations as well. Methodology is also being developed for the analysis of the NHANES Followup data as well as other methods for analyzing longitudinal data.

The EDB staff have used other national data sets, primarily integrating the data into ongoing EDB research. In particular, the macroeconomic demographic model has coordinated data from the Health Care Financing Administration, the Social Security Administration, the National Center for Health Statistics and the National Center for Health Services Research. Types of health expenditures and sources of funding have been studied by age and sex. A project entitled "Household Formation, Housing, and Aging Population" was initiated to study the rapidly changing patterns of household formation and housing tenure among the elderly. The study entitled, "Aging, Health and Consumer Expenditures," was extended this year for the purpose of re-estimating data which underly the consumer expenditures model. Simultaneously, the "Health Expenditures and Aging

Population" contract was extended to permit the estimation of the health expenditures model in conjunction with the consumer expenditures model. Microeconomic research is now being developed within the section focusing on studies of wealth. Work has begun to study the wealth-age profile with the inclusion of rights to private pensions and social security.

The project entitled, "The Evaluation of Senile Dementia Costs," has resulted in several manuscripts describing the cost of dementia in the elderly and related methodological issues for estimating cost of illness in the elderly. Efforts have been developed for international collaborative work. Plans for collaborative work are being established by Dr. Cornoni-Huntley with the United Kingdom which may allow for the collection of statistics comparable with the EPESE projects. Also, Dr. White has established ties with Japan which may lead to comparative studies related to dementia. There are also possibilities of collaborative work with Sweden and Italy. Such projects could provide not only comparison of prevalence and incidence data but a test of replication of identified associated factors.

The EDB Ad Hoc Scientific Advisory Committee, constituted in fiscal year 1982, continues to review our Program and is assuming an increasing role in our planning process. The primary purpose of the April 16, 1985, meeting was to review the current status and progress of ongoing research and to review concept clearance for two proposed projects: Microeconomics and Hip Fracture Risk Factor Study in the Breast Cancer Demonstration and Detection Program Followup. Reports describing the major research projects were favorably received. Both proposed projects were unanimously approved. It was decided that because of budget constraints we would hold one meeting each year. The next meeting is scheduled for April 8, 1986.

The EDB Program continues to be alert to the benefit of training programs for the staff. Ms. Paulette Campbell is currently completing her year as a Trainee Program Analyst. She has been reclassified as a Program Analyst and has taken over a substantial part of the administrative burden previously born by the scientific staff. As the training period is completed, she will assume an even greater responsibility for the EDB contract administration.

The EDB Program has benefitted greatly from the enthusiastic assistance of part-time employees: Ms. Katherine Dorton, University of Maryland, Mr. Thang Le, George Washington University, and Mr. Bao Loc Le, high school student from Dalton, Ohio.

The progression of the Program is on target but the current ability to attain the results is highly questionable. The lack of professional staff and associated support staff severely limits the output, in particular, the analysis of the vast data library accumulated through thoughtfully developed and well designed projects. These projects were initiated with the anticipation of a growing intramural program in epidemiology, demography, and biometry. The current size of the Program staff is unable to meet the demand for analysis of the vast amount of existing and accumulating data.

Overview of Epidemiology Office

Meetings to develop and exploit the research potentials of the four Established Populations for Epidemiologic Studies of the Elderly (EPESE) (AG-0-2105; AG-0-2106; AG-0-2107; and AG-4-2110) were held in Bethesda, December 17, 1984; March 14, April 23, July 8-9, 1985; and in Chicago, October 1984. Meetings were also held in conjunction with the American Statistical Association meeting in Philadelphia, and the American Public Health Association meeting in Anaheim. These were focused on conjoint analysis of specific data, planning for continuation of the interval of surveillance for an additional 3 years, resolution of methodologic issues, and review of proposed analyses and reports. The fourth EPESE project (Piedmont Health Survey of the Elderly - PHSE), in a predominantly black population in North Carolina, got under way during this fiscal year. Instruments were developed and pretested, specific research goals were defined, and coordination with the three existing EPESE projects developed. The smooth start of this new EPESE and its integration into the NIA-EPESE research program was largely the result of Dr. Mary Farmer's able management. A considerable effort was required to complete planning for extensions of the three primary EPESE projects, and to plan for specific research aimed at the "oldest old" participants at all four sites. It was decided that certain analyses must be undertaken in a systematic and coordinated fashion (the core analyses), to be certain that these are promptly and appropriately published. The definitions and assignments for these analytic tasks were accomplished during fiscal year 1985. They include fundamental descriptive and analytic studies relative to deaths, hospitalizations, nursing home events, and physical and cognitive disabilities. In addition, the work on the EDB Program EPESE Resource Data Book continued, with completion of all tables, graphs, and narrative components of that document. Other reports and presentations based on EPESE data were generated at each of the three sites as well as from the EDB staff.

The following publications are a result of the research at the EPESE centers in fiscal year 1985:

Branch, L.G., Scherr, P.A., Cook, N.R., and Taylor, J.O.: Functional status and service use among a community sample of elderly veterans. In: Wetle, T, and Rowe, J.W. (Eds.): Older Veterans: Linking VA and Community Resources. Cambridge, Harvard University Press, 1984, pp. 26-320.

Lavsky-Shulan, M., Wallace, R.B., Kohout, F.J., Lemke, J.H., Morris, M.C., and Smith, I.M.: Prevalence and functional correlates of low back pain in the elderly: The Iowa 65+ Rural Health Study. J Am Geriatr Soc. 33(1)23-28, 1985.

Loening-Baucke, V. and Anuras, S.: Effects of age and sex on anorectal manometry. Am J Gastroenterology. 80(1)50-53, 1985.

Mobily, K.E., Leslie, D.K., Wallace, R.B., Lemke, J.H., Kohout, F.J., and Morris, M.C.: Factors associated with the aging leisure repertoire: The Iowa 65+ Rural Health Study. J Leisure Research. 16(4)338-43, 1984.

Wallace, R.B.: Drug utilization in the rural elderly: Perspectives from a population study. In: Moore, S.R. and Teal, T.W. (Eds.): Geriatric Drug Use--Clinical & Social Perspectives. New York, Pergamon Press, 1985, pp. 79-85.

Wallace, R.B., Lemke, J.H., Morris, M.C., Goodenberger, M., Kohout, F., and Hinrichs, J.V.: Relationship of free-recall memory to hypertension in the elderly. The Iowa 65+ Rural Health Study. J Chron Dis. 38(6)475-81, 1985.

Excellent progress has been accomplished at all three of the primary EPESE sites with regard to: collection and coding of mortality data; acquisition and coding of hospitalization data using HCFA tapes; identification of nursing home events; continued participation of subjects through a second telephone contact and into the second cycle of household interviews; and comparable coding of prescription drugs identified during the household interview. Substudies are well under way at each site relating to a diversity of topics. The process of registering and interviewing "new" participants who have become 65 since the study began (i.e., the successive cohort component of the East Boston study) is progressing well. Information concerning nursing home events beginning to accrue at each site is especially interesting and promises to provide unexpected insights into this aspect of health care. The fourth EPESE got under way during this year with development and pretesting of interview instruments, further definition of the target population, and completion of OMB clearance tasks.

During this fiscal year the final data tapes from the NHANES I Epidemiologic Followup Survey (Y01-AG-9-0018) became available and analyses began. Several committees with representation from all of the involved institutions met to discuss specific analyses, and several of these began. EDB staff are guiding or are involved in analyses related to mortality, hypertension, disability, weight, cognitive functioning, arthritis, hearing, sleep complaints, and other subjects. The EDB Program has initiated plans to publish a book which will summarize findings from the NHANES I Epidemiologic Followup Survey. This book will provide new information on the epidemiology of problems of aging and will inform the scientific community about the contents of the data set in order to facilitate its use by other investigators. A workshop for all of the authors is planned for September 10, 1985. Authors will meet with Dr. Huntley and present the anticipated contents of their respective chapters. Small group discussions will be arranged for those authors whose chapters appear to overlap in content. Professional services contracts will be used to pay travel, per diem, and fees for six of the authors who are working in various universities around the country and who are familiar with the NHANES I data set. Several more workshops are planned for FY 1986. A conference is planned for the end of 1986, when the book will be presented to the public.

In the first and second quarter of FY 1985, EDB staff were actively involved in the planning of a National Cancer Institute (NCI) study which would involve the followback of approximately 60,000 women seen several years earlier as part of a breast cancer demonstration program. Specific studies were planned by EDB staff related to the determinants and predictors of osteoporosis and hip fracture. In the third quarter of the fiscal year the National Cancer Institute announced

that it was deferring this study because of unexpectedly high costs and limited personnel. We hope that the investigation may be revived at some future date so that the NIA studies can be carried out as originally planned.

Dementing diseases continued to be a major focus of activity during FY 1985. The study in East Boston (Natural History of Senile Dementia, AG-1-2106) has produced rather startling results. Based on the approximately 500 subjects examined as part of the study, the prevalence of moderate to severe cognitive impairment in the noninstitutionalized East Boston population over 65 is substantially higher than has been reported in other studies. In addition, approximately 80 percent of the persons identified as suffering from moderate or severe cognitive impairment were also identified as having Alzheimer's disease (definite or probable on the basis of the clinical evaluation). Overall, these data suggest that rates of Alzheimer's disease are substantially higher than expected among East Boston's elderly. Further analyses of these data are currently under way and are expected to result in the generation of manuscripts for publication in the final quarter of this fiscal year.

The Framingham Dementia Study (YO2-AG-2-0040) is now entering a phase when analyses related to the clinical diagnosis of dementia are becoming possible. An initial examination of the performance of study participants on a dementia screening test was presented at a national neurology meeting in Texas. In March, the involved investigators from Boston University, NHLBI, and NIA met in Bethesda to review progress to date and to plan the course of future investigations. A specific series of tasks and investigative goals have now been defined. In addition to a methodologic paper in press in the Journal of Chronic Diseases, three other analyses are now nearing completion: a presentation of neuropsychological test data from cycle 14/15 (first author is Dr. Mary Farmer); a related paper which focuses on the relative effects of education and age, and uses a composite score based on the eight tests given in cycle 14/15 (first author is Dr. Lon White); and a manuscript relating concurrent and prior blood pressures with level of cognitive function functioning at cycles 14 and 15 (first author is Dr. Farmer). This last mentioned paper is especially important in that it fails to confirm an association between elevated blood pressure and poor cognitive functioning.

In October 1984, Dr. White was invited to a meeting in Tokyo, the purpose of which was to encourage and facilitate collaborative and cooperative studies on aging between the United States and Japan. During that visit Dr. White met with a number of prominent Japanese scientists involved in studies on dementia. Contact was also made with representatives of the Tokyo Metropolitan Institute of Gerontology, an institution with which the NIA has established an agreement for reciprocal scientific activities. Also on this trip Dr. White discussed international epidemiologic research on dementia and the possibility of initiating comparative studies among Japanese subjects residing in the continental United States, Japan, and Hawaii. The possibility of NIA support for such studies is currently being considered, with NIA extramural staff members playing a prominent role.

A landmark paper by Dr. Farmer and other investigators was published in the American Journal of Public Health and has provided information on the incidence of hip fractures by age, sex, and race with a precision previously unavailable.

Dr. Guralnik, an EDB Program staff member who is also a PHS Epidemiology Trainee, is now completing his formal training at the School of Public Health in Berkeley, California. His doctoral thesis involves the predictors of disability, poor health, and good health in the Alameda County Study population. At the EDB Program these efforts will be extended to similar studies using the data sets available in Bethesda, and will result in publications comparing the predictors of both ill health and good health in several different populations.

A study collaboratively designed and executed by Dr. White and Dr. Andrea LaCroix defined the occurrence and correlates of digitalis use among EPESE subjects. A manuscript resulting from these analyses is currently in preparation, and results will be presented at the APHA meeting in November 1985.

A study based on NHANES I data related to hearing (pure-tone audiometry and self-assessment of hearing) was carried out to examine the sensitivity and specificity of self-assessment. These investigations, directed by Dr. Tatiana Kudrjavcev (on detail from NINCDS from August 1984 to July 1, 1985), are of additional interest because of their presentation of data related to pure-tone hearing thresholds by age, sex, education, and degree of self-perceived hearing impairment.

The EDB Program provided a special training opportunity for several individuals at various phases in their professional careers. Dr. Mary Farmer, continuing her staff fellowship with the EDB Program, has become an indispensable member of our research team and has continued to carry out her work at the highest level of excellence. Ms. Debbie Moritz (Ph.D. candidate from Yale) spent considerable time with us as a guest worker involved in the analysis and planning of studies on sleep problems and dementia. Ms. Toni Miles, a senior medical student from Howard University, spent one month working on anthropometric data of utility for evaluating the nutritional status of elderly persons. Dr. Roberta Bergman (a medical intern from Bellevue Hospital, New York) spent one month with us working on item non-response in survey questionnaires, and on the planning of studies related to superior health. Ms. Yuko Palesch, a doctoral candidate in statistics at George Washington University, has been a guest worker over a period of some months and has generated some very interesting data related to the occurrence of varicose veins. These initial observations now serve as the foundation of a planned study on the correlates, predictors, and prognostic significance of varicose veins in later life. Ms. Dorly Deeg, an epidemiologic researcher and doctoral candidate from Erasmus University (Rotterdam, the Netherlands), spent one week visiting our Program, during which she presented the results of her own research on the predictors of longevity. Dr. Andrea LaCroix (RN, cardiovascular fellow, and recent Ph.D. in epidemiology from the University of North Carolina) spent a time with us as a guest worker becoming familiar with EDB research and approaches, and later was able to complete a

series of specific tasks related to an epidemiologic study on digitalis, the development of new investigations of the EPESE "oldest old," and epidemiologic analysis of NHANES data. Dr. Tamara Harris (NRSA candidate) was also a guest worker with EDB at intervals during the year.

Epidemiology Office Research Highlights, FY 1985

- EPESE - new study established at Duke University in a predominantly black community--design, instruments, clearances, and pretesting all completed
- EPESE - 3-year extensions of surveillance period approved
- EPESE - plans begin for in-depth studies of the "oldest old" participants
- EPESE - many analyses completed or under way; Resource Data Book expected to go to press in final quarter this fiscal year
- NHANES I Epidemiologic Followup Survey - plans for book formalized, authors working on assigned components
- NHANES I Epidemiologic Followup Survey - all data tapes received and analyses for many studies begin
- Natural History Of Senile Dementia - first wave (approximately 500) of clinical evaluations completed, second wave begins. Analyses show unexpectedly high prevalence of presumptive Alzheimer's disease
- Framingham Dementia - first wave of clinical evaluations of screening test failures nearly complete. Survival and performance on the MMSE screening test both predicted by scores on the neuropsychologic tests given 5 years earlier
- Hip Fracture - report on incidence by age, sex, and race published in the American Journal of Public Health, (Farmer, et al.)
- International Ties - Dr. Cornoni-Huntley established ties with the United Kingdom which may allow comparative studies with EPESE. Dr. White established ties with Japan which may allow comparative studies related to dementia

CONTRACT

Name and Number: YALE UNIVERSITY (NO1-AG-0-2105)

Title: Established Populations for Epidemiologic Studies of the Elderly (EPESE)

Date Contract Initiated: June 30, 1980

Current Annual Level: $600,000

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. Studies are to be completed on problems of pain, vision, hearing, sleep, drug use, constipation, social support and other pertinent areas.

Methods Employed: The project shall include cross-sectional and prospective studies in a carefully defined and accessible population using standard field and analytical techniques. Yearly surveillance of the population will be included.

Major Findings: Participants at each site have been monitored for deaths, hospitalizations, and nursing home events by community surveillance and yearly telephone interviews. EDB staff and the investigators at each locality worked in close cooperation to develop the methods and instruments for these tasks.

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. 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. High priority short term studies will be encouraged.

Proposed Course: The contract was extended through FY87. Extensive work has been accomplished on coding of hospitalization data using HCFA tapes; and identification of nursing home events. Participation of subjects continues through a second followup (telephone interview) and into the third contact (household interviews). Substudies are well underway relating to a diversity of each site is especially interesting and promises to provide unexpected insights into this aspect of health care.

Publication: Cornoni-Huntley, J.C., Foley, D.J., White, L.R., Suzman, R., Berkman, L.F., Evans, D.A., and Wallace. R.B.: Epidemiology of disability in the oldest old: Methodologic issues and preliminary findings. Milbank Memorial Fund Quarterly/Health and Society. 63(2)350-76, 1985.

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: $700,000

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. Studies are to be completed on problems of pain, vision, hearing, sleep, drug use, constipation, social support and other pertinent areas.

Methods Employed: The project shall include cross-sectional and prospective studies in a carefully defined and accessible population using standard field and analytical techniques. Yearly surveillance of the population will be included.

Major Findings: Participants at each site have been monitored for deaths, hospitalizations, and nursing home events by community surveillance and yearly telephone interviews. EDB staff and the investigators at each locality worked in close cooperation to develop the methods and instruments for these tasks.

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. 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. High priority short term studies will be encouraged.

Proposed Course: The contract was extended through FY87. Extensive work has been accomplished on coding of hospitalization data using HCFA tapes; and identification of nursing home events. Participation of subjects continues through a second followup (telephone interview) and into the third contact (household interviews). Substudies are well underway relating to a diversity of each site is especially interesting and promises to provide unexpected insights into this aspect of health care.

Publication: Cornoni-Huntley, J.C., Foley, D.J., White, L.R., Suzman, R., Berkman, L.F., Evans, D.A., and Wallace. R.B.: Epidemiology of disability in the oldest old: Methodologic issues and preliminary findings. Milbank Memorial Fund Quarterly/Health and Society. 63(2)350-76, 1985.

CONTRACT

Name and Number: PETER BENT BRIGHAM HOSPITAL (NO1-AG-0-2107)

Title: Established Populations for Epidemiologic Studies of the Elderly (EPESE)

Date Contract Initiated: June 30, 1980

Current Annual Level: $900,000

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. Studies are to be completed on problems of pain, vision, hearing, sleep, drug use, constipation, social support and other pertinent areas.

Methods Employed: The project shall include cross-sectional and prospective studies in a carefully defined and accessible population using standard field and analytical techniques. Yearly surveillance of the population will be included.

Major Findings: Participants at each site have been monitored for deaths, hospitalizations, and nursing home events by community surveillance and yearly telephone interviews. EDB staff and the investigators at each locality worked in close cooperation to develop the methods and instruments for these tasks.

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. 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. High priority short term studies will be encouraged.

Proposed Course: The contract was extended through FY87. Extensive work has been accomplished on coding of hospitalization data using HCFA tapes; and identification of nursing home events. Participation of subjects continues through a second followup (telephone interview) and into the third contact (household interviews). Substudies are well underway relating to a diversity of each site is especially interesting and promises to provide unexpected insights into this aspect of health care.

Publication: Cornoni-Huntley, J.C., Foley, D.J., White, L.R., Suzman, R., Berkman, L.F., Evans, D.A., and Wallace. R.B.: Epidemiology of disability in the oldest old: Methodologic issues and preliminary findings. Milbank Memorial Fund Quarterly/Health and Society. 63(2)350-76, 1985.

CONTRACT

Name and Number: DUKE UNIVERSITY MEDICAL CENTER (NO1-AG-4-2110)

Title: Established Populations for Epidemiologic Studies of the Elderly (EPESE)

Date Contract Initiated: September 30, 1984

Current Annual Level: -0-

Objectives: Duke University Medical Center will study an elderly population of at least 4500 noninstitutionalized persons, 65 years of age or older, and of which at least 50 percent is black and approximately 30 percent to 40 percent is white. The population shall be 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 will be conducted. Investigators will conduct 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. During the first year the population shall be defined ecologically in terms of social, political, and demographic characteristics; it shall also be necessary during this first year to establish working relationships with the public and professional groups within this population.

Major Findings: Instruments were developed and pretested, specific research goals were defined, and coordination with the three existing population studies developed.

Significance to Biomedical Research: The NIA is at present 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, are not fully representative of the U.S. elderly, specifically, they do 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: A baseline survey of the population shall be planned during the first year and conducted in the second year to obtain baseline data and an estimate of the participation rate for the specific problem-related studies. The 2nd through the 6th years shall be devoted to continual surveillance of the population, analysis of data, and development and completion of problem-related studies. A final household interview shall be conducted in the 5th year.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 02010 07 EDBP

PERIOD COVERED
October 1, 1984 to September 30, 1985

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Followup of National Health and Nutrition Examination Survey I (NHANES I)

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

PI: Joan Cornoni-Huntley, Ph.D., M.P.H.
Acting Deputy Associate Director, EDBP, NIA

COOPERATING UNITS *(if eny)*
National Center for Health Statistics, Division of Analysis; NCI; NHLBI; NIADDK, NIMH; NIAAA; NIAID; and NINCDS.

LAB/BRANCH
Epidemiology Office

SECTION
Epidemiology, Demography, and Biometry Program

INSTITUTE AND LOCATION
NIA, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.40	.20	.20

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 design and complete a followup of persons examined in the HANES I to study how factors previously measured relate to the health conditions that have developed since the survey. The three major areas for prediction of outcome are 1) nutrition 2) risk factors for chronic disease and 3) health care utilization. The survey will have a household interview including self-reporting of health conditions, utilization of health servics and behaviorial and social status plus some physical measurements as blood pressure, height, and weight.

The field work for the NHANES I Epidemiologic Followup was completed in 1984 and the final data tapes have become available to the cooperating units. NIA/EDB staff are involved in analyses in the areas of hypertension, disability, cognitive functioning, osteoarthritis, hearing, sleep complaints, height/weight, and other subjects. A major area of investigation is nutrition and dietary behavior. The EDB Program is involved in publishing a book which will summarize findings from the NHANES I Epidemiologic Followup Survey.

Continued Followup of the Elderly 1986 is underway. The first half of the pretest of the telephone interview is completed. The continued followup telephone interviews will be completed in fiscal year 1986. The response rate continues to be very high.

PHS 6040 (Rev. 1/84)

GPO 914-918

CONTRACT

Name and Number: PETER BENT BRIGHAM HOSPITAL/
EAST BOSTON NEIGHBORHOOD HEALTH CENTER (N01-AG-1-2106)

Title: Senile Dementia: Natural History in a Noninstitutionalized Population

Date Contract Initiated: June 16, 1981

Current Annual Level: $400,000.

Objectives: The objective of this study is to describe the course of general health and cognitive decline in a group of SDAT victims and controls.

Methods Employed: Persons suspected of being demented because of performance on a screening examination will receive a neurological and neuropsychological evaluation. SDAT cases and a number of matched controls will then be reexamined at yearly intervals over a period of approximately 3 years; thereafter the cases and controls will be followed as defined by their participation in another EDBP study (EPESE)--for death, hospitalization, and institutionalization end points.

Major Findings: Based on the approximately 500 subjects examined as part of the study, the prevalence of moderate to severe cognitive impairment in the noninstitutionalized East Boston population over 65 is substantially higher than has been reported in other studies. In addition, approximately 80 percent of the persons identified as having Alzheimer's disease (definite or probable on the basis of the clinical evaluation). Overall, these data suggest that rates of Alzheimer's disease are substantially higher than expected among East Boston's elderly.

Significance to Biomedical Research/Justification: This study will provide a better understanding of the prognosis and clinical course of SDAT.

Proposed Course: Further analyses of these data are currently under way and are expected to result in the generation of manuscripts for publication in the final quarter of this fiscal year.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 04003 04 EDBP

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Dementing Illnesses in the Framingham Heart Study

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

Lon R. White, M.D., M.P.H.
Chief, Epidemiology Office, EDBP, NIA
Mary E. Farmer, M.D., M.P.H.
Senior Staff Fellow, Epidemiology Office, EDBP, NIA

COOPERATING UNITS *(if any)*

NHLBI

LAB/BRANCH

Epidemiology Office

SECTION

Epidemiology, Demography, and Biometry Program

INSTITUTE AND LOCATION

NIA, NIH, Bethesda, MD 20892

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.)*

Demented subjects are currently being identified by a two-phase evaluation: administration of the screening test as part of the regular biennial examination, coupled with neurological and neuropsychological evaluations of participants who fail the screening test. A second group of dementia cases will be identified from among recently deceased study participants based on: (a) poor perfromance on neuropsychological tests administered approximately 5 years ago, (b) review of medical records, and (c) telephone interviews with a surviving family member. Approximately 300 deceased, poor performers, and matched controls (prior testing) have been identified for record review and telephone interview followup; this will begin in fiscal year 1986. A third group of dementia cases will be generated as a result of reevaluation during the current (cycle 18) examination. Current funding supports the continuing neuropsychological and neurological evaluations of all study participants suspected of dementia, the gathering of information related to the diagnosis of dementia from family members of possible cases, data managing, and statistical analysis related to the information generated by these examinations and interviews, and coordination of the dementia/aging disability components of the study.

PHS 6040 (Rev. 1/84) GPO 914-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 04004-03 EDBP

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Healthy Aged--Honolulu Heart Study

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

PI: Lon R. White, M.D., M.P.H.
Chief, Epidemiology Office, EDBP, NIA

COOPERATING UNITS *(if any)*

Honolulu Heart Program, NHLBI

LAB/BRANCH

Epidemiology 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 unreduced type. Do not exceed the space provided.)*

A professional services contract was awarded to Dr. Benfante to carry out research using the data and facilities of the Honolulu Heart Study. The objective of this study is to define the correlates and predictors of survival and good health in later life. From more than 30 variables examined in multivariate analyses, blood pressure, obesity, cigarette smoking, alcohol consumption, serum glucose, uric acid, and triglyceride were inversely associated with staying healthy while forced vital capacity and birthplace in Japan were directly associated with health. Of these nine variables, blood pressure was the strongest discriminator between healthy status and all categories of disease while cigarette smoking and alcohol consumption were the next most important factors. This study suggests that the use of individuals who remain free of disease as a "standard" for health can facilitate the evaluation of risk factors for both total illness and a broad range of specific chronic diseases in a single population.

Publication: Benfante, R., Reed, D., and Brody, JA. Biological and social predictors of health in an aging cohort. J Chron Dis 38(5)385-95, 1985.

PHS 6040 (Rev. 1/84)

GPO 914-918

Overview of the Demography and Economics Office

The Demography and Economics Office has emphasized work in population aging with the continual development of the Macroeconomic-Demographic Model (MDM). This model focuses on the current and future trends of population whose mean age is rising or whose population is made up of an increasing proportion of older individuals. This research is closely associated with the concept of demographic transition to a stable and older population structure. We have also begun to focus on the aged population per se through our wealth studies, NHANES studies, and a new project on the microeconomics of aging that examines the health expenditures and health status of the elderly.

A major enhancement to the MDM continues under a contract to ICF, Incorporated (AG-2-2138) for "Health Expenditures and the Aging Population." This effort involved briefings and coordination with such agencies as the Health Care Financing Administration, Social Security Administration, DHHS Assistant Secretary for Planning and Evaluation, National Center for Health Statistics, and the National Center for Health Services Research in order to avoid duplication and waste. Analysis of these data has been started with the generation of numerous age- sex-expenditure breakdowns for type of health expenditures and source of funding and a paper was presented at the International Health Economics and Management Association in Rome, Italy. The contract was extended a year to allow revisions to the Model's data base. The National Health Accounts were recently revised, thus making the Model's data obsolete. A paper was written by the investigators to compare National Health Account payments to their counterparts in the National Medical Care Utilization and Expenditures Survey (NMCUES).

An RFP, No. NIH-AG-84-19, had its deadline extended into FY85. This project is entitled "Household Formation, Housing, and an Aging Population." Of great concern are the rapidly changing patterns of household formation and housing tenure among the elderly. A contract award was made to ICF, Incorporated.

The contract "Aging, Health and Consumer Expenditures" (AG-3-2117) was also extended a year along with the health expenditures modeling contract. The purpose of this research is to disaggregate consumption by age in the (MDM) so that the effects of the aging population may be examined with particular attention to the aggregate share going to health care services. We shall examine the effects of public policy on the welfare of the elderly, using the latest cost-benefit techniques. This contract is also being supported under an interagency agreement with the Assistant Secretary of Planning and Evaluation, DHHS. The Health Expenditures Model shall be estimated simultaneously with the Consumer Expenditures Model to provide one consistent demand system.

A contract entitled "Update and Revision of the Macroeconomic-Demographic Model" (AG-84-05) was awarded in September 1984. It has also been extended to FY86 in order to coordinate its activity with the consumer and health expenditure modeling. The original NIA/MDM was completed in 1981 and is obsolete because of new data and changes in social security and private pension legislation. This proposed contract has been coordinated with the Office of the Assistant Secretary for Planning and Evaluation, DHHS, who is particularly interested in

the analysis of social security. We shall also update and rewrite a previously planned publication on the future of the retirement income system.

Microeconomic research has focused on wealth studies. Dr. Cartwright and Dr. Robert Friedland, Health Economist at Employee Benefits Research Institute (former temporary Demography and Economics staff member), are publishing in the September issue of the Review of Income and Wealth an article entitled "The President's Commission on Pension Policy Household Survey 1979: Net Wealth Distribution by Type and Age." George Washington University has accepted the dissertation research proposal of Mr. Alfred Drummond, Assistant Professor at Goucher College and temporary Demography and Economics staff member. Dr. Cartwright and Mr. Drummond have initiated work to study the wealth-age profile with the inclusion of rights to private pensions and social security.

A pilot study entitled "Evaluation of Senile Dementia Costs" (AG-3-2123) has been completed. This is a pilot study that led to the preparation of the following papers:

- Economic Costs of Senile Dementia: Issues and Recommendations (Cartwright, Hu, and Huang)

- Evaluation of the Costs of Caring for the Senile Demented Elderly: A Pilot Study (Hu, Huang, and Cartwright)

- Cost of Illness and the Elderly (Cartwright, Hu, and Huang)

- The Economic Cost of Senile Dementia in the United States, 1983 (Huang, Hu, and Cartwright)

- A Review of Prevalence and Incidence of Senile Dementia Among the Elderly Population (McDonnell, Hu, and White)

These have been provided to the Senate Select Committee on Aging and to the Office of Technology Assessment. We are attempting to publish the papers. Two of the papers are under review.

Professor Karen Davis from Johns Hopkins delivered a computer model for the EDB IBM/XT under professional services contract No. 263-MD-504549. The computer model provides an interactive graphical display of trends in the elderly which will be useful to depict long-term trends on future health needs, health conditions, and economic factors. European trends may be examined and compared to U.S. trends.

Demography and Economics Office Research Highlights, FY 1985

° Contract AG-4-2107 "Update and Revision of the Macroeconomic-Demographic Model" has been awarded to ICF, Incorporated. This project will lead to a number of important publications on the future of the retirement income system and social security.

- An RFP No. NIH-AG-84-19 "Household Formation, Housing, and the Aging Population" was completed and issued. An award was made to ICF, Incorporated.

- The article "The President's Commission on Pension Policy Household Survey 1979: Net Wealth Distributions by Type and Age" is published. Net wealth for those 65 and over was $61,957 which includes imputed value of employer-based pensions, but no social security values.

- An evaluation of the costs of senile dementia has been completed. Total direct costs are estimated to be 38.4 billion dollars. Of this, community home care costs were 26.7 billion dollars.

- An RFP No. NIH-AG-85-12 "Microeconomics of Aging, Health Status and Conditions, and Health Expenditures" was completed and issued.

- Joseph Anderson and Emmanuel Thorne, investigators on "Health Expenditures and the Aging Population" (AG-2-2138), presented a research paper entitled "Estimates of Aggregate Personal Health Care Expenditures in 1980--Comparisons of the National Health Accounts and the National Medical Care Utilization and Expenditures Survey Data" to the National Center for Health Statistics. The National Medical Care Utilization and Expenditures Survey (NMCUES) accurately captured household sector payments, but differences exist in government payments in comparing the two data sources.

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 and integrated 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. The contractor is required to acquire existing data bases for utilization in the modeling.

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 must be continually studied. For example, the health and welfare of the elderly will be affected both by the evolution of the economy and the income security system. The current NIA model has previously focused on retirement income issues and is now being developed in the area of a detailed health expenditures model.

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 model shall permit an examination of the implications of an aging population in the United States.

CONTRACT

Name and Number: ICF Incorporated (N01-AG-3-2117)

Title: Aging, Health, and Consumer Expenditures

Date Contract Initiated: September 13, 1984

Current Annual Level: $20,363

Objectives: This research shall investigate the determinates of consumer behavior and the interrelationship between health and other consumer expenditures. The research shall represent an expansion of the NIA Macroeconomic-Demographic Model (MDM) (Contract No. N01-AG-0-0024) that projects the U.S. economy and details of the retirement income system. The research shall be useful for investigating population aging and other economic phenomena directly related to aging research issues.

Methods Employed: Within the new consumer model, prices, income, family size, age of household head, region of residence, race, and type of residence will be among the determinants of consumer expenditure shares. The model shall be implemented from the latest available data and shall include both cross-section and time-series data. Particular attention shall be placed on the allocation of expenditures by households with different ages for household head and other demographic characteristics. In addition, the determination of health expenditure shares shall consider cost-sharing arrangements that include governmental programs, private insurance, and out-of-pocket expenses. The consumer expenditure model shall be integrated with the NIA MDM and the detailed model being developed of health expenditures. A base case consistent with the NIA model shall be established for the simulation model and used for investigating such effects as population and policy change on the welfare of the elderly and a comparison of such effects to other nonelderly groups.

Major Findings:

Significance to Biomedical Research: The NIA supports a unique MDM that 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 must be continually studied. For example, the health and welfare of the elderly will be affected both by the evolution of the economy and the income security system.

Proposed Course: This contract was extended for one year. The purpose of this research is to dissaggregate consumption by age in the MDM so that the effects of the aging population may be examined with particular attention to the aggregate share going to health care services. We shall examine the effects of public policy on the welfare of the elderly, using the latest cost-benefit techniques. This contract is also being supported under an interagency agreement with the Assistant Secretary of Planning and Evaluation, DHHS. The Health Expenditures Model shall be estimated simultaneously with the Consumer Expenditures Model to provide one consistent demand system.

CONTRACT

Name and Number: ICF, Incorporated (AG-4-2107)

Title: Updating and Revising the Macroeconomic-Demographic Model

Date Contract Initiated: September 26, 1984

Total Cost of Contract: $250,000

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. There are ongoing contracts to develop health and consumption expenditures modeling that shall add equations to the computer simulation model.

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 civil service retirement system.

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.

CONTRACT

Name and Number: Applied Systems Inst., Inc. (NO1-AG-5-2107)

Title: Microeconomics of Aging, Health Status and Conditions, and Health Expenditures

Date Contract Initiated: September 23, 1985

Current Annual Level: $100,000

Objectives: The specific objective of this contract is to focus on the microeconomic analysis of aging and health, i.e., the health status and condition of the elderly and their health care demand. This work will involve reviewing the relevant litreature on aging and health economics, estimating the effect of health status and health conditions, as well as other independent variables on health utilization, and analyzing the results with regard to the elderly population and their health needs.

Methods Employed: The work performed under this contract is of a scientific and technical nature and directed to understanding health expenditures in the elderly population. An important aspect of health expenditures is understanding the role of health status and health conditions in the demand for health care by the elderly. Therefore, a careful development of the joint demand for insurance and health care must be done along with consideration of such aspects as Medicare, Medicaid, and Private Supplemental Insurance. The simulation model will be developed to explore the various aspects of health expenditures with respect to prices, income, private insurance programs, Medicaid, and demographic groups. Such notions as risk spreading and resource allocation are particularly important as well as the implications of elderly welfare and the role of private and governmental insurance markets. In addition, an empiracal model of elderly health expenditures will be developed and estimated with data available from cross sectional surveys such as the National Medical Care Expenditure Survey, National Medical Care Utilization and Expenditure Survey, and National Health Interview Survey. Thus, analysis will be done on publicly available data resources and no primary collection of household survey data will be made. The results of the simulation modeling and econometric modeling shall be presented in final reports.

Significance to Biomedical Research: The NIA/EDB Program is already supporting the development of a health expenditures model for the NIA Macroeconomic-Demographic Model of the U.S. economy. This work emphasizes a population aging focus within a macroeconomic framework. The current work requested focuses on microeconomic considerations in the health market for the elderly.

Proposed Course: The contractor will review the literature in aging and health economics in order to evaluate the state-of-the-art and current aging issues and will provide a literature search and a report systhesizing the various issues. The contractor will also develop and supply a theoretical model of the demand and supply for health services. The model will focus on both societal and individual distinctions. The theoretical model will examine risk and health attributes for individuals identified as belonging to various demographic groups, but with particular attention to elderly groups.

CONTRACT

Name and Number: Applied Systems Inst., Inc. (NO1-AG-3-2123)

Title: Evaluation of Senile Dementia Costs

Date Contract Initiated: June 1, 1983

Total Cost of Contract: $74,283

Objectives: The purpose of this evaluation is to examine the NIA's program for senile dementia research in the context of determining the cost of this disease and the implications for the nation's overall commitment to biomedical research on this disease.

Methods Employed: The investigator shall evaluate the cost of illness methodology and in particular the general problems involved in application to the population, 65 years of age and older. The investigator shall identify unique cost elements of senile dementia that distinguish it from other diseases. This shall involve examining such costs as those that are incurred by the health delivery system, the patients, the family, and society. In this stage, specific case studies shall be used to highlight problems for policymaking in settling research priorities. Based on this research, and also other sources of national and community data on senile dementia, the investigator shall estimate a national cost of senile dementia. Finally, the investigator shall report recommendations with regards to the cost of illness methodology, the NIA research program, and the extent and quality of data.

Major Findings: An evaluation of the cost of senile dementia has been completed. Total direct costs are estimated to be 38.4 billion dollars. Of this, community home care costs were 26.7 billion dollars.

Significance to Biomedical Research: The NIA is deeply involved in stimulating and actively doing research in senile dementia. This disease is tragic as it proceeds through stages to severe memory loss, disorientation, general decline in mental functions, and finally death. Currently, there is no thorough evaluation of the cost of this illness, and data often is not sufficiently detailed to create easily cost elements.

Proposed Course: This pilot study led to the preparation of the following papers. These have been provided to the Senate Select Committee on Aging and to the Office of Technology Assessment. Publication of the papers is planned. Two are under review.

Cartwright, W.S., Hu, T., and Huang, L. Economic Costs of Senile Dementia: Issues and Recommendations
Hu, T., Huang, L., and Cartwright, W.S. Evaluation of the Costs of Caring for the Senile Demented Elderly: A Pilot Study
Cartwright, W.S., Hu, T., and Huant, L. Cost of Illness and the Elderly
Huang, L., Hu, T., and Cartwright, W.S. The Economic Cost of Senile Dementia in the United States, 1983

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 01055 04 EDBP

PERIOD COVERED
October 1, 1984 to September 30, 1985

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Retirement Income System Research with MDM

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

William S. Cartwright, Ph.D., Chief,
Demography and Economics Office, EDBP, NIA

COOPERATING UNITS *(if any)*

LAB/BRANCH
Demography and Economics Office

SECTION
Epidemiology, Demography, and Biometry Program

INSTITUTE AND LOCATION
NIA, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.10	.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.)*

The NIA enters into an agreement with the Assistant Secretary for Planning and Evaluation (ASPE) for the purpose of research on pensions, retirement, and labor force as well as issues involved in integration of micro and macroeconomic models. We have supported the revision and reestimation of the labor market model and simulation studies of the labor supply of the elderly.

We have received a detailed proposal specifying the work to be undertaken. A new version of the Pension Model has been prepared and delivered to NIA's MDM.

PHS 6040 (Rev. 1/84)

GPO 914-918

Overview of Biometry Office

The FY 1985 activities and achievements of the Biometry Office parallel those of previous years, including initiation and maintenance of intramural and contract-supported research, as well as continued methodological consultation and statistical support for research programs conducted by other EDB offices, other NIA programs, and organizations outside the Institute. An increasingly large share of Biometry Office resources (staff and budget) is consumed with a variety of data management activities and statistical computing in support of the EPESE and NHANES I Epidemiologic Followup projects, the two largest data-producing projects of the Program. In recognition of the importance of these latter functions, we have recruited a computer programmer, Ms. Bette Pollard, to replace Ms. Mary Beth Grigson who left the Program in FY 1984. Ms. Pollard is working as an assistant to Ms. Mary Lafferty, our Data Manager, in the preparation of much of our data for analysis. In addition, Ms. Pollard has been named the EDB lead user for the IBM PC/XT and is performing a variety of tasks involving novel applications of the PC to the work of the Program as well as training EDB staff in its use. Aside from this one change in personnel, the Biometry Office staff has remained the same.

As mentioned above, our involvement in data management and statistical analysis of data from the EPESE projects continues at a high level. The EPESE Resource Data Book is now nearing completion, with all tabular and graphical material having been finalized. Draft texts for all the chapters have been completed and all but one chapter have been reviewed by the EDB review group (Dr. Huntley, Dr. Brock, and Ms. Lafferty) and approved for publication by the EPESE Principal Investigators. The remaining chapter is being reviewed, and the technical appendices, including fitting of generalized variance functions to the Yale data by Mr. Everett, are underway. As work on the baseline survey data book winds down, activity is beginning to pick up in other aspects of the EPESE projects. We have received data tapes from each of the three centers containing the first and second telephone followup interview data. In addition, we have also begun to receive endpoint data tapes from the three locations, including data on hospitalizations, nursing home admissions, and mortality. Cause-of-death information was included on the mortality tape, having been coded by the nosologist for the state of Iowa under a professional services contract initiated by the Biometry Office. The coding activity will continue as deaths occur in the three populations. This will require further EDB support through additional professional services contracts with the nosologist.

The arrival of the first endpoint data marks the beginning of another activity with the EPESE data, namely "core" analyses to be done collaboratively by the investigative teams and EDB staff. Several committees have been appointed to conduct these core analyses in the areas of mortality, hospitalization, nursing home utilization, and disability. For each endpoint topic an overall coordinating committee has been appointed, with subcommittees established for analyses relating various exposure data for the particular endpoint of interest. Dr. Brock has been named chairman of the mortality endpoint coordinating committee which also has responsibility for analyses relating demographic

characteristics to mortality. This group will oversee the work of five subcommittees relating various exposure characteristics to mortality. The committee met in July 1985, to make plans for the analysis of demographic characteristics and outline steps to be taken in completing the analysis. Mr. Foley is a member of the coordinating committee for core analysis of disability as an endpoint. He is currently developing an index of disability for possible use in the core analysis.

The Biometry Office staff continues its involvement in several other aspects of the EPESE projects. Dr. Brock continues as chairman of the Documentation Committee which met twice during the year. This group, with considerable work and input from Ms. Lafferty, has developed common specifications for formatting the baseline survey, telephone followup surveys, mortality, hospitalization, and nursing home data sets. With the award of a contract to Duke University for a fourth center, it will be necessary to orient that group to the activities of this committee and work closely with them to insure standardization of procedures, documentation, formatting, and data management across all the centers. In other areas of EPESE, Ms. Cruz continues as staff liaison to the Publications Committee, and Mr. Foley continues to apply his expertise in the means and methods of obtaining Office of Management and Budget (OMB) clearance of survey forms and documents, although Ms. Campbell is gradually assuming those responsibilities. Finally, Dr. Brock has been Project Officer for a professional services contract to study patterns of incomplete responses in the Iowa baseline survey, and he has been asked to participate in a study of the characteristics of refusals in the East Boston location.

In early 1985, the EDB Program received the data tapes for the full data collection of the NHANES I Epidemiologic Followup Survey. Since that time, data management and analytic activities have increased substantially. Many of the working groups formed earlier (with receipt more than a year ago of the data from the Northeast Region) have begun to meet and divide up the work involved in carrying out literally dozens of analyses on these data. National Cancer Institute staff have generously offered to share computer files they created from the raw data to help save expenses of on-line storage. Ms. Lafferty is working closely with NCI staff in this effort. Analyses already under way span a wide variety of topics including height, weight, other anthropometry, functional ability, blood pressure, arthritis, and a host of other exposure and endpoint variables. Data analysis for drafts of two papers on hearing loss has been completed by Ms. Losonczy. Working with a group from the University of Iowa, she has conducted analysis to relate hearing loss and bone density. In the other paper, methodological comparisons between pure tone audiometry and self-assessment hearing scales were made. Mr. Everett has been involved in analyses of weight and weight history, arthritis, and blood pressure. A group headed by Dr. Brock is beginning an analysis of the circumstances of death as ascertained from proxies of individuals in the original NHANES I who died before the followup study was done. Many of the questions in this latter analysis were included in the Survey of the Last Days of Life which will be discussed below. As in the past, Ms. Cruz continues to serve as the EDB staff person responsible for tracking abstracts for the NHANES I Followup Publications Committee. This is similar to the work she does for the

EPESE Publications Committee. The topic of nutrition, one of the most unique aspects of this study, is the subject of a professional services contract initiated by Mr. Everett of our staff. The purpose of this first project is to achieve commonality between the NHANES I and Followup food groupings and to examine eating patterns in the elderly. We anticipate a good deal of further work in this area after the completion of this beginning effort.

As mentioned above, the Survey of the Last Days of Life (AG-2-2137) has continued throughout FY 1985. After a lengthy delay in obtaining OMB clearance of the questionnaire in 1984, a pretest was conducted in the study area (Fairfield County, Connecticut) in the summer of 1984. Analysis of the pretest results showed that the basic methodology of approaching the informant 3 months after the death of the decedent would elicit the response required for successful conduct of the study. Further results of the pretest showed that some changes in the questionnaire would be necessary to eliminate awkward sequencing and high incompletion rates for some questions. After revisions were made the study went into the field in January 1985. At a recent site visit to DMH Associates, the fieldwork contractor in New York City, it was learned that excellent progress is being made in the data collection phase of the study. Close examination of the first two months' data showed that response rates are continuing at an 85 percent level and the data are showing the same kinds of patterns expected based on the pretest data. We anticipate that the fieldwork will continue until March 1986, and that data will be available for analysis in the fall of 1986.

Dr. Brock continues to serve as a member of the interagency consulting group for the National Mortality Followback Survey (NMFS) being conducted by the National Center for Health Statistics (NCHS). This survey, based on a national probability sample of 20,000 deaths, is designed to collect information from the next of kin listed on the death certificate. Topics for the survey include health care in the last year of life, lifestyle factors and the risk of "premature" death, socioeconomic differentials in mortality, and the quality and reliability of non-cause-of-death items on the death certificate. Because of the similarity between this study and the Survey of the Last Days of Life (see paragraph above), we executed an interagency agreement with NCHS this year to support the study (AG-5-0057). As a result, questions on nursing home utilization and cognitive function taken from our Last Days of Life questionnaire are included in the NMFS and will be available for providing national norms to which we may compare our data. At this time, a pretest has been conducted and, although final results will not be available for some time, preliminary indications are that the methodology and questionnaire appear to work well. Plans call for the analysis of the pretest and revision of procedures to be completed in the fall and the main study to begin in January 1986.

Our interest in the National Nursing Home Survey (NNHS) has continued in FY 1985. Following the pretest in 1984, it was decided to be infeasible to implement a full admissions cohort to be followed over time as part of the 1985 NNHS. Instead, NCHS is implementing collection of information on the next of kin component to be used to describe the nursing home utilization patterns of

persons admitted to nursing homes in a specific time window. As with the NMFS, we have supported this study with an interagency agreement (AG-5-0062).

Our previous work in analysis of national mortality data for U.S. elderly is currently being updated. Dr. Brody presented the latest available mortality and morbidity data on cancer in the elderly at a recent meeting in Israel. Mr. Everett is continuing to work on the analysis of those data. In addition, Dr. Brock has been asked to update two chapters recently published on epidemiologic and statistical characteristics of the U.S. elderly population. Further, we are developing a professional services contract to reopen the topic of climatic extremes and mortality in the elderly, a subject which was being actively pursued by Dennis Cosmatos until his leaving the Program in 1983.

Two other topics deserve mention in this report. As clearly indicated earlier in this narrative, a great deal of effort is going into analyses and studies based on the NHANES I and its associated Followup Survey. Since this study was originally designed as a complex sample survey, the assumptions required for standard statistical analysis techniques are not met or, in some cases, even approximately met. Therefore, to make optimum use of these data, considerable work in methodology development needs to be done. The National Institute of Child Health and Human Development (NICHHD) has recently signed a contract with Research Triangle Institute, an experienced and reputable firm in survey research, to study and develop methods for performing regression analyses on complex survey data. Since this topic is highly relevant to our needs in analyzing NHANES, and since one of the products of this work will be software to be applied to these data, we are proposing to join with NICHHD through an interagency agreement to support this research and extend the scope to topics highly relevant to NIA interests. The other topic of interest in this area is longitudinal data analysis, especially as it may apply to our EPESE data. We are developing a professional services contract to evaluate specific ways of analyzing longitudinal data, specifically to assess the "bootstrap" as a tool for the study of longitudinal data in estimating the degree of a polynomial, in finding simultaneous confidence bands for a repeated response at all time points, and to estimate the distribution of a new test for trend. It is our belief that these developments, while mathematically complicated, will make our data even more useful.

Biometry Office Research Highlights, FY 1985

- Developmental work on the Survey of the Last Days of Life (Contract No. NO1-AG-2-2137) was completed early in FY 1985. Analysis of pretest results demonstrated the feasibility of contacting the death certificate informant and obtaining satisfactory responses to interviews to learn about the decedent's last days of life. Numerous revisions to the questionnaire were made following the pretest, and they have proven to be valuable modifications to the main study which went into the field in January 1985. To date, the data collection has gone very well and preliminary results from the main study corroborate what was found in the pretest, namely, the ability to locate a knowledgeable respondent for virtually all cases; a high degree of cooperation from respondents, physicians, and health facilities; and low rates of item nonresponse and missing data.

- Data management activities have been completed for the EPESE baseline survey Resource Data Book. All tabulations and graphical materials have been finalized and approved for publication by the principal investigators. All text chapters, save one, have been completed and approved for publication. With the completion of this work, data management activities will be shifted to the two telephone followup surveys, the hospitalization and nursing home data, and the mortality surveillance data.

- Biometry Office staff have been named to two coordinating committees for "core" analysis of EPESE endpoint data, one on mortality and the other, disability. The mortality committee has met and made assignments for a group of papers to be written on the relation between demographic factors and mortality for the first 2 years' surveillance data. We anticipate completion of this work in FY 1986.

- The first collaborative analysis of EPESE baseline data was published in FY 1985. This paper discusses methodologic issues and preliminary findings on the epidemiology of disability in the oldest old for the first three EPESE locations. Biometry Office staff provided the analysis and discussion on physical functioning.

- A professional services contract (No. 263-MD-432151) was completed to examine nonrandom item nonresponse for the Iowa EPESE baseline survey. The investigator adapted weighted least squares (WLS) analyses for categorical data to identify factors related to the probabilities of nonresponse for bowel and bladder problems, the CES-D Depression scale, and cognitive recall data. For the bowel and bladder questions, nonresponses were explained as separate functions of age, education, and marital status, depending on which questions were examined. Many of the CES-D questions had item nonresponse rates characterized by age-sex interactions, and virtually all responses from females were affected by the age of the respondent. The cognitive recall data are far more complicated in the types of nonresponse due to higher overall percentages of incomplete response as well as a variety of types of nonresponse ("unable to participate," "don't know" responses, and refusals). Eight analyses were performed on these data, providing a variety of informative results on nonresponses and how to deal with them. In summary, the WLS analyses conducted here provide the simultaneous treatment of the different types of nonresponse, with each type retaining its own identity, so that biases are not recognizably pooled, and the technique allows for the identification of separate cross-classifications for imputation classes, creating more stable estimation procedures for each type of item nonresponse. It is concluded that imputation for missing values is a viable technique for remedying the incomplete data due to item nonresponse in the Iowa study. We believe similar results may apply to the other studies as well.

- The final data tapes for the NHANES I Epidemiologic Followup Survey arrived in EDB in the middle of FY 1985. A number of analyses involving Biometry Office staff have begun, with writing committees established for collaboration among several NIH Institutes and the National Center for Health Statistics. Draft papers have been completed on two studies involving hearing ability, one related to bone density and the other comparing three methods of obtaining data on hearing loss. Analyses are under way in the areas of weight and weight history, functional ability, mortality as related to a variety of predictors, and the circumstances of death.

- A professional services contract (No. 263-MD-504816) was awarded to study eating patterns in the elderly based on food frequency data from the NHANES I and the Followup Study. The investigator has established rules for comparing food groupings from the two surveys. Although they were not based on the same questions at baseline and followup, they can be used for comparison of dietary behavior over time. Principal components analyses were used to establish seven patterns of food groups which explain a majority of the variance in food groupings. These analyses will be used to compare eating patterns for the NHANES I versus the Followup, men with women, age groups 55 to 64 with 65 to 74 (at baseline), married versus non-married (i.e., all other marital status categories) elderly, and black versus white elderly.

- A professional services contract (No. 263-MD-523425) awarded to analyze NHANES I Epidemiologic Followup Survey data relating self-assessment of fatigue and of health to dietary patterns will be matched to the original NHANES I data. Changes in self-assessment of fatigue and of health will be related to each other and to dietary changes. Specifically, the hypothesis that constant fatigue indicates potential health problems and that self-assessment of health is a good indicator of health-status is related to dietary intake.

- An interagency agreement (AG-5-0057) was signed with the National Center for Health Statistics to support the National Mortality Followback Survey (NMFS). This is a study of characteristics of a national probability sample of 20,000 decedents whose next of kin will be surveyed via mail questionnaires to collect data on health care use in the last year of life, lifestyle and risk factors for "premature" death, socioeconomic differentials in mortality, and the reliability of certain non-cause-of-death items on the death certificate. This study bears a strong relationship to the Survey of the Last Days of Life and will permit investigation of associations between risk factors and lifetime prevalence of diagnosed dementia, as well as the lifetime history of nursing home admissions. The survey is being pretested at the present time, with the main study scheduled to begin in January 1986.

- An interagency agreement (AG-5-0062) was signed with the National Center for Health Statistics to support a study of nursing home admissions in the National Nursing Home Survey (NNHS). The original proposal to establish an

admissions cohort to be followed for a period of time as a part of the NNHS was evaluated in a pretest conducted in 1984. The results of that study indicated that it was not practically feasible to embed in the NNHS such an admissions cohort to be followed over time. Instead, the NCHS will identify, for a sample of nursing home residents, a next of kin for the sample resident who will be interviewed concerning the resident's history of nursing home admissions up to the time of the NNHS. In this way, it will be possible to establish, retrospectively, patterns of admission, discharge, and length of stay for a representative sample of persons admitted to nursing homes.

CONTRACT

Name and Number: DMH ASSOCIATES, INC. (N01-AG-2-2137)

Title: Survey of the Last Days of Life

Date Contract Initiated: September 30, 1982

Total Cost of Contract: $475,550.

Objectives: The purpose of this project is to collect descriptive data on the last days of life for a community sample of persons age 65 and older whose deaths occurred in a one-year period. In addition to providing specific data on basic events and circumstances surrounding death, the study will provide lifetime prevalence data for a set of conditions related to, but not necessarily causing death. The new knowledge gained from this study will be extremely valuable in relieving the burden of anxiety on family, friends of the dying person, and to providers of care.

Methods Employed: A sample of death certificates will be selected over a period of one year in Fairfield County, Connecticut. Retrospective information concerning the decedent's last days of life will be obtained in a face-to-face interview with an informant identified from the information contained on the death certificate. Followup information will be obtained from medical sources identified by the informant for those cases in which it is appropriate.

Current Status/Major Findings: The pretest was completed in June 1984 with an overall response rate of 85 percent and successful location of a knowledgeable informant for each responding case. Thus, the feasibility of our approach to the study has been established. The pretest data have been analyzed, appropriate modifications have been made in the questionnaire and procedures, and the main field work began in January 1985. Two papers have been presented to the American Statistical Association meetings describing the design and pretest results.

Significance to Biomedical Research: A considerable body of literature exists in the geriatric and psychological fields as well as in the lay press about dying. Yet specific data about basic events associated with dying are lacking --such as who dies peacefully in his/her sleep, who dies in great pain, what persons are present at the time of death, who dies after a long illness with full awareness of his impending demise, and who dies suddenly with no warning. Further, the proportion of the dying who need and actually receive pain medication is unknown. The study will provide an opportunity to obtain epidemiological data on the numbers of persons affected by the major health conditions that confront the dying elderly as well as the lifetime likelihood of certain events and conditions such as blindness, deafness, dementia, hip fracture, and others.

Proposed Course: After revisions to the originally tested questionnaire were made the study went into the field in January 1985. Excellent progress is reported being made in the data collection phase of the study. Close examination of the first 2 months' data showed that response rates are continuing at an 85 percent level and the data are showing the same kinds of patterns expected based on the pretest data. We anticipate that the fieldwork will continue until March 1986, and that data will be available for analysis in the fall of 1986.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 06060 01 EDBP

PERIOD COVERED
October 1, 1984 to September 30, 1985

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

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

Dwight B. Brock, Ph.D., Chief, Biometry Office, EDBP, NIA

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:

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 survey will provide information on the characteristics of decedents and on the circumstances associated with their deaths that would supplement existing information on the death certificate. Specific areas to be studied include socioeconomic differentials in mortality, risk factors associated with what NCHS refers to as "premature" death, health care in the last year of life, and reliability of certain items reported on the death certificate. Through this interagency agreement NIA would be providing support to enrich the NCHS survey in those areas of importance to NIA research goals. Specifically, we are interested in obtaining national data concerning those characteristics of elderly decedents related to cognition, and the use of health care in the last year of life. A nationally representative sample of deaths could provide much needed data on the proportion of decedents showing signs of cognitive impairment, or decedents who were reported by their proxies to have been diagnosed by a physician to have had Alzheimer's disease or other dementing illness. This would provide better information than has been previously available on the relationship between dementing illness, cause of death and associated risk factors. In addition, these data will complement and enhance community-level data on similar topics being collected for NIA in the Survey of the Last Days of Life.

PHS 6040 (Rev. 1/84)

GPO 914-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 06050 02 EDBP

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Pretesting of the 1984 National Nursing Home Survey

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

Daniel J. Foley, EDBP, NIA
W. Edward Bacon, Ph.D., Director, Division of Health Care 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:

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 interagency agreement between NIA and NCHS covers the cost of work to be done by NCHS in developing and implementing survey instruments and procedures for the 1985 National Nursing Home Survey. This agreement is to reimburse the Center for costs related to the collection of information on the Next of Kin Component to be used to describe the nursing home utilization patterns of an admissions cohort. All necessary clearance and sampling procedures will be developed by NCHS; all data collection and followup will be performed by a contractor under the direction of NCHS. NCHS will provide NIA with an analysis of the survey data identifying the characteristics and utilization of an admission cohort.

PHS 6040 (Rev. 1/84)

GPO 914-918

OFFICE OF THE SCIENTIFIC DIRECTOR (OSD)

The Scientific Director, NIA, is responsible for the quality and direction of research undertaken by the intramural program. In addition, the Office of the Scientific Director embraces selected administrative and support functions essential to the program's efficient operation. The current structure of the OSD will be significantly changed when a reorganization plan goes into effect in the next fiscal year--both through the consolidation of research resources and technical support services, currently housed in OSD, in the new Research Resources Branch, and the abolition of the Comparative Nutrition Section and the Experimental Morphology Section.

The OSD reorganization will reduce the number of functions and personnel assigned to the Scientific Director's immediate office, thereby ensuring a more appropriate span of control, promote increased efficiency and responsiveness in the provision of services to intramural investigators, and provide an operating structure which is both logically and functionally more coherent.

The objectives, and recent accomplishments of the current constituent units of the Office of the Scientific Director follow.

ADMINISTRATIVE SERVICES

Objectives:

Administrative Office:

The Administrative Office provides a wide range of support services essential to the effective operation of the Intramural Research Program. The nature and extent of the administrative function differs significantly from that of other Institutes due to the distance from the NIH complex and the requirement to operate and maintain a separate facility. Responsibilities encompass budget management, station support contract monitoring and administration, building operations, travel review and authorization, property accountability, administrative reporting, personnel ceilings, timekeeping and payroll disbursing activities, space, telephone service, and safety.

The Administrative Officer also participates in many of the intramural committees which plan an instrumental role in the internal governance of the IRP. The role and functions of the Procurement/Receiving Unit, which reports to the Administrative Officer, are as follows:

Procurement/Receiving Unit:

The Procurement/Receiving Unit is responsible for the direct purchase and receipt of all procurement actions within the delegated authority of $2,500, and the monitoring of all requisitions sent to the NIH Central Procurement for the GRC.

Activities and Achievements

Administrative Office:

- The primary objective of the Administrative Office throughout the past year, considering the staff reductions, has been to keep abreast of the routine activities and requirements, such as travel review and approval, initiation and review of personnel action requests, FTE monitoring and reporting, budget record maintenance, verifications, and reporting, property record control and accountability, and the review, monitoring, and renewal of building operation contracts.

- Participation in the pending reorganization of the Intramural Research Program.

- Initiation of quarterly meetings with the GRC secretarial staff to communicate changes in administrative processes, review various procedural requirements, and to answer questions and exchange information.

- Continued involvement in major renovation projects.

- Participation in various activities/meetings concerning research support contracts.

Procurement/Receiving Unit:

- GRC procurement actions processes from June 1984 through July 1985 are as follows:

SF-147 (Purchase Orders)	1,701
TCO	644
Record of Calls	1,886
Reprint Orders	75
NIH-402 & On-line Market Requisitions	241
Repair Orders	86
SF-44 (Petty Cash Vouchers)	478
Stock Requisitions	1,252

- Established an Interagency Agreement with the GSA Customer Supply Center, PA, which provides 24-hour supply delivery from GSA stock.

- Implementation of market requisitioning system for the on-line transfer of requisitions to the Central Procurement Branch.

INFORMATION OFFICE

Objectives

The IRP Information Office acts as the overall communications vehicle for the Institute's Intramural Research Program. Its audiences are varied and include the local and national public-at-large, the Congress, electronic and print media, staff of the IRP and NIA, various educational and voluntary agencies, and other government units.

This office's responsibilities involve both internal and external information dissemination on research progress by both intramural investigators and those conducting studies elsewhere. The communications methods used include written reports, articles, releases, seminars, slide presentations, lectures, briefings, and tours. The office conducts community outreach programs dealing with constituent groups, senior adult programs, medical and nursing schools, universities and high schools, and private agencies or community groups.

Another primary objective involves internal communications regarding educational opportunities, training available, merit awards, cultural activities, research seminars. The office actively seeks to promote these events via the monthly GERON-NEWS, the NIH RECORD, flyers, bulletin boards, and through other available means.

In addition, the IO helps with advice, arrangements and staff for the periodic award ceremonies, cultural events, various drives, and other programs.

Activities and Achievements

A major achievement this year was the completion and publication of Normal Human Aging, partially edited and wholly processed by IO staff. This office coordinated the distribution of this definitive volume on the Baltimore Longitudinal Study of Aging. Arrangements were made for mailings to all volunteer subjects, journal book review and books received editors, VA Geriatric Research, Education and Clinical Centers, depository libraries, authors, staff, interested media, and key government, as well as NIA advisors such as the Board of Scientific Counselors and the National Advisory Council on Aging.

Considerable efforts this year were expended to enhance IRP and NIA internal communications. Staff served on the NIA ad hoc committee on communications and worked with the Personnel Office in planning and implementing NIA-wide orientation programs. Educational programs were arranged for staff on cholesterol and nutrition, the national cancer test, blood testing for AIDS antibody, and handicapped employment awareness. The office also helped recruit for and publicize retirement education programs and an effective English training course.

Staff gave 43 briefings and tours for some 317 people and, through speaking engagements, addressed another 430 individuals. Articles, stories, and highlights were written for the NIH RECORD, NIH NEWS and FEATURES, the NIA Special Report, 13 newsletters (GERON-NEWS and "Six S's News").

Achievement highlights for the year are as follows:

- Planned, coordinated distribution of Normal Human Aging to BLSA subjects, journal reviewers, authors, staff, libraries, etc.
- Helped plan and participated in two NIA-wide orientation programs.
- Arranged laboratory sessions at GRC for Maryland Junior Science and Humanities Symposium.

- Coordinated and ran two IRP Awards Ceremonies (February/July).

- Chaired, publicized and recruited for two Red Cross Blood Drives (December/June) with 110 units collected.

- Three stories researched, written for NIH News and Features on stress and coping, behavioral treatment of incontinence, and dual photon absorpiometry.

- Four media alerts and press summaries prepared on International Gerontology Workshop at GRC, 13th ICG papers (2), and selection of Dr. James Fozard for appointment as BLSA Associate Director.

- Communications Officer served as assistant press officer for 13th ICG; helped stimulate WOR Radio interview with Dr. Williams, another with St. Petersburg Times, and press summary resulted in Medical World News story on incontinence work.

- Staff helped edit and process a number of manuscripts for various IRP investigators.

- Editorial assistance provided NIH Scientist Emeritus for manuscript in preparation on the history of the International Association of Gerontology.

- Revised or updated IRP portions of NIH Medical Staff Fellow and Summer Fellow catalogs, as well as the NIH Almanac.

- Updated Research Training Opportunities fact sheet for 1985 and IRP fact sheet.

- Aided Network for Continuing/Medical Education (NCME) in filming show "PVC's and the Elderly," with Dr. Fleg (Aired Jan.-Feb. 1985).

- Helped number of TV stations, including Channels 7 and 9, NHK-TV (Tokyo), KCET-TV, and RAI-TV for aging stories.

- Speaking engagements outside addressed 430 people, including retiree home residents, pre-retiree groups, church members, congressional senior interns, and nurses.

- Hosted, briefed or toured 317 persons on 43 different occasions. Those toured included administrators, physicians, and scientists from Australia, France, Italy, Japan, the United Kingdom, and New Zealand.

- Handled more than 300 direct public inquiries and 200 contacts with the media such as National Geographic, Ladies Home Journal, Dallas Times-Herald, Los Angeles Times, Catholic Review, Newsday, Newhouse News Service, Science Wire, Health Plus, Self, New York Times, Modern Maturity, Geriatrics, Discover, and Science '85.

- Continued to foster cross-NIA and IRP communications with 12 issues of GERON-NEWS, posting of seminars on bulletin boards and distribution of information on special educational opportunities.

- Updated IRP staff profiles (biographies) and took new profile photos as needed.

- Publicized and recruited for pre-retirement seminars offered by NIA and the Baltimore Federal Executive Board and did the same for training course offered at GRC on effective English.

- Coordinated IRP portions of NIA Annual Report and NIH Scientific Directory and Bibliography.

- Prepared intramural section of FIC International Report.

- Set up educational video showings for GRC staff on cancer prevention, cholesterol and nutrition, donor screening for AIDS antibody, and "Employ the Handicapped Week."

- Publicized and helped run programs for Black History Month.

- Staff served on NIA Communications Task Force Committee, GRC EEO (Human Relations) Committee, Cultural Committee, Library Committee, NIH Handicapped Employees Advisory Committee, and NIH R & W Council.

- IO employees earned five cash or honorary awards including, NIH Merit Award, Special Achievement Group Award, Sustained Superior Performance, and Quality Increases.

- Communications Officer served on Advisory Committee for the Beacham Adult Day Care Center at Francis. Scott Key and drafted information brochure for the same center.

LIBRARY

Objectives

The Gerontology Research Center Library serves both as a specialty collection in gerontology and geriatrics and as a resource for intramural investigators. The Library holdings include books and periodicals addressing the scientific disciplines represented at the Center as well as a collection of thousands of books, journals, and reprints covering the entire gamut of literature on aging.

Activities and Achievements

The Library has continued to provide services to meet the essential needs of intramural investigators despite personnel reductions and temporary crowding problems attendant to the basement renovation project. The Library has withstood the loss of one of its two full-time permanent staff. Furthermore, since July, the Librarian has been on maternity leave. This central resource is

now staffed by two Stay-in-Schoolers supervised initially by an employee detailed from the Information Office and currently by a rotating group of OSD staff. During the absence of the Librarian, computerized literature searches have been discontinued, and cataloguing which requires specialized training is in abeyance. Despite this situation, the following achievements can be cited for the past year:

- The basement renovation is essentially complete. Preparations for moving materials to be housed in this new library storage facility are underway.

- The photocopier and word processor requested last year have been installed.

- An extensive number of computerized literature searches were successfully completed.

- In collaboration with the GRC Library Committee, the herculean task of reviewing the list of all journals currently ordered and maintained was completed. A survey of Library users was conducted to solicit their views concerning journals the Committee deemed possible candidates for discontinuation. The survey results will be considered in decisions about reordering journals and determination of those to be moved to the basement facility.

- Information on the GRC Library collections, services, and operating procedures was developed for users.

PHOTOGRAPHY AND ARTS

Objectives

- Art Services: The Photography and Arts Unit provides a full range of services including publication design, poster design, general art work, and illustrations prepared for printing or for presentation as color or black and white (B&W) slides and overhead transparencies. Statistical, technical, and scientific illustration, statistical drafting, general graphic production, including tables and formulae, and schemas portraying experimental direction and design are prepared.

  The unit has added a Compugraphic Photo Typesetter which is online with the VAX System to electronically transfer text and tables from remote word processors throughout the building. This equipment provides high quality text and tables for poster presentation and for B&W slides. A computer graphics system has been developed and is in use in the building. This system will speed up the production of many of the art services. It has already become an interactive vehicle between the unit and the scientific staff of the GRC.

- Photographic Services: Photographic services include general photography, medical photography, photomacrography, patient photography, temporary identification badges, photographic copying, production of B&W and color projection slides, slide duplicating, photographic printing, overhead transparency production, and miscellaneous processing.

The work done in the unit also provides photographic documentation of experimental processes or products in the lab. The unit's personnel will either do the photography, time permitting, or consult as to the proper techniques and/or equipment needed. This again becomes an interactive process by which the Unit works closely with the individual scientists to provide the best possible service to meet program needs.

- o Audio-Visual Services: The Unit equips and services the audio-visual equipment located in the two conference rooms on the first floor. In addition to the 2 X 2 projectors found in these two rooms 24 hours a day, the Unit also has available upon request video equipment, 16mm sound projector, overhead projector, and a lantern slide projector.

Activities and Achievements

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. Approximately 350 charts and graphs were produced on the computer system this year. 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.

TECHNICAL DEVELOPMENT SECTION (TDS)

Objectives

This section is responsible for providing technical support to GRC research staff in the operation and enhancement of central ADP functions. The Section:

- o Operates and develops the GRC central computer system and provides consultation and assistance to its users.
- o Supports the design, development, and installation of small computer systems for specialized laboratory and clinical applications.
- o Coordinates the GRC system and ADP policy with the NIH Division of Computer Research and Technology.
- o Maintains existing electronic equipment and devises new electronic instruments to meet the special needs of intramural staff.

Activities and Achievements

In the past year, a major expansion to the central VAX computer system has been accomplished. This expansion involved the installation of a second, equally powerful CPU, tightly integrated into the existing system. It has relieved several of the data processing pressures and in addition allowed some new applications to get under way. Additional memory for the old CPU has been purchased and will be installed soon.

The multi-microprocessor system (developed and fabricated by the TDS Section) to maintain up to 12 monkeys on operant conditioning schedules is being expanded to support blood flow measurements. The replacement of the CPM-based master controller in this system by a small VAX computer which is part of our network has been accomplished.

A small microprocessor-based PROM reader was developed for the several programs at GRC that are collecting data in this manner.

Two general purpose STD bus cards wee developed that allow real-time laboratory software to be written in and run by a Basic Interpreter. These are currently in use by the Cognition Section.

An intelligent interface between a mass spectrometer and a VAX computer is currently being developed for the CV laboratory.

In the past year, along with many thirty-minute to two-hour projects, the Section has designed, fabricated, and installed equipment such as a Tibia positioning platform; a shielded light-isolation cage for a Volt-age Clamp Apparatus; an instrument for a Reacxtion Time Response Test; additions to Photomultipliers on Microscopes; a passive rat restraint for NMR Spectroscopy and Imaging; chambers to record electrical and mechanical measurements of heart muscle; profusion chambers for investigation of myocardial cells; and other longer term projects.

ANIMAL RESOURCES FACILITY

Objectives

The Animal Resources Facility (ARF) is responsible for the supply of experimental laboratory animals to support the aging research conducted at the Gerontology Research Center. These animals are supplied through inhouse production and contracts.

Production and quality control programs are currently concerned with mice, rats, rabbits, dogs, monkeys, hamsters, and chickens. All animals are maintained under strictly controlled environmental conditions. In addition to the production and procurement of these animals, the majority are aged to the near limits of their life expectancy within the Center. Approximately 25,000 animals, supporting 50% of the research projects at the GRC, are issued and maintained by the Animal Resources Facility.

Activities and Achievements

- A full day site inspection of the ARF, by the American Association for Accreditation of Laboratory Animal Care (AAALAC), proved very rewarding, as we again maintained accreditation for the 8th consecutive year. The AAALAC Council pointed out several of the outstanding aspects of the ARF:

  > Council particularly commends Mr. French for his efforts in providing and maintaining a high quality animal program. Aspects of the program that are especially meritorious include housing and care of the Aging Dog Colony and the overall sanitation. The overall condition of the physical plant was excellent.

- Maintained institutional membership with the national organization of the American Association of Laboratory Animal Science (AALAS), as well as with the local National Capital Area Branch (NCAB) of AALAS.

- Approximately 135 hours were utilized in support of 60 aseptic surgical procedures.

- All requests for animals from the aging colonies were met. Over 7,000 mice and rats, of varying ages, were issued.

- In addition to our stock animals, approximately 8,536 mice, 4,520 chicks, 2,683 rats, 333 rabbits, 25 primates, and 6 hamsters were received and housed by the ARF.

- The ARF was able to supply approximately 200 rats and 100 mice to other institutions throughout the country, to conduct aging research.

- Technician training conducted at GRC by the ARF supervisory staff, resulted in national certification of four Laboratory Animal Technologists. Many more will be tested for certification at the National Convention in November.

- With the purchase and implementation of two computer terminals and a printer, statistics and procedures in the animal facility have become more efficient. Many of the staff have been trained to operate the computer programs.

- A portable X-ray unit and fiber-optic scope have been added to enhance our diagnostic capabilities.

- The Wistar Rat Colony was able to decrease the mortality of young male rats, 1-12 months, by 48%. This was due to increased use and improved animal husbandry techniques.

- The Wistar Breeding Colony increased its monthly production by 10% (1,000 weanlings/month) to meet the demands for younger animals.

- One viral outbreak concerning Rat Sendai and Mouse Hepatitis occurred. the outbreak was curtailed with little or no disruption to scientific research.

- Rodent rooms have had a significant reduction in the ammonia levels due to the addition of paper pan liners.

- Our large pass-through autoclave have been refurbished and will be operational by September.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01-AG-00101-09-OSD

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Relation Between Nutritional State and Aging

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

PI: C. H. Barrows, Jr. Chief, Section on Comparative Nutrition OSD, NIA

Others: G. C. Kokkonen Chemist OSD, NIA

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Gerontology Research Center, Office of the Scientific Director

SECTION

Section on Comparative Nutrition

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
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 spece provided.)*

1. Mortality statistics indicate that the addition of a non-nutritive dietary additive (cellulose) markedly increased the life span of middle-aged male mice (16 months).

2. The life span of genetically determined diabetic mice was essentially doubled by feeding diets containing a low level of protein; by reducing the intake of an adequate diet by intermittent feeding; and by adding a non-nutritive additive (cellulose) to an adequate diet. This increased life span was most likely the result of a delay in the onset of the disease as indicated by a marked reduction in polyuria and glucosuria found in the experimental animals.

3. Age and dietary restriction lowers the amount of protein synthesized and degraded by the cell but does not affect these overall processes per se.

Project Description:

Objectives: To ameliorate the deficiencies and diseases associated with aging by means of various dietary manipulations.

Methods Employed: In a series of studies to evaluate the effectiveness of feeding diets containing cellulose on life span, adult C57BL/6J male mice (16 mos. of age) were fed ad libitum the following diets: 1) 24% protein (control); 2) 24% protein diluted 50% with cellulose; or 3) 24% protein diluted 33% with cellulose.

In another series of studies to determine whether the development of specific diseases could be influenced by dietary manipulations the diabetic C57BL/KsJ(db/db) strain of mouse was employed. The animals were subjected to the following dietary manipulations: 1) 24% protein ad libitum; 2) 4% protein ad libitum; 3) 24% protein intermittently fed; and 4) 24% protein diluted 50% or 33% with cellulose fed ad libitum.

In another series of studies the turnover rate of liver protein was determined in C57BL/6J male mice of different ages as well as 9-month old animals subjected to the following dietary manipulations since weaning: 1) 24% protein ad libitum; 2) 4% protein ad libitum; or 3) 24% protein intermittently fed. The animals were injected intraperitoneally with ^{14}C-labelled bicarbonate and the loss of radioactivity from precipitated protein was determined over a 3-week period. In addition to the protein content of the tissue, the DNA content was also determined so that protein turnover rates on a cellular basis could be determined.

Major Findings: In the study to evaluate the effect of non-nutritive dietary additives (cellulose) on the life span of middle-aged mice (16 mo. old), the results indicate a marked increase in life span. The survival rates at twenty-eight months of age of the animals fed the control diet or one containing 50% or 33% cellulose were 30%, 63%, and 67% respectively.

The 50% mortality of the control, low protein, and intermittently fed diabetic animals occurred at approximately 5, 9, and 11 months respectively. Dietary restriction essentially doubled the life span. Preliminary studies have shown that after 3.5 months of age, control diabetic animals have severe polyuria and glucosuria (more than 2000 mg.%). In contrast, animals fed the 4% protein diet show no overt polyuria and minimal glucosuria (less than 200 mg.%). Animals fed intermittently are in between these groups. The beneficial effects of intermittent feeding may be due to a reduced dietary sugar intake whereas those due to 4% protein feeding must be attributed to other causes, since the dietary sugar intake of the animals is at least 30% higher than that of the controls. A second study was initiated and the following data are now available. During the first month on diet all animals approximately doubled their body weight (from 20 to 40 gr.). Surprisingly, the animals fed the 33% cellulose diet continued to gain an additional 20 grams during the next four months while those fed intermittently or the 4% protein diet maintained their body weight during this period of time. In contrast, animals fed the 24% protein diet (control)

severely lost body weight. These latter animals during this period experienced approximately 80% mortality whereas the experimental animals experienced essentially none. Thus it becomes apparent that feeding a diet containing a non-nutritive fiber (cellulose) has a marked beneficial effect.

The half-life of liver proteins determined in vivo in 12, 24, and 34 month old C57BL/6J male mice was 2.94, 3.47, and 3.38 days respectively and statistically were not significantly different. Assuming that the liver proteins are in a state of equilibrium, these data may be interpreted as indicating that age does not affect the overall rate of synthesis and degradation of proteins. However these data fail to provide information regarding the amount of protein synthesized and degraded during this period of time. Data presently available indicate that, on the basis of cell number as estimated by DNA and the fact that 50% of the proteins are renewed every 3 to 4 days, the mg. of protein synthesized and degraded per unit DNA daily was 11.2, 6.7, and 5.8 for 12, 24, and 34 month old mice respectively. Thus it would appear that age alters the amount of protein synthesized and degraded by the cell but does not affect these overall processes per se. Similarly, dietary manipulations which have been shown to increase life span does not affect the half-life of liver proteins. However the amount of protein synthesized and degraded per unit DNA daily was determined to be 9.6, 5.3, and 7.1 in the livers of 24% protein (control), 4% protein, and intermittently fed 9-month old C57BL/6J male mice respectively. Thus one characteristic common to both groups of dietary restricted animals is a low amount of protein synthesized and degraded by liver cells. Furthermore this condition is positively correlated with cellular protein levels and cellular size.

Significance to Biomedical Research and the the Program of the Institute:

Dietary restriction initiated in adulthood, in addition to increasing life span, brings about a retardation of age decrements and a delay in the onset of diseases in animals with minimal body weight reduction i.e. 15% or less. However even a 15% reduction in body weight is associated with marked hunger and therefore not easily tolerated by most people. Therefore the addition of non-nutritive additives to diets, which result in the above beneficial effects without dietary intake reduction is of great importance.

Diabetes mellitus is common among the elderly. This report includes three dietary manipulations which double the life span of genetically- determined diabetic mice. This increased life span is associated with either a retardation of the development of the disease or a marked reduction in its severity. Two of these dietary manipulations allow the animals to feed ad libitum, so that the discomfort of reduced dietary food intake is not necessary.

Data now available indicate that one characteristic common to animals subjected to a variety of dietary manipulations which increase life span is the low amount of protein synthesized and degraded by liver cells. Furthermore this condition is positively correlated with the cellular protein levels and cellular size. These data suggest an important probe to study the mechanism of aging may be an inquiry into experimental procedures other than dietary ones, that may bring about a reduction of liver cell size and an increased life span.

Publications:

Kokkonen, G.C. and Barrows, C.H.: The effect of dietary vitamins, protein and intake levels on the life span of mice of different ages. Age 8: 13-17, 1985.

Barrows, C.H. and Kokkonen, G.C.: The effect of age and diet on biochemical characteristics of the tissues of mice. Age 8: 100-109, 1985.

Kokkonen, G.C. and Barrows, C.H.: Nutrition and aging. In Encyclopedia of Aging. Springer Publishing Company, in press.

CARDIOVASCULAR SECTION

During FY 1985, the Cardiovascular Section has focused on the following three major research areas:

Studies in man (Z01 AG 00232-01 CPB) have focused on (1) the effect of age on coronary artery disease and left ventricular performance (Contract NO AG 42109); (2) on peripheral blood flow (Z01 AG 00038-04 CPB); (3) on ambulatory electrocardiography and blood pressure measurements (Z01 AG 00033-07 CPB, Z01 AG 00223-04 CPB); (4) on complications of treadmill exercise, i.e., arrhythmias and hypotension in apparently healthy normals (Z01 AG 00228-02 CPB); and, (5) on the efficacy of digitalis in congestive heart failure (Z01 AG 00029-8 CPB).

Studies in chronic animal models include an examination of aging, chronic exercise, and altered nutritional pattern and thyroid state, on cardiac muscle contractile and electrophysiologic function, and biochemistry associated with certain aspects of function, i.e., myofibrillar ATPase activity and myosin isozyme composition, energy metabolism and morphology (Z01 AG 00036-05 CPB, Z01 AG 00224-04 CPB, Z01 AG 00227-03 CPB, Z01 AG 00230-01).

Studies of mechanisms of excitation-contraction in the heart focus on the detection of mechanisms that regulate cell Ca^{2+}, and the functional implications of spontaneous Ca^{2+} oscillations in the intact heart, in intact muscles and isolated cells (Z01 AG 00035-06 CPB, Z01 AG 00226-03, Z01 AG 00231-01, Z01 AG 00233-01 CPB).

Research progress in each of these areas is described in the following individual project reports.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00029-08 CPB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Efficacy of Digitalis in Congestive Heart Failure and in Normal Subjects

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

PI:	J. L. Fleg	Staff Cardiologist	CPB, NIA
Others:	E. G. Lakatta	Chief, Cardiovascular Section	CPB, NIA

COOPERATING UNITS *(if any)* Division of Cardiology, Francis Scott Key Medical Center, Baltimore, MD (S. H. Gottlieb), Peter Bent Brigham Hosp., Boston, MA (T. Smith), University of Arizona, Tucson, AZ (F. Marcus), Massachusette General Hospital, Boston, MA (R. Johnson), Duke University, Durham, NC (H. Strauss and M. Hlatky)

LAB/BRANCH

Gerontology Research Center, Clinical Physiology Branch

SECTION

Cardiovascular Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

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

CHECK APPROPRIATE BOX(ES)

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

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

We have previously shown in a double-blind crossover study that digitalis could be discontinued for three months without adverse clinical effect and only minor changes in cardiac size and function in 30 subjects with stable congestive heart failure (CHF) and sinus rhythm. Long-term follow-up of these patients verified this favorable early response to digitalis withdrawal. We have initiated a new study to investigate the effects of digitalis on aerobic performance and cardiac function during exercise (measured via gated blood pool scan) and its effects on cardiac rhythm in a new group of patients with chronic CHF and sinus rhythm.

Our group has helped to develop a questionnaire in conjunction with experts in cardiology at different universities. This questionnaire has been implemented with the help of the American Heart Association to sample representative groups of academic and practicing physicians in their current use and understanding of the effectiveness and toxicity of digitalis glycosides. The results will be important in identifying areas of consensus and areas in which major uncertainties exist; the important categories within the latter will serve as a basis for future research projects in which NIH and NIA may find a direct role.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00033-07 CPB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Ambulatory Electrocardiography and Blood Pressure Measurement in Normal Man *

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

PI:	J. L. Fleg	Staff Cardiologist	CPB, NIA
Others:	E. G. Lakatta	Chief, Cardiovascular Section	CPB, NIA

COOPERATING UNITS *(if any)*

Saint Louis University School of Medicine, St. Louis, MO (H. J. Kennedy)

LAB/BRANCH

Gerontology Research Center, Clinical Physiology Branch

SECTION

Cardiovascular Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.4	0.2	0.2

CHECK APPROPRIATE BOX(ES)

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

X ☐ (a1) Minors

☐ (a2) Interviews

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

Initial ambulatory electrocardiographic data from this laboratory has characterized the normal heart rhythm patterns in healthy elderly subjects. We have extended these efforts to include younger men and women (ages 25-60). In addition, we have added a new dimension - 24 hour ambulatory blood pressure (BP) recording - simultaneous with the ambulatory ECG recording, in normal subjects as well as hypertensives and those with congestive heart failure.

We have analyzed the circadian variability of blood pressure, recorded every 7.5 min, over 24 hours in 26 healthy normotensive BLSA women ages 35-75 years using this technique. Both the mean waking systolic blood pressure (SBP) and its standard deviation increased with age whereas during sleep, the mean SBP but not its standard deviation increased with age. The difference between maximum and minimum hourly-averaged waking SBP increased with age whereas the difference during sleep was not age-related. Thus, in ambulatory, normotensive women, the variability of SBP increased with age during waking hours but not during sleep.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00035-06 CPB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Fluctuations in the Intensity of Light Scattered thru Diastolic Cardiac Muscle

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

PI:	E. G. Lakatta	Chief, Cardiovascular Section	CPB, NIA
Others:	M. D. Stern	IPA	CPB, NIA

COOPERATING UNITS *(if any)* Cardiology Division, Dept. Medicine, Johns Hopkins Hosp., Baltimore, MD (G. Gerstenblith, D. Renlund and E. Marban), Dept. Physiology, Univ. of Maryland, Baltimore, MD (W. G. Wier), Albany Med. Ctr., Albany, NY (A. A. Kort), Dept. Pharmacology, Southwestern Medical School, Dallas, TX (J. Sutko)

LAB/BRANCH

Gerontology Research Center, Clinical Physiology Branch

SECTION

Cardiovascular Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
2.8	2.7	.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.)*

We have discovered that scattered light intensity fluctuations (SLIF) are present in isolated rat ventricular muscle even under conditions formerly considered to be quiescent. Subsequent experiments indicated that SLIF are highly dependent on Ca^{2+} loading of the cell and could be reversibly terminated (1) by maintaining constant Ca^{2+} concentration in the myofilament space in skinned fibers or (2) in intact fibers by caffeine. These results were interpreted to indicate that cellular myoplasmic Ca^{2+} concentration oscillates in diastole, producing motion of the myofilaments, which modulates the laser beam and results in SLIF. This myofilament motion which is asynchronous within a cell, and among cells, results in a small degree of diastolic force or "tone" in the muscle. Additional experiments have demonstrated SLIF in atrial, ventricular, and conduction tissues in a range of mammalian species including man and indicate the universality of this phenomenon in excitable cardiac tissues. In collaboration with the Department of Physiology at the University of Maryland, we have directly demonstrated these Ca^{2+} oscillations utilizing intracellular injects of the chemiluminescent protein, aequorin. In our most recent studies we have time gated SLIF measurements following stimulation in order to determine the restitution of action potential stimulated Ca^{2+} release relative to the restitution of SLIF following a previous action potential mediated release. We found that stimulation increases SLIF frequency in this diastolic window and that antiarrhythmic aspects suppress this increase. In our most recent studies we have also demonstrated the presence of SLIF in the intact perfused heart and have shown that it covaries with Ca^{2+}-dependent tone.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

PROJECT NUMBER

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00036-05 CPB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Interaction of Age and Physical Conditioning on Myocardium and Vasculature

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

PI:	H. A. Spurgeon	Physiologist		CPB, NIA
Others:	E. G. Lakatta	Chief, Cardiovascular Section		CPB, NIA
	E. S. Beard	Chemist		CPB, NIA
	M. B. Effron	Senior Staff Fellow	DOD 06/25/85	CPB, NIA

COOPERATING UNITS *(if any)*

Department of Dermatology, Johns Hopkins Hospital, Baltimore, MD (G. M. Bhatnagar)

LAB/BRANCH

Gerontology Research Center, Clinical Physiology Branch

SECTION

Cardiovascular Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS	PROFESSIONAL	OTHER:
2.0	0.5	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.)*

Our laboratory has shown in many previous studies that myocardial function in rats is affected by aging, specifically by by prolonging isometric twitch duration. Biochemical correlates have been shown to change in parallel as well. We have, in previous studies, demonstrated that mild exercise which is not sufficient to induce a training effect in young animals is nonetheless able to reverse/retard cardiovascular aging when applied relatively late in the lifespan of the rat. We have subsequently attempted to define the limits of exercise in terms of type, duration, and age at which exercise is begun. The present study, utilized a swimming model begun at 5 weeks of age and continued up to 17 months of age. The contractile and biochemical parameters of the myocardium did not differ between the two groups. The absence of a training effect on heart weight or the ratio of heart weight to body weight precludes a definitive interpretation of these results. One possibility is that up to 17 months (and unlike the case for senescence) in order for physical exercise to alter myocardial properties, a training effect on heart weight or body weight must occur.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00038-04 CPB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Evaluation of Peripheral Blood Flow in Normal Man by Plethysmography *

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

PI:	J. F. Fleg	Staff Cardiologist	CPB, NIA
Others:	E. G. Lakatta	Chief, Cardiovascular Section	CPB, NIA
	E. S. Beard	Chemist	CPB, NIA

COOPERATING UNITS *(if any)*

Department of Anesthesia and Critical Care, Johns Hopkins Hospital (G. Bause)

LAB/BRANCH

Gerontology Research Center, Clinical Physiology Branch

SECTION

Cardiovascular Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.60	.30	.30

CHECK APPROPRIATE BOX(ES)

- [X] (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.)*

Although the incidence of degenerative changes in the blood vessels is well known to increase with advancing age, quantitative data on the changes in peripheral blood flow due to the aging process per se are lacking. Venous occlusion plethysmography has been shown to be the most accurate and reproducible method to measure the peripheral blood flow. We used this method to evaluate peripheral blood flow in the subjects of the Baltimore Longitudinal Study of Aging (BLSA) with ages ranging from 20 to 83 years. The study was designed to evaluate the effect of age on peripheral blood flow by venous occlusion plethysmography at rest and in response to post-occlusion hyperemia and thermal stress, both of which result in near-maximal flow. Neither resting nor post-occlusion hyperemic blood flow as relate to age in these 146 BLSA men and women who underwent occlusions of 1, 2, and 3 minutes both at 26°C and 35°C. These results suggest that peripheral blood flow is not limited by age per se in man.

In a second protocol, the response of peripheral blood flow to intravenous infusion of isoproterenol and sodium nitroprusside was determined by plethysmography in 25 healthy volunteers ages 25-84 years.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

PROJECT NUMBER

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00221-04 CPB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Sodium-Calcium Dependence of Resting Force in Rat Cardiac Muscle

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

PI: E. G. Lakatta Chief, Cardiovascular Section CPB, NIA

COOPERATING UNITS (if any)

Division of Cardiology, Department of Medicine, Johns Hopkins Hospital (G. Gerstenblith)

LAB/BRANCH

Gerontology Research Center, Clinical Physiology Branch

SECTION

Cardiovascular Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

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.)

In unstimulated isolated, rat ventricular muscle, the increase in resting force (ΔRF) which occurs with an increase in external calcium concentration ($\Delta[Ca^{2+}]_e$) can be largely abolished by lowering cellular sodium content by removing sodium from the perfusate and can be potentiated by raising cellular sodium content by adding ouabain. We hypothesized that this demonstrated the activity of a membrane Na/Ca exchange (see Z01 AG 00221-02 CPB). Since this membrane exchange is well known to exhibit graded activity, we sought to extend our observations by demonstrating a graded response between $[Na^+]_i$ and ΔRF. External potassium concentration ($[K^+]_e$) was set at gradually lowered values for each experiment in the series to give graded inhibition of the Na-K pump and thus graded elevation of $[Na^+]_i$. $[Ca^{2+}]_e$ was then increased from 0 to 2 mM and the ΔRF recorded. The results shown that increasing ΔRF occurs with decreasing $[K^+]_e$ (and thus increasing $[Na^+]_i$. Thus, not only does the ΔRF for a $\Delta[Ca^{2+}]_e$ depend on $[Na^+]_i$, but does so in a graded manner. This is further evidence for the activity of the Na/Ca exchange in controlling ΔRF in isolated rat muscle. In extending these studies to the intact heart we hypothesized that after a Ca^{2+} free period the magnitude of the Na^+ gradient at the onset of Ca^{2+} reperfusion would grade the ensuing cell Ca^{2+} gain. Our results indicate that (1) myocardial cell Na^+ increases during Ca^{2+} free perfusion and (2) the magnitude of the Na^+ gradient at the end of the Ca^{2+} free period is an important determinant of the extent of cell Ca^{2+} gain, cell K^+ loss, and reduction of contractile function with Ca^{2+} reintroduction, which collectively have been referred to as the "calcium paradox" in the heart.

Combined into Z01 AG 00035-06 CPB.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00223-04 CPB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Effect of Age on the Components of Atrioventricular Conduction in Normal Man*

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

PI:	J. L. Fleg	Staff Cardiologist	CPB, NIA
Others:	E. G. Lakatta	Chief, Cardiovascular Section	CPB, NIA

COOPERATING UNITS *(if any)*

LAB/BRANCH

Gerontology Research Center, Clinical Physiology Branch

SECTION

Cardiovascular Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL	OTHER:
0.2	0.1	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.)*

We have utilized a signal averaging, high resolution ECG to record His bundle potentials from the body surface of 111 normal Baltimore Longitudinal Study (BLS) volunteers ages 21 to 79. By allowing measurements of conduction time both proximal and distal to the bundle of His, this technique should enhance our understanding of the age-related changes in the cardiac conduction system. In 52 women, neither PR nor HV interval was related to age. In 59 men, the following age relationships were found:

PR interval	= 142.4 msec + .477 age	.388 <.01
PH interval	= 105.3 msec + .427 age	.393 <.01
PR segment	= 47.6 msec + .315 age	.328 <.02
Proximal PR segment	= 10.5 msec + .267 age.	330 <.02

Thus, an age-related prolongation of PR interval is found only in men and appears to be due largely to a delay in the proximal PR segment, presumably reflecting delay within the atrioventricular junction.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00224-04 CPB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Cardiac Myofibrillar ATPase Activity Across a Broad Age Range

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

PI:	M. B. Effron	Senior Staff Fellow DOD 6/25/85	CPB, NIA
Others:	G.M. Bhatnagar	Guest Researcher	CPB, NIA
	E. S. Beard	Chemist	CPB, NIA
	E. G. Lakatta	Chief, Cardiovascular Section	CPB, NIA

COOPERATING UNITS *(if any)*

LAB/BRANCH

Gerontology Research Center, Clinical Physiology Branch

SECTION

Cardiovascular Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.5	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 previously reported, myofibrillar ATPase activity decreases with age while the duration of the isometric twitch in papillary muscles increases and do not appear to be related. Myosin ATPase activity and the percent of myosin isoenzyme V_1 have also been shown to decrease with age as well as with pathologic hypertrophy. Animals treated with thyroxine increased myosin ATPase activity and decreased the contraction duration and have suggested that the two parameters are related. Therefore, we treated young (2 mo), adult (8 mo), and senescent (24 mo) rats with thyroxine to produce a hyperthyroid state and were able to show that the isometric contraction time parameters decreased without altering the maximum myofibrillar ATPase activity in any group. However, when the myosin isoenzymes V_1 and V_3 were examined, a redistribution of these isoenzymes in the euthyroid state occurred with age and that was reversed by thyroxine treatment. Similarly, Ca^{2+}-myosin ATPase activity in euthyroid animals showed a linear decrease with age that was only reversible in the 24 month animal where the percent of myosin isoenzyme V_1 and ATPase activity were severely depressed. Therefore, we conclude that age associated decrease in the Ca^{2+}-myosin ATPase activity, myosin isoenzyme distribution, and prolongation of isometric contraction time parameters is not fixed and can be reversed with thyroxine treatment. These changes were present even though T_4 treatment caused hypertrophy of both sides of the heart. This suggests that while the myosin isoenzymes and ATPase activty may play an important role in myocardial contraction, other functions of the cell, such as sarcoplasmic reticulum Ca^{2+} sequestration, also have an important role in excitation-contraction coupling. The results also suggest that ventricular hypertrophy may be only a response, and not a cause, of alterations in myocardial biochemistry and contractile activity.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

PROJECT NUMBER

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00226-03 CPB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Excitation-Contraction in Isolated Cardiac Cells

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

PI:	M. C. Capogrossi	Senior Staff Fellow	CPB, NIA
Others:	E. G. Lakatta	Chief, Cardiovascular Section	CPB, NIA

COOPERATING UNITS *(if any)*

LAB/BRANCH

Gerontology Research Center, Clinical Physiology Branch

SECTION

Cardiovascular Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2	0.8	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.)*

We have dissociated myocardial muscle cells from adult rats and rabbits. These preparations are being used to study the contractile, electrophysiological, and biochemical characteristics in a variety of different conditions. In particular we have been able to identify in these isolated cells a longitudinally propagating wave which occurs spontaneously when the cell is not being electrically stimulated and is considered at rest and has a normal resting membrane potential. These "waves" are likely to represent the phenomenon of calcium induced calcium release (CICR) and are the cause of the scattered light intensity fluctuations (SLIF) which our laboratory has studied in the past in multicellular preparations. With our work we have initially attempted to validate single cells as a model for the study of mechanisms of excitation-contraction coupling and in particular of CICR. Subsequently we have measured the effect of (1) electrical stimulation and (2) on the spontaneous waves.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

PROJECT NUMBER

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00227-03 CPB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Excitation-Contraction in Rat Myocardium: Alterations with Adult Aging

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

PI:	E. G. Lakatta	Chief, Cardiovascular Section		CPB, NIA
Others:	C. Orchard	Visiting Fellow	DOD 8/31/85	CPB, NIA

COOPERATING UNITS *(if any)*

LAB/BRANCH

Gerontology Research Center, Clinical Physiology Branch

SECTION

Cardiovascular Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 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.)*

It has been suggested that the sarcoplasmic reticulum (SR) is involved in the response of heart muscle to changes of perfusate $[Ca^{2+}]$, $[H^+]$ and stimulaion rate. Two series of experiments were undertaken to investigate these suggestions. In the first, intracellular $[Ca^{2+}]$ (Ca_i) and developed tension were measured in papillary muscles from 6 and 24 moth old rat hearts, during changes of perfusate $[Ca^{2+}]$ and stimulation rate. Heart muscle from the old animals, in which SR function is thought to be depressed, responded differently to changes of stimualtion rate when perfusate $[Ca^{2+}]$ was high. This age-related difference was compatible with a model in which developed tension depended on Ca^{2+} cycling by the SR. In the second series of experiments, Ca_i and developed tension were measured in papillary muscles during exposure to different types of acidosis. Inhibitors of the SR were used to examine the role of the SR in the response of the muscle to acidosis. This study showed that there is an early, transient recovery of tension during acidosis which is due to increased Ca^{2+} release from the SR. Oscillations of Ca_i which are generated by the SR, and which may be important in the genesis of some types of arrhythmias, could also be produced by acidosis. Preliminary analysis of data from 6 and 24 month old rats suggests that this early recovery of tension observed during acidosis may be less than in 24 month old rats.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00228-02 CPB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Complications of Maximal Treadmill Exercise in Apparently Normal Subjects *

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

PI:	J. L. Fleg	Staff Cardiologist	CPB, NIA
Others:	E. G. Lakatta,	Chief, Cardiovascular Section	CPB, NIA

COOPERATING UNITS *(if any)*

LAB/BRANCH

Gerontology Research Center, Clinical Physiology Branch

SECTION

Cardiovascular Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

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.)*

We have assessed the prevalence of exercise-induced ventricular tachycardia, exercise-induced supraventricular tachycardia and post-exercise hypotension in BLSA volunteers without clinical evidence of heart disease.

Out of 925 subjects undergoing maximal treadmill exercise between September, 1977 and December, 1983, 10 subjects (1.2%) developed nonsustained ventricular tachycardia (VT) during or after exercise. Episodes varied in length from 3 to 6 beats and were never associated with symptoms. The prevalence of VT was 3.8 % in subjects aged 65 and older. Over a follow-up period averaging 2.0 years, no subject with exercise-induced VT developed syncope, pre-syncope, angina, myocardial infarction or sudden death.

Exercise-induced supraventricular tachycardia (SVT) occurred in 50 subjects (5.3%). All episodes were paroxysmal atrial tachycardia; heart rate varied from 120 to 250 bpm ($\bar{x}$ = 175 $\pm$ 40). Of the 70 episodes of SVT, only 12 were $\geq$ 10 beats in length; 4 of these were associated with symptoms. The prevalence of SVT was 12.7% in the 245 subjects $\geq$ 65 years old but only 2.7% in those < 65 years. An ischemic ST segment response to exercise occurred in 14% of subjects.

Hypotension following treadmill exercise, defined by a fall in systolic blood pressure (SBP) at least 20 mm Hg below sitting pre-exercise level to a value < 90 mm Hg , occurred in 15 subjects (1.7%) with a mean age of 44.2 years. Bradycardia was associated with hypotension in only 3 subjects. When compared with age-matched controls, hypotensive subjects had higher maximal heart rates (183.9 $\pm$ 14.7 vs 173.1 $\pm$ 11.2 bpm) but no difference in SBP at submaximal or maximal effort. Post-exercise ST segment abnormalities suggestive of myocardial ischemia occurred in one third of the hypotensive subjects but none of the controls, $p<.05$.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00229-02 CPB

PERIOD COVERED

October 1 1984 to September 30, 1985

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

Age-Related Changes in Adrenergic and Cholinergic Responses in Rat Atria

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

PI:	M. McIvor	Medical Staff Fellow	CPB, NIA
Others:	E. G. Lakatta	Chief, Cardiovascular Section	CPB, NIA

COOPERATING UNITS *(if any)*

LAB/BRANCH

Gerontology Research Center, Clinical Physiology Branch

SECTION

Cardiovascular Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.6	.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.)*

While the effects of age on the adrenergic responsiveness of cardiac ventricular tissue has been delineated, data is scanty on how age may affect the cholinergic modulation of these adrenergic effects. Neither adrenergic nor cholinergic modulation of aged atrial tissue have been studied. Isolated transmural left atrial strips from adult (12 mo) and senescent (24) virgin male Wistar rats were stimulated isometrically at L_{max} at 30°C in krebs buffer containing 0.5 mM Ca^{+}. A dose response relationship to progressively greater concentration of isoproterenol (10^{-12} to 10^{-6}M) was established for both groups. A progressive dose response relationship was similarly established for acetylcholine (10^{-10} to 10^{-3}M) in atria superfused with Krebs already containing 10^{-6} isoproterenol. Changes in time to peak force, total developed tension, resting tension, contraction duration, and maximal rate of force development were measured. While age-related changes in time to peak force and contraction duration were found, an initial analysis of the data failed to shown any age-related changes in adrenergic responsiveness as measured by these parameters. However, the developed tension in isoproterenol-potentiated senescent atria was more sensitive to suppression by acetylcholine.

Discontinued.

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

PROJECT NUMBER

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00230-01 CPB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Effect of Aging on Ca^{2+} Homeostasis and Neurotransmitter Synthesis and Release

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

PI	R. Hansford	Research Chemist	CVS, CPB
Other:	F. Castro	Chemist	CVS, CPB

COOPERATING UNITS *(if any)*

LAB/BRANCH

Gerontology Research Center, Clinical Physiology Branch

SECTION

Cardiovascular Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.9	0.9	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 based upon the premise that the homeostasis of Ca^{2+} ion concentrations in neuronal tissue may be perturbed in old-age, and that this perturbation may underlie the decreased production and release of the neurotransmitter acetylcholine which has been described in old-age. We have further suggested that a decreased activation of the enzyme pyruvate dehydrogenase by Ca^{2+} ion may occur upon depolarization of nerve-terminals from aged animals, and that this may be responsible for decreased production of acetyl-CoA, and thence acetylcholine. Using rat synaptosomes (pinched-off presynaptic nerve endings from cerebral cortex) as a model, we have demonstrated decreased acetylcholine synthesis and release in response to KCl-induced depolarization in old-age. We have also completed a study in which concentrations of cytosolic free Ca^{2+} were measured with the fluorescent chelating agent Quin-2, in response to plasma membrane depolarization. Further, we have studied the degree of activation of pyruvate dehydrogenase, by covalent modification, in response to membrane depolarization and to inhibitors of mitochondrial Ca^{2+} transport. These latter two studies were conducted using young adult rats, and we are currently in the process of extending them to senescent animals, in order to answer the questions posed above.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00231-01 CPB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Role of Ca^{2+} in the Regulation of Energy Metabolism

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

PI:	R. Hansford	Research Chemist	CVS, CPB
Others:	F. Castro	Chemist	CVS, CPB
	J. Staddon	Visiting Fellow	CVS, CPB
	G. Salerno	Visiting Fellow (DOD 6/30/85)	CVS, CPB

COOPERATING UNITS (if any)

LAB/BRANCH

Gerontology Research Center, Clinical Physiology Branch

SECTION

Cardiovascular Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.4	2.4	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 designed to assess the physiological importance of Ca^{2+}-ions in the regulation of energy metabolism. Specifically, we have exposed isolated cardiac myocytes to a variety of conditions expected to alter cytosolic free Ca^{2+} concentration ($[Ca^{2+}]_c$), and have measured the amount of the active form of pyruvate dehydrogenase ($[PDH_A]$) which results, as well as estimating $[Ca^{2+}]_c$ by use of fluorescent chelating agents. Protocols used to increase $[Ca^{2+}]_c$ include depolarization of the plasma membrane with KCl, abolition of the Na^+ electrochemical gradient with ouabain and gramicidin, inhibition of sarcoplasmic reticulum Ca^{2+} uptake by caffeine and the use of metabolic inhibitors to deplete cellular ATP. We have demonstrated an increased value of PDH_A in response to each of these interventions, and an important role of Ca^{2+} transport into the mitochondria in mediating these increases. Further, we have taken advantage of the fluorescent chelating agent technology to characterize the mechanism of the increase in $[Ca^{2+}]_c$ due to KCl-induced depolarization, and have established a sensitivity to beta-adrenergic agonists and to phorbol esters. We have also initiated a study of isolated hepatocytes, in order to investigate the importance of increased values of $[Ca^{2+}]_c$ in mediating the increased activity of 2-oxoglutarate dehydrogenase and pyruvate dehydrogenase which occurs in response to the hormones glucagon and vasopressin.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00232-01 CPB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Effect of Age on Hemodynamic and Metabolic Exercise Peformance in Normal Man *

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

PI:	J. F. Fleg	Staff Cardiologist	CPB, NIA
Others:	A. Ziemba	Visiting Fellow	CPB, NIA
	R. Andres	Chief	CPB, NIA
	E. G. Lakatta	Chief, Cardiovascular Section	CPB, NIA

COOPERATING UNITS *(if any)*

LAB/BRANCH

Gerontology Research Center, Clinical Physiology Branch

SECTION

Cardiovascular Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

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

CHECK APPROPRIATE BOX(ES)

- [X] (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.)*

Maximal treadmill exercise with measurement of expired gases has been performed in more than 600 clinically normal BLSA volunteers over the past 5 years. Although a formal data analysis is currently in progress, it appears that the strong age-related decline in both maximal heart rate and maximal aerobic capacity (VO_2max) noted in small BLSA samples will be confirmed.

To determine the role of catecholamines in the well known age-related decline in exercise capacity, we measured plasma norepinephrine (NE) and epinephrine (E) at rest ant during maximal treadmill exercise in 24 healthy men. Resting NE was not age-related but resting E was higher in men 68-77 years old than in those 22-37 or 44-55 years of age. At maximal affort both NE and E were higher in the elderly men. Furthermore, at submaximal workloads NE and E increased with age, both before and after normalization as a percent of peak VO_2.

In another study, the metabolic effect of relatively prolonged aerobic exercise, is being assessed in healthy men.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00233-01 CPB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Autonomic Modulation of Myocardial Cell Ca^{2+}

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

PI:	M. E. McIvor	Medical Staff Fellow	CPB, NIA
Others:	E. G. Lakatta	Chief, Cardiovascular Section	CPB, NIA
	C. H. Orchard	Visiting Fellow DOD 8/30/85	CPB, NIA
	H. A. Spurgeon	Physiologist	CPB, NIA

COOPERATING UNITS *(if any)*

LAB/BRANCH

Gerontology Research Center, Clinical Physiology Branch

SECTION

Cardiovascular Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.6	.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.)*

Calcium is a critical agent in the activation and deactivation of contraction in the heart. When calcium binds to the myofilaments, contraction is initiated; when calcium comes off the myofilaments, relaxation occurs. Two mechanisms have been proposed for the regulation of relaxation in cardiac tissue: (1) regulation could occur by altering the sensitivity of the myofilaments for calcium, modulating the off rate of calcium from the contractile apparatus, or (2) calcium could be sequestered away from the myofilament, so the calcium necessary for contraction would no longer be available. Beta-adrenergic agonists, such as isoproterenol, both increase the off rate of calcium from the myofilament and increase the rate of calcium sequestration. We monitored these effects by injecting ferret papillary muscles with the photoprotein aequorin, which luminesces in the presence of free calcium. In the presence of isoproterenol, more calcium was needed for a given twitch force, consistent with the hypothesis that the myofilaments were less responsive to calcium, i.e. the off rate of calcium from the myofilaments was increased. The free calcium concentration also fell faster in the presence of isoproterenol, implying a more rapid rate of sequestration. Isoproterenol also accelerated relaxation. The cholinergic agonist acetylcholine was also applied to papillary muscles microinjected with aequorin. For a given level of twitch force, less calcium was required in the presence of acetylcholine than in the absence of drug, suggesting the myofilaments had become more responsive to calcium. However, acetylcholine had no effect on relaxation. When both isoproterenol and acetylcholine were applied to the muscles, the myofilament sensitivity to calcium was not decrease, but relaxation was accelerated. It is concluded that the modulation of relaxation by isoproterenol and acetylcholine does not occur at the level of the myofilaments.

CLINICAL IMMUNOLOGY SECTION

Research Objectives

The research objective of the Clinical Immunology Section is the study of control mechanisms in the immune response. The research activity in this area is divided between basic experimental animal studies and clinical studies. Both *in vivo* and *in vitro* tissue culture assays are used to defining the cellular immune function and the mechanisms of controlling that function. Further, the possible reasons for an immune deficiency are to be detailed including an analysis of genetic factors and DNA abnormalities which are age associated. These studies are designed to further the understanding of normal immune function and to detail the mechanisms and significance of the immune deficiency of aging.

Selected Research Accomplishments

- Flow Karyotyping: Methods have been developed to allow the karyotyping of the human chromosomal complement using the laser-cell sorter. It is also possible to sort specific chromosomes or groups of chromosomes directly on to supporting filters for the subsequent use of DNA probes.

- B Cell Activation: The activation of B lymphocytes depends on the translocation of the protein kinase C activity within the cell. This activation results in the expression of membrane receptors for various cytokines which then allow cell proliferation and differentiation.

- Immunodeficiency: Immunodeficiencies associated with aging, chronic renal disease, AIDS, and burn trauma, show various lines of pathogenesis. Elderly individuals and renal disease both have immunodeficiencies of the T cell system. Burn patients have a lack of natural killer function, and AIDS and some elderly show a defect in monocyte function as well as the T cell defect. There is a connection between viral disease and immunodeficiency as both cause and effect events. In some cases it is possible to return a deficient result in an assay system to normal levels by the use of IL-2, a T cell active lymphokine. This is especially the case in assays of cells from elderly individuals.

- Granulocyte Function in the Elderly: Elderly individuals, although having normal numbers of granulocytes, are functionally granulocytopoenic since about half of their cells do not function in a phagocytic assay system.

- Biorhythms and Immune Function: There is a difference in the periodicity of the rhythmic patterns of lymphocytic responses to mitogens in cells from mice of different ages.

FY 1984 Annual Report and Research Highlights

The clinical research in the Section includes studies on the volunteers of the Baltimore Longitudinal Study of Aging and patients with various * illnesses who are hospitalized or clinic patients at hospitals in the Baltimore area. Studies of normative human aging have detailed defects in the T cell population of elderly people in which these cells have less numbers of IL-2 receptors, respond less well to mitogenic signals, and are less able to support the in vitro antibody formation ability of B cells. These individuals also fit certain phenotypes as determined by HLA typing. In some cases it is possible with the addition of IL-2 exogenously to bring the level of function of these deficient populations up to normal levels seen in younger people. The role of accessory cells such as monocytes is also being investigated, and it has been demonstrated that monocytes are necessary for IL-2 production by T cells and that the monocytes from elderly individuals are more active in some assays than are monocytes from young people. Sorting of chromosome preparations along with molecular probes will allow future investigations into the mechanism of this deficiency in IL-2 production by T cells from elderly individuals.

The studies on B cell activation show that the cell membrane receptor can be induced by agents which do not drive the cell into division cycles. This mechanism is mediated through the protein kinase C enzyme which undergoes a translocation in the cell when the activation signal is given to the B cell. Cytotoxic T cell preparations also can be triggered into development to functional units by the lymphokine IL-2 and other factors which have not yet been identified. The clinical role of cytotoxic T cells is being investigated in elderly individuals who have received various influenza vaccines. The activity of the immune T cells will be studied along with the role of IL-2 and other factors in driving or augmenting this activity.

The circannual rhythms in lymphocyte reactivity that has been previously reported has now been shown to have different periodicity in cells from different aged mice. This could explain the difference in results seen in studies comparing cells from young and old mice in mitogen assay systems.

Clinical studies in the Section will concentrate on in vivo immune responses of elderly people, host defense systems of debilitated individuals, and the study of change in a normal aging population. Basic studies will concentrate on control mechanisms and genetic regulation of lymphokine synthesis, receptor generation and action.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01-AG-00093-13-CPB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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	CPB, NIA
Others:	J. J. Proust	Visiting Associate	CPB, NIA, EOD 10/3/83
	G. D. Collins	Biologist	CPB, NIA
	M. A. Buchholz	Bio. Lab Tech	CPB, NIA
	R. K. Chopra	Visiting Fellow	CPB, NIA, EOD 4/2/85
	B. Bender	Medical Staff Fellow	CPB, NIA

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Gerontology Research Center, Clinical Physiology Branch

SECTION

Clinical Immunology Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.8	2.5	2.3

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 role of soluble factors produced by lymphocytes and monocytes in controlling the activation, proliferation and differentiation of lymphocytes participating in immunological functions was studied. Studies were performed with B and T lymphocytes to establish the requirement of various soluble factors (interleukins) in the development of functional lymphocytic populations.

B-cells. Purified G_0 B-cells activated under controlled conditions by anti μ reagents remain in G_0 state. However such cells have undergone significant changes since they gained the ability to proliferate in response to soluble mediators. The biochemical changes that occur as a result of stimulating G_0 B-cells with various agents implicates the turnover of phosphatidylinositol as an early event in B-cell activation.

T-cells. The in vitro activation of cytotoxic lymphocyte precursors requires, in addition to IL-2, components present in fetal calf serum (FCS). The active substance(s) from FCS after partial purification display none of the biological properties of the known classical interleukins.

The significance of these studies is that soluble factors play an ever increasing critical role in regulating lymphocyte activity. Characterization of these pharmacologically active substances and their role(s) in establishing immune function are important aspects in the understanding of the immune system.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01-AG-00095-12-CPB

PERIOD COVERED

October 1, 1984 - September 30, 1985

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	CPB, NIA
Others:	J. E. Nagel	Medical Officer, PHS	CPB, NIA
	B. S. Bender	Medical Staff Fellow	CPB, NIA

COOPERATING UNITS *(if any)*

Dr. R. Winchurch, Dept. of Surgery, and Dr. M. Liu, Dept. of Medicine, Johns Hopkins Univ., Francis Scott Key Med. Ctr., 4940 Eastern Ave., Balto., MD 21224

LAB/BRANCH

Gerontology Research Center, Clinical Physiology Branch

SECTION

Clinical Immunology Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.1	1	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.)*

Investigation of immuno-deficiencies of various etiologies demonstrated that individuals with physical trauma, AIDS, and chronic renal failure have certain defects in cell mediated immune function. AIDS patients show a defect in mononuclear cell phagocytic function. Burn patients lack NK cell function and NK precursor cells. Patients in renal failure carry high titers against the EBV virus and if they have been transfused they also carry antibodies to CMV.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01-AG-00096-12-CPB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Low Temperature Effects on Cells of Aging Individuals

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

PI:	M. A. Brock	Research Biologist	CPB,NIA
Others:	W. H. Adler	Medical Officer, PHS	CPB,NIA

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Gerontology Research Center, Clinical Physiology Branch

SECTION

Clinical Immunology Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.2	1.1	.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.)*

Splenic lymphocytes from young, 15 month old and 24-28 month old C57BL/6 mice housed in a constant environment were studied. Single cell suspensions were cultured in vitro with T cell mitogens, phytohaemagglutinin and Concanavalin A, and the B cell mitogen, lipopolysaccharide. Functional capacity of the T and B lymphocytes was assessed by the mitogen-induced incorporation of tritiated thymidine by dividing cells.

Circannual rhythmicity in levels of in vitro activation of T and B lymphocytes was expressed by cells from mice of all ages, however the properties of the rhythms were modified in cells from older mice. Phases of elevated responses alternated with phases of depressed responses; the freerunning periods of these rhythms increased from approximately 12 to 15 months in the two older groups of mice. Greatly extended phases of depressed responses, from 1 to 8 months, were characteristic of the rhythms of older animals and consequently extended the time of possible increased susceptibility to environmental assaults. Amplitudes of both T and B lymphocyte rhythms were unchanged in young and adult mice, but the T-cell rhythms were damped in senescent animals. This change in the relationships of T to B cell activation rhythms is another example of imbalance in the immune system with age. The age-related changes in expressed circannual rhythms by a population of mice suggest genetic control and parallel changes in gene expression over the lifespan. Since freerunning periods of the circannual rhythms increased with age, they were out of phase with those of young mice. The resulting continuously changing phase relationships periodically obscured the expected age-related decline in lymphocyte activation. This explains discrepancies in data reported by others showing no change in, increased or decreased lymphocyte activation with age. The significance of these results is that they show decay of temporal organization of circannual rhythms with age which may be associated with the physiological deterioration of organisms.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01-AG-00104-09-CPB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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	CPB, NIA
Others:	A. A. Nordin	Research Chemist	CPB, NIA
	J. E. Nagel	Medical Officer	CPB, NIA
	B. S. Bender	Medical Staff Fellow	CPB, NIA
	F. J. Chrest	Biologist	CPB, NIA
	R. S. Pyle	Bio. Lab Tech.	CPB, NIA
	B. A. Dorsey	Bio. Lab Tech.	CPB, NIA

COOPERATING UNITS *(if any)*

Dr. M. Liu, Department of Medicine, Johns Hopkins University, Francis Scott Key Mecidal Center, 4940 Eastern Avenue, Baltimore, MD 21224

LAB/BRANCH

Gerontology Research Center, Clinical Physiology Branch

SECTION

Clinical Immunology Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.5	2.0	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.)*

The immune function of participants in the Baltimore Longitudinal Study of Aging was evaluated to determine age-associated changes, and to relate these changes to clinical disease. Another major goal is to evaluate the ability of existing assays of immune function to provide an accurate assessment of the level of immune competence of aging individuals and to develop new methods and assays to evaluate host immune function.

ENDOCRINOLOGY SECTION

Annual Report Summary for the October 1, 1984 to September 30, 1985

The Endocrinology Section is engaged in a variety of projects that are directed to the goal of better understanding the biochemical and physiologic basis of age-related alterations of hormone secretion and action. The studies involve intact human subjects, animal models, tissue and cell culture techniques, and cell-free systems.

The fat cell offers unique advantages for aging research. Accordingly, we established a facility for in vitro culture of fat cells. Preadipocytes have been obtained from animals of varying ages. The immediate question to be answered was whether age of animal would program the developing and differentiating preadipocytes to exhibit the same type of biochemical change (decreased lipolytic responsiveness) that one sees in-vitro. If so, a valuable new approach to in vitro cellular aging would be available.

Preadipocytes from young animals replicate at a faster rate than do those of older animals. These cells differentiate readily into cells containing fat, but the lipolytic mechanism develops only partially. Thus, β-adrenergic receptors do appear although in small numbers and have low affinity. Other components (N_S; catalytic unit) of the cyclase system do appear. Lipolysis has not been demonstrable. The preadipocytes have a cyclase system that is stimulated by prostaglandins in a specific fashion. This finding is in sharp contrast to the situation in the normal rat fat cell in which prostaglandins are inhibitory. The future usefulness of these cultured cells for aging result remains promising but uncertain.

Because of these results with preadipocytes, we have attempted to obtain cells which are derived from mature adipocytes. We are now able to culture such cells from what are usually thought of as post-mitotic cells. We have termed these cells "post-adipocytes." They are morphologically different from preadipocytes, and their biochemical characteristics are under intense study. β-receptors and the adenylate cyclase system develop quite readily. These are an exciting new cell type holding great promise for research into aging and obesity.

We previously reported that in the liver of old rats a doubling of epinephrine-sensitive adenylate cyclase activity was apparent. Our evidence suggested that the mechanism seemed to involve some alteration of the liver cell membrane. Using the β-antagonist, ^{125}I-pindolol, to quantitate the β-receptors we find that β-receptors increase three-fold, i.e., more than the two-fold increase of epinephrine-sensitive adenylate cyclase. The β-receptor affinity is unchanged. No similar increase of β-receptor number has ever been seen under any other physiologic or pathophysiologic condition, including aging. Studies of animals at 6, 12, 18, and 24 months now show that there is no simple relationship between the increase of β-receptors and the increase of cyclase. Up to 18 months, a close correlation exists between the number of β-receptors and the activation of cyclase, i.e., the system is coupled. Thereafter, receptor numbers increase further but cyclase activity does not and is no longer closely correlated. We suspect that aging results first in an alteration of the

membrane to increase the number of receptors and then a further change which uncouples the response. This dramatic change with age can be reversed with food restriction, a maneuver which blunts many age-related changes of biochemical events. This observation should prove useful in understanding both sets of phenomena.

Our investigations of the effects of aging on neuroendocrine regulation continue. The neuropeptide growth hormone releasing (GRF) and corticotropin releasing (CRF) factors are the most recent members of the family of hypothalamic releasing factors to be isolated and characterized. In collaboration with investigators at the Developmental Endocrinology Branch, NICHD, we have used synthetic growth hormone releasing factor (GRF-44) to demonstrate that in healthy BLSA men the growth hormone (GH) response is unaltered with aging. Basal somatomedin-C (SM-C) levels are lower in the older men, but the magnitude of the incremental SM-C response is unchanged with age. The lower basal SM-C levels with similar incremental responses suggests that the overall integrated daily GH levels may be reduced in older BLSA men. We have also found that in BLSA men the basal ratio of AM/PM cortisol decreases significantly with age. There was a non-significant upward trend with age in the magnitudes of both peak ACTH and peak F responses to CRF and peak F responses occurred significantly earlier in the older men. Basal plasma levels of DHEA decreased profoundly with age as did the magnitude of peak DHEA responses to CRF-stimulated rises in endogenous ACTH. Our results are consistent with the hypothesis that negative feedback regulation of ACTH secretion by cortisol is diminished and that ACTH and F responses to CRF are well-maintained with age. The response of DHEA is discordantly decreased in healthy men, a finding compatible with the hypothesis that there is an ACTH-independent, age-related diminution in the regulation of adrenal androgen secretion.

Our investigations of prolactin (PRL) response to constant TRH infusion have shown that basal PRL is elevated in a significant number of older men and that the PRL level rises earlier and higher in the older men, in contrast to prior findings for TSH and the gonadotropins.

Thus it appears that, as a broad generalization, the so-called "stress hormones" ACTH and PRL may actually have a tendency to be more easily secreted in older men, while the reproductive and vegetative hormones (TSH, FSH, LH, GH) may be less actively secreted.

In a previous study we found the serum concentrations of the male sex hormone, testosterone, to be affected very little by age. New work examining total and free T levels in men with various kinds of illness has been consistent with our hypothesis that disease, rather than age per se, is the most important factor producing pathologically low T levels in aging men.

Our experiments on isolated rat pituitary cells <u>in vitro</u> have revealed that the previously reported reproducible deficiency in LH secretion is partially reversible by treating rats with luteinizing hormone releasing factor (LRH), the hypothalamic peptide which regulates pituitary LH secretion. This suggests that the pituitary defect may be secondary to deficient hypothalamic secretion of LRH, but further experiments using long term pulsed delivery of LRH will be needed to determine whether there is a residual non-reversible intrinsic defect or not.

Efforts will continue to be divided between studies of human physiology relevant to issues of effects of aging on endocrine function and research into mechanisms of aging using endocrine systems as the model in experimental animals and their cells *in vitro*.

Planned human studies include research into diurnal variations in hormones and the effects of age on diurnal rhythms and integrated hormone levels, a study comparing the effects of physiologic-level estradiol-progestin replacement on young castrate vs. older menopausal women, and investigations of the possibility that aging pituitary gonadotropes may secrete qualitatively altered glycoprotein hormones.

Experimental animal studies planned at this time will emphasize the effects of aging on pituitary physiology and biochemistry. Special emphasis will be placed on determining the cell-specific effect of phenomena previously described in mixed cell populations. In order to do this we will employ novel differential counting and cell sorting techniques. We also hope to investigate the role of local cell-cell interactions in altered pituitary function with age. A sophisticated perifusion device will make it possible to study pituitary cells under conditions more closely approaching the physiologic milieu than has been previously possible. Experiments investigating reversibility of age-related alterations in secretory capacity, modulating effects of steroids and neurotransmitters on cells derived from aged vs. young animals, effects of oxygen free radicals on "*in vitro* aging", and alterations in immunologic to bioactive hormone potency are planned. In addition, we hope to initiate a program of study to compare the biochemistry of protein synthesis and post-synthetic processing of glycoprotein hormones in cells from young and old rats.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00011-13 CPB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Hormones and Aging. I. Adenylate Cyclase and Hormone Action

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

R.I. Gregerman, M.D., Chief, Endocrinology Section, Clinical Physiology Branch, National Institute on Aging

COOPERATING UNITS *(if any)*

Division of Endocrinology, Johns Hopkins Hospital
Department of Surgery, Francis Scott Key Medical Center
Oncology Center, Johns Hopkins Hospital

LAB/BRANCH

Gerontology Research Center, Clinical Physiology Branch

SECTION

Endocrinology Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 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.)*

The project includes studies on the biochemistry of hormone-sensitive adenylate cyclase in a variety of tissues. Their purpose is to explore the mechanisms by which age produces alterations of hormone-responsiveness in biological membranes, with special emphasis on the relationship between adenylate cyclase and hormone receptors. Aging in fat cells is being studied in tissue culture of preadipocytes from rats.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00013-11 CPB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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, Clinical Physiology Branch, NIA

COOPERATING UNITS *(if any)*

Developmental Endocrinology Branch, NICHD, NIH
Department of Medicine, Francis Scott Key Medical Center

LAB/BRANCH

Gerontology Research Center, Clinical Physiology Branch

SECTION

Endocrinology Section and Human Performance Sections

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.6	1.4	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.)*

These studies gather data on pituitary function as it relates to gonadal, thyroid, adrenal, and growth hormone regulation in normal aging men from the Baltimore Longitudinal Study on Aging (BLSA). Recent results have shown that healthy men have no apparent change in growth hormone secretion compared with the decrements of secretory capacity reported for less well selected populations, but subtle alterations in diurnal secretory pattern for ACTH and cortisol, with a decrease in AM/PM cortisol ratio and a trend toward increased pituitary ACTH response to corticotropin releasing factor (CRF). The DHEA secretory response for ACTH is greatly decreased with age, in contrast to the results for cortisol, suggesting independent regulation of cortisol and DHEA secretion.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00023-10 CPB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Hormones and Aging. Pituitary, and Hypothalamic 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., Senior Investigator, Clinical Physiology Branch, NIA

COOPERATING UNITS *(if any)*

LAB/BRANCH

Gerontology Research Center, Clinical Physiology Branch

SECTION

Endocrinology Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.0	1.4	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 spece provided.)*

Secretory cells from rat pituitaries are studied in vitro to compare their physiology in old and young animals. Production of TSH and prolactin in response to TRH and production of LH and FSH and their subunits in response to LRH are being measured in order to investigate altered function of pituitary secretory cells. Deranged function of aged pituitary cells in vitro has been found. Castration increases LRH responsiveness of gonadotrophs of aged and young rats to the same extent. Pretreatment of rats with LRH has partially restored LH secretory function of cells from old animals, suggesting that hypothalamic deficiency is, at least in part, responsible for the observed age-related reduction in LH secretion.

HUMAN PERFORMANCE SECTION

Research Objectives

The Human Performance Section, in addition to the scientific efforts involved in the study of performance changes with aging, currently is responsible for the administration and maintenance of the Baltimore Longitudinal Study of Aging (BLSA). These administrative/service aspects (60% of staff time) include the clerical and administrative staff involved in the maintenance of the BLSA study sample, the computer staff involved with data entry and retrieval, the statistical staff who serve as consultants as well as developing new methodologies, and the scheduling and testing staff who coordinate all and perform some of the testing of the BLSA volunteers.

The objectives of the Human Performance Section are divided into those addressed to (1) the core functioning of the BLSA, and (2) specific BLSA and non-BLSA research projects.

The core function objectives include:

- Maintenance and expansion of the BLSA study panel with increased participant satisfaction, increased retention of the participants, and recruitment of new 75 and over males and females.

- Efficient planning for scheduling of visits and tests to make maximum use of the volunteers' time. This involves coordination of the many scientists from eight different Sections who are the primary users of this resource.

- Efficient and accurate data entry and retrieval from the master file to facilitate both management and research needs.

- The stimulation and facilitation of collaborative and multidisciplinary research within the GRC and with outside scientists to foster use of this valuable resource.

BLSA research project objectives include:

- The relationship of levels and rates of change of levels of physiologic and non-physiologic variables in health and disease.

- The definition of longitudinal aging changes in osteoarthritis and osteoporosis.

- The development and application of new statistical methodology for longitudinal studies.

Non-BLSA research project objectives include:

- Genetic studies on ALS and Parkinson's Dementia on Guam.
- The relationship of Dermatoglyphics to disease states.
- The development of bone in diverse cultures.
- The effect on care givers of chronic diseases including Alzheimers Disease.
- The relationship of obesity to mortality, disease and metabolism.

Selected Research Accomplishments

- o Osteoporosis: Analysis of the longitudinal bone measurement data on male BLSA participants confirmed earlier cross-sectional findings that bone loss is related to aging. The longitudinal results demonstrate that bone loss in males begins in the fourth decade of life and that males lose about 0.03mm of cortical thickness per decade, amounting to a 20% loss of cortical bone over the life span. It also showed no significant secular or cohort contributions to bone loss. Data on BLSA female participants are presently not sufficient for longitudinal evaluations. *

- o Kidney Function: At least five serial tests of kidney function (Creatinine Clearance) were performed in 254 normal volunteers, 118 with histories of renal and urinary tract abnormalities and 74 currently under treatment for hypertension. There was a significant longitudinal decline in clearance with older subjects declining faster than younger subjects in all three groups. These changes were normally distributed, and despite the highly significant mean declines one-third of the subjects in each group did not demonstrate a decline in clearance, and 7 actually had a significant increase. These findings are consistent with the thesis that there is an effect of age on renal function independent of disease and point out the difficulty of making judgments on individuals from average changes in a population. *

- o Water Homeostasis: The ability of older normal volunteers to handle a water load was tested in 37 males. Older subjects (60-75) were not as able to increase their free water clearance or urine flow and volume as well as middle age (40-59) or younger (29-39) subjects in response to the initial ingestion of 20ml/kg body weight of water. Arginine vasopression levels during these studies are being measured in an effort to define the mechanism responsible for these changes. The defect in water clearance has potential impact on the care of elderly patients and especially for those on diuretics. *

FY1985 Annual Report and Research Highlights

SUMMARY OF WORK PERFORMED IN THE HUMAN PERFORMANCE SECTION

1. The Baltimore Longitudinal Study of Human Aging. *

Objectives: The BLSA provides a well characterized group of subjects as a resource in support of a wide variety of scientific investigations in gerontology and other disciplines. While long-term planning is encouraged, important studies of shorter duration have also been undertaken. The long-term general goals of the study are to: (1) secure replicate measures of physiological, pathological, biochemical and psychological variables on longitudinal study participants at specified intervals; (2) summarize and compare the results of testing in relation to age according to cross-sectional and longitudinal formats; (3) identify characteristics of individual participants which may be related to changes of function over time and to age at death; and, (4) determine whether the data obtained support one or another theory of the mechanisms responsible for age-related functional decrements.

The Sample: Study participants are male and female volunteers recruited by other participants in the program. Recruits agree to return to GRC in Baltimore for 2½ days of testing every 2 years for an undetermined period. Our sample continued to be highly educated, mostly married, describing themselves as financially comfortable or better, and of the group who returned for the fifth visit, 90% rated their health as good or excellent on both first and fifth visits. Recent intake has focused on male and female volunteers 75 years of age and older.

Status: By August 19, 1985 a total of 1675 men and women (1246 men and 429 women) have participated in the testing program on one or more visits to the GRC.

From October 1, 1984 to August 19, 1985, 36 women were newly admitted to the program as compared to 31 men. Of the 429 women who have joined the BLSA since January 1978, 13 have died. Of the 1247 men who have joined the BLSA since the inception of the study in 1958, 350 have died. Age distribution of the active subjects is shown in Table 1.

Table 1.

Distribution of Active SLE+ Subjects by Age and Se 10-Aug-95

Age Group at least	but under	Males #	% of se	% of total	Females #	% of se	% of total
	20	0	0.00	0.00	1	0.30	0.14
20	24	4	1.66	0.42	3	0.91	0.43
25	29	18	2.95	1.90	16	4.79	2.29
30	34	28	4.59	2.95	24	7.19	3.43
35	39	38	6.23	4.00	20	5.99	2.86
40	44	68	10.32	6.98	23	6.79	3.29
45	49	59	8.38	6.11	21	6.29	3.00
50	54	40	6.56	4.21	19	5.69	2.72
55	59	46	7.54	4.84	21	6.29	3.00
60	64	71	11.64	7.48	26	8.68	4.15
65	69	60	9.84	6.32	41	12.28	5.86
70	74	67	10.98	7.06	34	10.18	4.86
75	79	71	11.64	7.48	36	10.78	5.15
80	84	40	6.56	4.21	22	6.59	3.15
85	89	19	3.11	2.00	4	1.20	0.57
90	94	4	0.66	0.42	3	0.90	0.43
95		0	0.00	0.00	0	0.00	0.00
TOTAL		610	100.00	64.28	334	100.00	35.72

2. Illness & Disability Study. *

It is important in any long term investigation to gain as much information as possible on the inactive as well as the active subjects. Toward that end the Illness & Disability Study was initiated in 1977. At that time, there were 299 dropouts and 296 were located. Since then, there were 38 female and 149 male participants who dropped out from the BLSA.

In order to obtain alive/dead status information on BLSA subjects, the National Death Index (NDI) was utilized. Records of 1313 BLSA subjects were sent to NDI. The results are shown in Table 2. As a result of this search, we learned about the death of six dropouts (not previously known) and date of death on 6 deceased subjects. As NDI expands their death registry and we obtain social security numbers on our subjects, NDI perhaps would become a useful tool in the future. In addition, procedure for obtaining death certificates on BLSA subjects have been established through the Department of Vital Records, School of Hygiene and Public Health, Johns Hopkins University.

To gain further information regarding the alive/dead status on dropouts, a second follow-up study was initiated. The results are shown in Table 3. A similar follow-up study will be conducted every year.

Table 2. Results of the National Death Index Search.

	STATUS				
RESULTS	ACTIVE	FAIL	WITHDRAWN	DECEASED	TOTAL
Number of BLSA Subjects involved	887	277	112	37	1313
Number of records matched	66	28	22	15	131
Wrong Match (Verified death date against visit date)	66	3	2	1	72
Match on all variable		2	4	6	12
Match on some variables		23	16	8	47

Of the 22 deceased subjects who were not matched on NDI list, 18 were not expected to be on NDI list because they died before 1979 or after 1982. Four deceased subjects were missed in this search.

Table 3. Alive/Dead Status of BLSA Dropouts.

	Dropouts from 1st Follow-up	Dropouts since July 1, 1977			
	Men	Men	Women	Both	TOTAL
Total Number of Dropouts	151	162	66	228	379
Found Alive	129	121	60	181*	310
Found Deceased	15	3	2	5	20
Unable to Locate	4	38	4	42	46
Do Not Contact Again	3				3

*2 subjects notified in 2nd follow-up study stipulated they not be contacted again.

3. Development of Statistical Methodology. *

Statistical methodology is being developed which is applicable to longitudinal data sets, particularly data coming from the Baltimore Longitudinal Study of Aging (BLSA). Besides developing methods for the analysis of the many possible time-dependent processes observed during the course of such a study, attention is also being given to developing methods for comparing specific statistical measures between various identifiable groups in the study as well as developing basic structures potentially applicable to the design of specific experiments arising in the study. This methodological development includes experimental design, modeling, multiple comparison, and interpretation of data; and will help to fill the need for more appropriate methods of analysis for not only longitudinal data but other types of data as well.

Data from the BLSA is an example of prospective data involving multiple measurements taken at different times over the life of an individual with complications such as varying lengths of subject follow-up and irregular points of observation. The proportional hazards model as introduced by Cox and generalized by Kalbfleisch and Prentice is a stochastic model with wide-ranging and important implications for the analysis and interpretation of such data. This model has been successfully used to examine the problem of subject attrition in the BLSA. Factors have been identified which are associated with subjects dropping out of the BLSA. The initial model for this study of attrition has been extended to examine possible associations between the attrition of subjects recruited by other subjects in the study and the attrition of each such subject recruitor in the study.

The proportional hazards model is also being used to examine the relationship between obesity and long-term mortality in the BLSA. The model is being developed so as to study such things as cigarette smoking as a confounding variable with body mass index (BMI) and the relationship of each to mortality, the possible influence of an individual's birth cohort (cohort effect) on the model, and an examination of other related variables as well. After considering the aspects of the modeling just mentioned, one object of this analysis is to obtain relative risks and survival probabilities associated with different levels of the risk factors such as obesity and to examine how these relative risks change as an individual gets older. In addition, plans are underway to include in the model additional factors which would examine the relationship between diet and long-term mortality.

Efforts are also in progress to expand the capabilities of over proportional hazards model to effectively use time-dependent covariates or risk factors, competing risks and multiple outcomes such as death due to different causes, and comprehensive and transparent graphic displays of results from the model. A recent paper "Effective Presentation of Results from Multivariate Analyses of Gerontological Data" published in the 1984 Social Statistics Section Proceedings of the American Statistical Association by Brant, et al. demonstrates several ways in which results obtained from such a sophisticated and powerful statistical model can be communicated or presented in an easily understandable manner.

Another area of statistical development is being carried out in research involving simultaneous statistical inference or multiple comparisons. After estimates of desirable parameters or functions of parameters from specific models for data like those of the BLSA are obtained, it is often of interest to statistically test or compare differences among the different estimates. Decision theory along with Bayesian statistical theory is being used to develop innovative methods for performing multiple comparisons testing. Following an approach originally introduced by Duncan, our present work extends this early work to the solution of more complex simultaneous t testing, t interval and point estimation problems that arise in a wide variety of experimental situations. The Bayesian approach used, unlike traditional approaches provides extremely flexible (adaptive) a posteriori rules or procedures for relevant testing problems. Decisions made about specific hypotheses can range from being highly conservative on the one hand to less conservative and highly powerful on the other, depending on certain statistics derivable from the data under consideration.

At present, a paper is being prepared demonstrating how between-group and within-group comparisons can be made all at one time within a comprehensive Bayesian simultaneous testing plan. This work will enhance the ability to make comparisons between various groups of subjects observed during the course of a longitudinal study as well as comparisons in other data sets. In addition, computer software continues to be developed which will enhance the application of these methods.

Work in the area of the design of experiments is being carried out through the study of specific mathematical structure such as Latin squares and frequency squares. Such squares allow experimenters to specify the randomization procedure necessary for the validity of statistical tests made in specific analyses of data. For example, in studies requiring repeated measures such as in longitudinal studies, Latin squares and frequency squares can be used to counterbalance order effects of such measurements. Research is being carried out in collaboration with G. L. Mullen of The Pennsylvania State University in which the VAX 11/780 of the Gerontology Research Center is used to study and classify various types of Latin and frequency squares needed in experimental designs. A paper entitled "A Note on Isomorphism Classes of Reduced Latin Squares of Order 7" by Brant and Mullen has been published in Utilitas Mathematica (Vol. 27, 1985). In addition, work is in progress on a comprehensive study of frequency squares, a study whose need has been expressed in the literature by several other investigators.

Other methodology is under consideration for application to longitudinal and cross-sectional data. These methods have been demonstrated with other researchers and scientists at the Gerontology Research Center and at the Center for Disease Control. A regression model was developed for the study of the relationship between body mass index and the mortality ration for various populations of people. A manuscript has been written and accepted for publication ("Impact of Age on Weight Goals" by Andres, Elahi, Tobin, Muller and Brant) using his model to study the relationship in an age-specific manner. Other collaborative efforts have resulted in coauthorship on manuscripts such as "Diet and Cardiovascular Death in Men of the Baltimore Longitudinal Study on Aging" and "Proposed Age-Adjusted Standards for Recommended Body Weight."

Work has begun on exploring the development of a model for classifying individuals into either a diseased or disease-free group based on dermatoglyphic characteristics obtained on each individual. In trying to develop some diagnostic index for a specific disease such as Alzheimer's disease, for example, based on dermatoglyphics, the first step undertaken has been to develop a classification method for differentiating individuals into the correct ethnic group based on dermtoglyphic characteristics. Using data from male subjects representing five different ethnic groups, several strategies for correctly classifying a given individual are being explored. Also, research is being completed on an evaluation study of a disease control program which utilizes additional features of the proportional hazards model. The model analyzes data from a series of subjects whose periods of observation are staggered at different times during the calendar year, thus controlling for any effects resulting from the time of measurement of a given group. This method of analysis shows potential application to studies of certain aspects of the BLSA.

4. BLSA Computer Operations. *

As in previous years, the Computer Group's principle focus has been on the huge BLSA master file of data and on the medical charts which feed into it. Efforts have continued toward streamlining data and paper flow, so that the efficiency of both the science and administration of the BLSA is improved. To this end, the Group uses four computer systems, maintains the chart library, and assists in the administration of some of the more technical testing operations.

The Digital Equipment PDP 11/70, which serves as the computer repository for the BLSA data, has been improved. A cost effective method of acquiring memory was uncovered which allowed the doubling of the computer's main memory size; this in turn increases the capacity of the machine as well as the operating efficiency. More terminal ports have also been installed, bringing the current total to 40. Along with the terminal lines, the user base has increased, and better tools have been provided to the users. A word processing package has been installed, allowing all users to generate their own drafts and documentation. Admissions processing has been greatly automated and simplified from the BLSA volunteer participants' viewpoint. Correspondence generation has been significantly simplified, and some of the more tedious coding and data reduction has been eliminatd by the creation of straightforward data entry and analysis routines. The quality of the data has also been addressed. Integrity checks have been installed on input, and the data base is reviewed continually for consistency and general well-being. In these efforts, approximately 200 routines have been generated and tested. The result has been an acceleration in the growth of the data base, to about 797,000 records (80 million characters), or about 7.7% larger than last year.

The Data General Eclipse system which serves as a Remote Job Entry port to the large computer resource at NIH, Bethesda, has also been upgraded. Disk storage in the amount of 73 million characters has been added, and a new version of the operation system has been installed. While this has not resulted in any expansion of the primary purpose of this system, it has made for better utility.

The group has also provided consultation on the NIH 370 computers and the GRC's VAX installation. A clinical data base system, MEDUS/A has been installed for testing on the 11/70.

On the non-computer side of the shop, progress has been made in the medical record library. Microfiching of the charts has proceeded at a steady pace, and a fire-proof vault has been installed to safeguard this irreplaceable data. Procedures in chart tracking have also been implemented to reduce overall turn-around time.

Staff has also been involved in the use of newly acquired computer driven bone scanning equipment. Testing on this equipment is being performed at a heavy level for both BLSA and non-BLSA projects, and Group personnel have been principally involved.

5. Studies of Performance Changes with Aging. *

Physiology: Serial creatinine clearances (5-14 studies) were obtained on 446 normal volunteers in the BLSA followed between 1958 and 1981. Subjects were subcategorized into "normal" (n=254), renal and urinary tract abnormalities (n=118), and "treated" hypertensives (n=74). The normal group showed an average decline in clearance of 0.75ml/min/year with the older subjects tending to have larger declines than the young ($p<.0001$). In all three categories there was a normal distribution of slopes of the rates of decline in clearance with age, a finding consistent with the hypothesis that the decline is secondary to an aging phenomena rather than to disease states. In each of the categories approximately one third of the subjects had positives (though predominantly non-significant) slopes. Seven of the 446 volunteers had statistically significant increases of their clearance over time. This demonstrates the difficulty of making individual judgments from group data. Consistent with previous reports (Wobbly analysis of Schlesselman) while group data on the rate of change of a variable with time may be very significant, it is harder to define the accuracy an individual's rate of change.

In collaboration with Drs. Frieberg and Spector of the Francis Scott Key Medical Center studies on the effect of age on water excretion were carried out on 37 normal male volunteers. They were screened for any diseases or medications that might influence their salt and water metabolism, and after an overnight fast underwent a Water Load test. They ingested 20ml/kg of water at "0" time and voided at 30 minute intervals for the first 2 hours and hourly thereafter. At each time they ingested a quantity of water equal in volume to the urine collection. There were significant differences in the ability of the older subjects (60+, n=11) to increase their urine flow or free water clearance as much as the middle aged (40-60, n=16) or the young (29-30, n=10). There were not only changes in the maximum free water clearance but also in the time course, with older subjects reaching their maximum later ($p<.005$). Differences in minimum urine osmolarity were of borderline significance and there was no difference in the time to reach minimum values.

	UFLOW	CH2O	UOSM
YOUNG	21.0 ± 1.27	16.1 ± 1.27	63.9 ± 3.21
MIDDLE	18.4 ± 1.70	13.2 ± 1.22	70.2 ± 6.32
OLD	15.1 ± 1.11	10.4 ± 1.01	84.4 ± 7.10
Correlation Coefficient	n = 37 0.576	0.576	0.290

These results indicate that older subjects do have a defect in their ability to handle a water load along with their previously described alteration in handling a hyperosmolar load. The mechanism of this change will be investigated by analyzing Arginine vasopressin levels obtained during the water load.

Nutrition: In collaboration with scientists at the NCI, the data on nutrient intake of BLSA subjects will be used to test the validity of a retrospective interview technique to ascertain past dietary habits. The question of the effect of diet on the development of cancers is an important one and is of great interest to the NCI. A prospective study, where large numbers of people are asked about their present diet and then followed to determine the incidence of cancers, would take years. A faster method would be to ask people what they were eating 10 or 15 years in the past and to determine if their past diet were related to their present health. Key to this approach is the accuracy of their memory, i.e., how valid is the data. BLSA volunteers have given extensive dietary information 10 years ago in the form of 7 day dietary diaries. There are 271 males who had two diaries collected between 1971-1975 and who are still active in the study. These volunteers have been contacted and asked to fill out a questionnaire about their diet during this period of time, and their estimates will be related to their actual diet as recorded in the old diaries. This will determine if it is possible to collect meaningful data by this retrospective questionnaire. If so, the questionnaire could be applied in large scale to epidemiologic studies and provide a valuable investigative tool.

Metabolism: Studies done in collaboration with the Metabolism Section on new efforts in nutrition (resurveying our entire population including females with 7 day dietary diaries) and analysis of body composition, glucose tolerance, obesity, and mortality data are addressed in the Metabolism Section report.

6. Investigations of Osteoarthirits and Bone Loss. *

Description: Bone loss and osteoarthritis are universal phenomena. 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. In trabecular bones, 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 verteral column also decreases with age. The vertebral plates decrease in density, lose resistance to vertical compression stress and are more vulnerable to vertebral collapse.

Major Findings: Both men and women lose cortical and trabecular bone with increasing age, although different parts of the skeleton may demonstrate different rates of bone loss.

Post-menopausal women lose more cortical bone than men. The possible sex differential and effect of menopause in trabecular bone loss is less well understood and is presently under investigation in our lab.

Analysis of the longitudinal bone measurement data on male BLSA participants confirmed our earlier cross-sectional findings that bone loss is related to aging. The longitudinal results demonstrate that bone loss in males begins in the fourth decade of life and that males lose about 0.03mm of cortical thickness per decade, amounting to a 20% loss of cortical bone over the life span. It also showed no significant secular or cohort contributions to bone loss. Data on BLSA female participants are presently not sufficient for longitudinal evaluations.

Guamanian patients with Amyotrophic Lateral Sclerosis showed striking ** reduction in cortical bone mass of the second metacarpal when compared to normal Guamanian controls or to Guamanian patients with Parkinsonism Dementia. The reason for this reduction is presently being investigated.

Bone evaluations of the ulnar and radial sides of the second metacarpal suggest differential bone growth and bone loss on the two sides. These results support our earlier suggestion that there is an association between bone mineral density and mechanical stress, excerted on the bone by the muscle.

7. Study of Normal Variability.

Description: Dermatoglyphics, the development and final configurations of digital and palmar dermal ridges, have proven to be excellent biological markers. While they are for the most part genetically determined, their final development, which is completed at the end of the first trimester of pregnancy, is also influenced by intrauterine disturbances. Once developed, dermatoglyphics do not change nor can they be altered. No two individuals (including identical twins) have identical dermatoglyphics. These qualities make dermatoglyphics very useful genetic, as well as early prenatal environmental, markers in clinical studies.

Major Findings: Patients with "constipation-mitral valve prolapse" syndrome have significantly higher frequency of digital arches than normal individually matched controls. On the other hand, contrary to an earlier published report, digital and palmar dermatoglyphics of 92 patients (47 male and 45 female) with Alzheimer's disease were not found to be significantly different from individually matched normal controls. The data are presently further compared with another control sample and with a sample of adult patients with Down's Syndrome.

No associations were found between dermatoglyphics and amyotrophic lateral sclerosis, Parkinsonism dementia or endemic cretinism.

An atlas of the world-wide distribution of dermatoglyphic traits was ** published so that patients with various disorders can be compared with controls of the same ethnic origin. Study of other forms of lateral dominance indicated that eye preference, digital interlocking and foot dominance are not closely related to each other or to handedness.

8. Epidemiological and Genetic Studies on Amyotrophic Lateral Sclerosis (ALS) and Parkinsonism Dementia (PD) of Guam. **

Description: In an effort to elucitate the etiology of high incidence of ALS and PD on the island of Guam, a patient-control prospective study (Registry) was established in 1958. The Registry includes, in addition to the patients and their individually matched controls, their respective parents, sibs, offspring and spouses. The objective of the registry has been to determine (1) whether relatives of ALS and PD patients have higher risk for developing the disease than relatives of controls; and (2) if familial occurrence does exist, to determine the extent of genetic involvement in the etiology of the disease. A twenty-five year follow-up analysis of the registry has just been concluded.

Major Findings: (See also project entitled "Investigations of Osteoarthritis and Bone Loss" relating to bone loss in ALS/PD patients and Gumanian controls.) The twenty-five year follow up of the patient-control prospective study has been completed and manuscript is in press. The results indicated that sibs, parents and spouses of patients have significantly higher risks for developing ALS and PD than the relatives of matched controls or the Guamanian population in general. This suggests that ALS and PD are indeed familial in occurence.

Offspring of patients do not show significantly higher risk for developing the disease than offspring of controls or the Guamanian population at large.

The increased risks among the spouses and the lack of increase in risk for the offspring of the patients taken together with other recent epidemiological findings suggest that an environmental involvement may be the primary cause of the disease although genetic predisposition to the disease seems to be quite likely. A segregation analysis of sibships with both one or neither parent affected is presently underway.

Significant reductions in cortical bone mass were observed in patients with motor neuron disease (ALS). Significant negative correlation was also found between percent cortical area of the second metacarpal of ALS patients and bone density muscle atrophy and weakness. No such decrease in cortical thickness was seen in Parkinsonism dementia patients.

9. Impact of Dementia and Chronic Diseases.

Description: The purpose of this study was to examine whether caring for an elderly relative with dementia results in different levels of burden on the caregiving family member (i.e. spouse or daughter) than caring for a disabled elderly person with other chronic physical disease/s. Whether different disabilities have the same or different impact on the caregivers is an important issue. Knowledge of differential impact can lead to a differential pattern of professional help for a patient as well as for his family.

Major Findings: A matched case comparison design was used in this study. The comparisons (caregivers of patients with chronic disease) were matched with the cases (caregivers of patients with dementia) for age, ethnicity (Jewish), type of relationship to the patient, and sex of the patient. All caregivers (age 50-84 years) were physically living with the patient in the same household for at least six months prior to the date of interview. The data was obtained by means of personal interviews in caregivers homes. The findings of this study indicate that despite the fact that cases were significantly older than matched comparisons and patients with dementia were significantly more dependent than patients with chronic diseases, caring for a demented elderly person did not result in greater psychological, physical, financial, social, and overall burden on the caregivers than caring for an elderly person with chronic diseases. The results of the univariate analyses indicated that matched comparisons experienced significantly greater overall social burden than cases. Multivariate analyses of the same data controlled for the effects of patients dependency, and showed that in addition to social burden, matched comparisons experienced significantly greater physical and overall burden while there were no significant differences with regard to psychological and financial burden.

This study also examined factors associated with depression among wives and daughters who were caregivers for elderly persons with chronic diseases. The data indicat that while there were no significant differences between the matched pairs with regard to the symptons of depression as measured by the Center for Epidemiological Studies Depression scale, 62 percent of the caregivers were found to have significant symptoms of depression. Further, the results showed that caregivers who were depressed were taking care of patients who were more dependent ($p < .05$) and had more problem behavior ($p < .005$). Caregivers' and environments' characteristics were not found to be associated with depression. These findings have important implications for understanding the depression caregivers experience.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00015-27 CPB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

The Baltimore Longitudinal Study of Human Aging

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

See Attached Page.

COOPERATING UNITS *(if any)*

LAB/BRANCH

Gerontology Research Center, Clinical Physiology Branch

SECTION

Human Performance Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 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.)*

The Baltimore Longitudinal Study of Human Aging (BLSA) serves as a resource for scientists working in the field of Gerontology. It provides a well-described group of men and women between 20 and 96 years of age for studies of the mechanisms of human aging. Projects in physiology, biochemistry, psychology, nutrition, pharmacology, endocrinology, sociology, and genetics, have been carried out or are in progress.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00021-22 CPB

PERIOD COVERED
October 1, 1984 to September 30, 1985

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

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

C.C. Plato Sr. Research Geneticist CPB NIA

COOPERATING UNITS *(if any)*

See attached page.

LAB/BRANCH
Gerontology Research Center, Clinical Physiology Branch

SECTION
Human Performance Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.00	0.30	0.70

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.)*

Dermatoglyphics, the development and final configurations of digital and palmar dermal ridges have proven to be excellent biological markers. While they are for the most part genetically determined, their final development, which is completed at the end of the first trimester of pregnancy, is also influenced by intrauterine disturbances. Once developed, dermatoglyphics do not change nor can they be altered. No two individuals (including identical twins) have identical dermatoglyphics. These qualities make dermatoglyphics very useful genetic, as well as early prenatal enviromental markers in clinical studies.

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. Specifically, the objectives of this project are: (A) To study the distribution of Dermatoglyphic markers in population isolates, family units, disease entities and normal control samples, and to utilize these genetic markers in understanding the etiology, development and early diagnosis of diseases or processes with late onset. (B) To determine the lateral functional dominance, grip strength, among BLSA participants, and assess their relationship to physiological processes or diseases demonstrating bilateral asymmetry. (C) Cross-sectional and longitudinal study of visual function in BLSA participants.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

PROJECT NUMBER

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00022-09 CPB

PERIOD COVERED
October 1, 1984 to September 30, 1985

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Investigations of Osteoarthritis and Bone Loss

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

C.C. Plato Sr. Research Geneticist CPB NIA

COOPERATING UNITS *(if any)*

Laboratory of Central Nervous System Studies, NINCDS

LAB/BRANCH
Gerontology Research Center, Clinical Physiology Branch

SECTION
Human Performance Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.5	0.95	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.)*

Osteoarthritis and bone loss are the two principal age related changes of the human skeleton. Even though these changes are considered inherent to aging, they may result in incapacitating ailments. Bone loss and osteoarthritis are universal phenomena. The advanced cases of osteoarthritis (degenerative joint disease) produce severe restrictions of movement associated with pain. Advanced bone loss may result in osteoporosis and frequent bone fractures. At some time during the fourth decade of life the human skeleton begins to loose bone. That is, bone mass decreases in relation to bone volume. In tabular bones, 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 verteral column also decreases with age. The vertebral plates decrease in density, lose resistance to vertical compression stress and are more vulnerable to vertebral collapse. Most prominent are vertebral compression fractures and fractures of the femoral neck. The following skeletal sites are involved in the present study: hand-wrist, ulna and radius and vertebral column. This project deals with the epidemiological, genetic and longitudinal aspects of osteoarthritis and bone loss among (1) the participants of the Baltimore Longitudinal Study, (2) in a sample of normal children and adult Guamanians (Chamorros), (3) among patients afflicted with Amyotrophic Lateral Sclerosis/Parkinsonism Dementia Complex of Guam, and 4) study of bone mineral density and effect of muscular activity on bone in rats.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

PROJECT NUMBER

NOTICE OF INTRAMURAL RESEARCH PROJECT

ZO1 AG 00028-09 CPB

PERIOD COVERED
October 1, 1984 to September 30, 1985

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Epidemiological & Genetic Studies of ALS/PD Complex of Guam

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

C.C. Plato Sr. Research Geneticist CPB NIA

COOPERATING UNITS *(if any)*

C & F Research Center, NINCDS

LAB/BRANCH
Gerontology Research Center, Clinical Physiology Branch

SECTION
Human Performance Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.60	0.20	0.40

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 an effort to elucitate the etiology of high incidence of ALS and PD on the island of Guam, a patient-control prospective study (Registry) was established in 1958. The Registry includes, in addition to the patients and their individually matched controls, their respective parents, sibs, offspring and spouses. The objective of the registry has been to determine (1) whether relatives of ALS and PD patients have higher risk for developing the disease than relatives of controls and (2) if familial occurrence does exist, to determine the extent of genetic involvement in the etiology of the disease. A twenty-five year follow-up analysis of the registry has just been concluded.

Other objectives of this study are: 1) to investigate the genetic and epidemiological factors contributing to the very high incidence of Amyotrophic Lateral Sclerosis and Parkinsonism Dementia (ALS/PD) on Guam; 2) to evaluate the distribution of the various estalished genetic and anthropological markers among the normal Guamanian population and compare them with those of the ALS/PD patients; and 3) to acertain 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 00241-04 CPB

PERIOD COVERED
October 1, 1984 to September 30, 1985

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Development of Statistical Methodology for the Analysis of BLSA Data

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

Larry J. Brant Mathematical Statistician CPB NIA

COOPERATING UNITS *(if any)*

LAB/BRANCH
Gerontology Research Center, Clinical Physiology Branch

SECTION
Human Performance 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.)*

The theoretical development of statistical methodology is progressing in the areas of epidemiological models, multiple comparisons, survival analysis, and the design of experiments, each of which is applicable to longitudinal studies. The research utilizes various regression methods for prospective studies, Bayesian theory in conjunction with decision theory, and numerical computing methods. The methodology created provides original contributions to experimental testing associated with longitudinal studies, the simultaneous comparison of specified effects (e.g. treatments against a control or placebo), epidemiological study of disease states, survival or failure analysis of longitudinal data and other longitudinal observations representing growth and other physical changes of humans and animals. Accomplishments in the creative use of Bayesian theory in the area of multiple comparisons will fill a void in the established statistical armamentarium.

METABOLISM SECTION

Research Objectives

The underlying objective of the Metabolism Section is to gain an understanding of the metabolic complexities associated with aging. In the simplest terms, "primary" biological processes of aging are associated with a wide variety of "secondary" processes. The latter processes include such variables as inactivity, diet, body composition changes (lean body mass, obesity, and fat distribution pattern), and the effects of multiple disease processes and medications. On the one hand, it is our objective to dissect away the secondary effects so that true biological aging processes in man can be understood. On the other hand, the secondary processes may well prove to be of equal or greater importance in the determination of the overall picture of the aging human being. An understanding of these effects and of their relationship to primary aging processes is a fundamental necessary for the planning of rational processes to maintain health during aging and to prevent the diseases and infirmities so characteristic of the elderly.

Specifically, the research objectives of the Metabolism Section are (1) to describe age differences and age changes in metabolic variables; (2) to determine biological mechanisms underlying those age effects; (3) to assess the impact of those age effects on other variables, on disease development, and on mortality; and (4) to define normative standards as influenced by age. The major metabolic variables include glucose homeostatic factors, insulin secretion and sensitivity to insulin, body composition including lean body mass, obesity, and fat distribution, acute effects of physical activity, long-term effects of physical fitness, and dietary variables, serum lipids, and adipose tissue metabolism.

Selected Research Accomplishments

- Age-Specific Weight-for-Height Tables: Further analytical refinements of the relationship of the weight-for-height relationship to mortality confirmed their U-shaped relationship in men and women across the entire adult age spectrum. A collation of all available data from the world's literature shows without exception that upper limits of the weight-for-height ranges for middle-aged and older individuals in the commonly used tables of the Metropolitan Life Insurance Co. are lower than justified by the data. The 1985 NIH Consensus Development Conference on the Health Implications of Obesity accepted the fact that the Metropolitan weight tables are limited by their failure to take age into account. The tables which we have generated and labeled as the Gerontology Research Center tables are the first to provide age-specific weight recommendations.

- Beneficial Effects of Weight Loss in Elderly Obese Sedentary Men: A moderately obese, sedentary group of elderly men, otherwise in good health, have been participating in a weight-losing regimen. In order to differentiate possible beneficial effects of weight loss from the effects of increased physical activity, this group lost weight predominantly by dietary means; another interventive group will maintain their weight while increasing their activity. The weight loss group on entry into the study showed the following physiological impairments: an impaired glucose tolerance, resistance of body tissues to insulin, low serum levels of high density lipoproteins (HDL) and especially of the HDL_2 fraction. There was, furthermore, a lack of effect of insulin on adipose tissue lipoprotein lipase (LPL) activity on insulin clamp studies, in marked contrast to insulin effects in young lean subjects who show an increase in adipose tissue LPL levels. Early results in a small member of subjects showed that after weight loss, significant improvement occurred in the lipid abnormalities: HDL rose by 19% (mainly in the important HDL_2 fraction) after only a 6% decrease in body weight. It is postulated that resistance of adipose tissue LPL to stimulation by insulin may be responsible for the low HDL levels of obese sedentary elderly men.

- Favorable Effect of Dietary Fiber on Coronary Risk Factors: An increase * in dietary fiber has been recommmended for its possible beneficial effects on the intestinal tract, including a preventive effect on carcinoma of the colon. Other possible beneficial effects have not received as much attention despite controlled laboratory studies demonstrating a variety of such effects. Epidemiologic differences among diverse population groups have also provided suggestive evidence of favorable effects. We now add to these studies a different kind of analysis: correlations of fiber intake with metabolic variables within an American free-living population, the male participants in the Baltimore Longitudinal Study of Aging. "Spontaneous" fiber intake was shown to be significantly and favorably related to both systolic and diastolic blood pressure and to the fasting plasma glucose level. In addition, there was a suggestively favorable effect ($0.05<p<0.1$) on serum cholesterol and triglyceride levels and on glucose tolerance.

- Dietary Fiber Associated with Decrease in Cardiovascular Mortality in Very Old Men: Dietary risk factors for death from cardiovascular disease have been shown to be of importance even into very old age. There were 23 such deaths in men over age 75 years who had been participants in the Baltimore Longitudinal Study of Aging. Their diets were compared with the diets of 23 control subjects matched for age, obesity, and time of entry into the study. The men who were destined to die consumed less fiber, ate fewer calories, and their dietary fatty acids had a lower polyunsaturated saturated ratio than was present in the survivor group. *

- Habitual Physical Activity and Coronary Risk Factors: Important risk factors for the development of coronary artery disease include elevated serum lipids, glucose intolerance, and hypertension. These are in turn influenced by age, degree of obesity, and the pattern of distribution of body fat. We previously showed that the fat pattern was more predictive of the metabolic risk factors (lipids and glucose abnormalities) and that total obesity was more predictive of the blood pressure level. Since the habitual pattern of physical activity can also influence these risk factors, we analyzed these relationships in male volunteers in the BLSA. When age, obesity, and fat pattern are simultaneously taken into account, physical activity influenced the serum cholesterol level but did not significantly affect the other risk factors. *

FY 1985 Annual Report and Research Highlights

A comprehensive summary of research progress is contained in the individual project reports which follow.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00202-2 CPB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Physical Activity, Body Weight, Age, and Coronary Risk Factors*

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

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Reubin Andres, M.D.	Chief, Metabolism Section, CPB, NIA
Patricia Coon, M.D.	Medical Staff Fellow, CPB, NIA
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Jordan Tobin, M.D.	Chief, Human Performance Section, CPB, NIA

COOPERATING UNITS *(if any)*

LAB/BRANCH

Gerontology Research Center, Clinical Physiology Branch

SECTION

Metabolism Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.25	0.85	0.40

CHECK APPROPRIATE BOX(ES)

- [x] (a) Human subjects
  - [ ] (a1) Minors
  - [ ] (a2) Interviews
- [ ] (b) Human tissues
- [ ] (c) Neither

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

Risk factors for coronary artery disease (CAD) include age, metabolic and cardiovascular factors (hyperlipidemia, hyperglycemia, hypertension) and also certain living habits (diet, cigarette smoking, and physical activity level). Overweight is known to be associated with these factors. More recently, the pattern of fat distribution is emerging as an important contributory variable. Data obtained on participants in the Baltimore Longitudinal Study of Aging (BLSA) have been analyzed. The Body Mass Index or BMI (weight/height^2) was used as an index of overweight and the waist:hip circumferential ratio (WHR) as a measure of fat distribution pattern. Both bivariate and multiple regression techniques were used to assess interrelationships among the variables designated as "independent" (age, BMI, WHR, and physical activity level) as well as to assess their influence on the variables designated as "dependent" (serum cholesterol, triglycerides, glucose tolerance, fasting plasma glucose and systolic and diastolic blood pressure). Habitual physical activity level was obtained from detailed activity history questionnaires completed on each visit since 1965 by most participants in the BLSA. The habitual activity level had very little independent effect on coronary risk factors except for the serum cholesterol level. Thus, although intensive physical activity can be shown under experimental laboratory conditions to alter many coronary risk factors in a favorable direction, in this study of a free-living population the effect of activity is minimal. These surprisingly negative results might be explained if physical activity exerts its effects in this population by acting on body weight, so that it loses its independent significance on multivariate analysis. Another caveat is necessary: population studies which include larger numbers of very highly active individuals may show activity effects not demonstrated in this population. This however remains to be shown.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 00204-2 CPB

PERIOD COVERED
October 1, 1984 to September 30, 1985

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Metabolic Studies in the Baltimore Longitudinal Study of Aging*

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

Reubin Andres, M.D.	Chief, Metabolism Section, CPB, NIA
Jordan Tobin, M.D.	Chief, Human Performance Section, CPB, NIA
Judith Hallfrisch, Ph.D.	Senior Staff Fellow, CPB, NIA
Walter Ettinger, M.D.	Medical Staff Fellow, CPB, NIA
Patricia Coon, M.D.	Medical Staff Fellow, CPB, NIA
Donald Drinkwater, Ph.D.	Visiting Associate, CPB, NIA
Denis Muller, B.S.	Chemist, CPB, NIA

COOPERATING UNITS *(if any)*

LAB/BRANCH
Gerontology Research Center, Clinical Physiology Branch

SECTION
Metabolism Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.42	1.77	2.65

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 fiber intake of 499 men in the BLSA was estimated from 7-day dietary diaries. Cross-sectionally there was an increase in intake of 0.03 g per year of age. Longitudinally, the increase was greater, 0.08 g per year; this increase occurred in all age groups. Thus, not only do older men consume more fiber, but there is also probably a secular or environmental effect as well. The question is: Is fiber intake related to health? To answer this we correlated fiber intake with certain coronary risk factors. There was a statistically significant ($p<0.02$) favorable effect of diet on systolic and diastolic blood pressure and the fasting glucose level. In addition, there was a suggestively favorable effect ($.05<p<0.1$) on serum cholesterol and triglyceride levels and on glucose tolerance. In a related analysis, dietary variables were examined in a group of 48 male BLSA subjects at age 53-95 years who subsequently died of cardiovascular disease; these were compared to 48 matched disease-free survivors. Significant dietary differences were present in the 23 men who died over age 75 as compared to their matched survivors: the group destined to die ate less fiber, fewer calories, and had a lower P/S fatty acid ratio. Thus, dietary risk factors have been shown to be present even into advanced old age. The dietary variable has been re-introduced into the BLSA after a nine year hiatus in the men. No previous dietary information had been available on the women. Thus far 167 weekly diaries have been completed and returned to us. Software to access a database of over 5,000 food entries with more than 90 possible nutrient variables per food has been developed. A study on the epidermiology of osteoarthritis has been initiated. Radiographs of the hands for evidence of both osteoarthritis (Heberden's nodes) and osteoporosis have been reported previously. The even more disabling osteoarthritis in weight-bearing joints will now also be studied, since x-rays of the knees have been started and a formalized history and physical examination for joint problems was simultaneously introduced. Since the year began, 246 subjects have been studied.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00205-2 CPB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Recommended Weight Tables: A Synthesis of the Literature

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

Reubin Andres, M.D.	Chief, Metabolism Section, CPB, NIA
Jordan Tobin, M.D.	Chief, Human Performance Section, CPB, NIA
Larry Brant, Ph.D.	Statistician, Human Performance Section, CPB, NIA
Denis Muller, B.S.	Chemist, Metabolism Section, CPB, NIA

COOPERATING UNITS *(if any)*

LAB/BRANCH

Gerontology Research Center, Clinical Physiology Branch

SECTION

Metabolism Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.65	0.20	0.45

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 issue of the effect of age on the recommended range of weights-for-height remains controversial. The major controversy involves the question of adjustment of recommended weights for age. The widely used Metropolitan Tables, most recently revised in 1983, are said to be applicable to ages 25 to 59 years. In the past year, a re-analysis of data from the insurance industry as published in Build Study 1979 has been initiated and comprehensive collation of all pertinent studies from the world's literature has been accomplished. The re-analysis was necessary consequent to the publication of a study on the adult population of Norway in 1984 by Waaler. That study showed clearly that the relationship between the Body Mass Index (BMI, wt/ht^2) and the mortality rate, although U-shaped, was not symmetrically so. The upswing in mortality in increasingly underweight subjects was sharper than the upswing in the increasingly overweight groups. The Norway Study is of major importance (1) because of its size and (2) because it includes men and women from 20-24 to 85-89 years of age. We have shown that the asymmetric data distribution could be well fit by a curve obtained by computing the log-log BMI vs. the mortality ratio. Examination of the Build Study 1979 data showed again that there was a tendency to similar asymmetry in the U-shaped relationship. For this reason these data were re-computed as noted for the Norway Study. It was found that the fit was indeed better. This may require re-computation of recommended weights, but the impact will be relatively small: the upper weight limits of our previously computed age-specific table may need to be adjusted upward slightly and the lower weight limits may need to be adjusted upward slightly in younger subjects and downward in older subjects. The Norway data are very similar to the Build Study data. Over the comparable age range of 20-69 years, there is less than a 1% overall difference despite the large differences in the types of populations studied.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00206-1 CPB

PERIOD COVERED
October 1, 1984 to September 30, 1985

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Aerobic Exercise and Age: Metabolic, Hormonal, and Cardiovascular Responses*

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

Andrzej Ziemba, Ph.D.	Visiting Fellow, CPB, NIA
Jerome Fleg, M.D.	Scientist, CPB, NIA
Reubin Andres, M.D.	Chief, CPB, NIA
Edward G. Lakatta, M.D.	Chief, CPB, NIA

COOPERATING UNITS *(if any)*

Ellen Rogus, Ph.D.	Francis Scott Key Medical Center, JHH

LAB/BRANCH
Gerontology Research Center, Clinical Physiology Branch

SECTION
Metabolism Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.45	0.30	0.15

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.)*

Physical working capacity decreases progressively during adult life. Contributing to this decline are decreases in function of the cardiovascular and pulmonary systems as well as a decrease in muscle mass. It is our hypothesis that decreased ability to perform physical work in the elderly is also associated with changes in the hormonal regulation of blood "fuel" regulation during exercise. The purpose of the present study is to examine the effect of age on plasma levels of glucose, free fatty acids (FFA) and of hormones responsible for regulating energy stores (catecholamines, glucagon, insulin) both at rest and during prolonged exercise. Plasma levels of glycerol, triglycerides and lactic acid are also measured. Exercise is accomplished by progressively increasing levels of treadmill walking. Subjects walk for 10 minutes at each of 3 exercise levels, 40, 50 and 60% of their previously determined maximal oxygen consumption (VO_2max), and for 30 minutes at 70% of VO_2max. Thus, duration of an exercise session is 1 hour. Blood samples for metabolite and hormone determinations are taken before exercise, at the end of each exercise stage, and 15 minutes after its termination. Samples of expired air are obtained before exercise, during the final 2 minutes of each submaximal workload and at the end of the recovery period for measurements of minute ventilation, oxygen consumption, carbon dioxide production, and respiratory quotient. The ECG is monitored continuously during the entire experimental period. Healthy subjects are selected from participants in the Baltimore Longitudinal Study of Aging according to the following criteria: no evidence of cardiovascular or other significant disease, negative treadmill maximal exercise test, no cardioactive medication, no cigarette smoking, non-obese, normotensive. During this report period, 13 subjects have been studied, four young adult (20-39 yr) six middle-aged subjects (40-59 yr), and three older subjects (60-75 yr). To obtain statistically acceptable samples for comparisons among the age groups, 10 participants will be studied in each of the 3 groups. The study should be completed within the next year.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00207-1 CPB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Isometric Exercise and Age: Cardiovascular-Sympathoadrenal-Metabolic Responses*

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

Andrzej Ziemba, Ph.D. — Visiting Fellow, CPB, NIA
Reubin Andres, M.D. — Chief, Metabolism Section, CPB, NIA
Patricia Coon, M.D. — Medical Staff Fellow, CPB, NIA

COOPERATING UNITS *(if any)*

Andrew Goldberg, M.D. — Francis Scott Key Medical Center, JHH
Ellen Rogus, Ph.D. — Francis Scott Key Medical Center, JHH

LAB/BRANCH

Gerontology Research Center, Clinical Physiology Branch

SECTION

Metabolism Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.40	0.20	0.20

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.)*

Static (isometric) muscle contractions are common components of effort in performing daily activities. The problem of static exercise becomes important since isometric contractions cause marked increases in blood pressure and catecholamine levels. This study is designed to describe the relationships among age, sex, body weight, pattern of body fat distribution, level of physical fitness, and static exercise responses. The subjects for the study are selected from three volunteer groups: participants in the Johns Hopkins Academic Teaching Nursing Home, the Baltimore Longitudinal Study of Aging (BLSA), and the Senior Athletes Study. They are divided into four age groups: 20-45, 45-59, 60-74 and 75 and over years. They are mildly to moderately obese ranging in body fat from 20 to 40% and are further subdivided into two subgroups of subjects representing upper and lower body segment type of obesity. Normal controls are lean but age and sex matched to these obese subjects. The experimental protocol is the same for all subjects: sustained hand-grip exercise on a hand dynamometer at 30% of their individual maximal voluntary force to fatigue (usually 3 - 6 minutes). Before the test, at one minute intervals during the test, and 3 minutes after its termination, blood pressure, heart rate and blood samples for catecholamines, glucose and free fatty acids are taken. To date, a total of 14 subjects have been studied from the Teaching Nursing Home and Senior Athletes groups. Studies in the BLSA participants will be initiated in the coming year. We plan to test 40 subjects in each of the 4 age groups. The study should be completed within the next year.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00208-1 CPB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Aging, Obesity, Sedentariness and Endocrine-Metabolic Function

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

Patricia Coon, M.D.	Medical Staff Fellow, CPB, NIA
Stephanie Kafonek, M.D.	Medical Staff Fellow, CPB, NIA
Donald Drinkwater, Ph.D.	Visiting Fellow, CPB, NIA
Andrzej Ziemba, Ph.D.	Visiting Fellow, CPB, NIA
Reubin Andres, M.D.	Chief, Metabolism Section, CPB, GRC, NIA

COOPERATING UNITS *(if any)*

Francis Scott Key Medical Center, The Johns Hopkins Hospital

Andrew Goldberg, M.D. — Eugene Bleecker, M.D.

Ellen Rogus, Ph.D. — Karen Dennis, R.N., Ph.D.

LAB/BRANCH

Gerontology Research Center, Clinical Physiology Branch

SECTION

Metabolism Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.00	1.15	0.85

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standerd unreduced type. Do not exceed the spece provided.)*

Obesity, sedentariness and aging are known to be associated with hyperlipidemia and glucose intolerance. In order to examine the interrelationship of age, adiposity, and physical fitness to endocrine-metabolic function, a study was designed to examine glucose and lipid metabolism and sympathoadrenal function in obese sedentary men aged 45-85 years at entry into the study and again after either weight reduction or aerobic training. The three areas of endocrine-metabolic function being studied include 1) glucose tolerance and insulin sensitivity studied by the euglycemic clamp technique, 2) lipoprotein metabolism as assessed by adipose tissue lipoprotein lipase activity, and 3) sympathoadrenal response to isometric exercise (handgrip), upright posture, oral glucose challenge, and hyperinsulinemia during a euglycemic clamp.

To date, 27 participants have completed the baseline studies and have been randomized to either weight reduction or aerobic exercise intervention. In 10 men after a 6 $\pm$ 1% weight loss, high density lipoprotein cholesterol levels increased by 19 $\pm$ 4% and the LDL-C to HDL-C ratio decreased by 16 $\pm$ 5% ($p < .02$). In addition, in 10 middle-age to old obese sedentary men, adipose tissue lipoprotein lipase (LPL) activity decreased and triglyceride levels remained constant during a 6 hr intravenous infusion of insulin (100 $mU/m^2.min$). In contrast, in 6 young non-obese men adipose tissue LPL activity significantly increased and plasma triglyceride levels decreased to 60% of basal. In addition, the older, obese men had significantly lower HDL and HDL_2 levels than the younger participants. Whether resistance of adipose tissue LPL to stimulation by insulin is the cause of the low HDL cholesterol seen in these older obese men, will be further studied.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00209-1 CPB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Aging and Cardiovascular, Endocrine and Metabolic Function in Master Athletes

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

Donald Drinkwater, Ph.D.	Visiting Fellow, CPB, NIA
Patricia Coon, M.D.	Medical Staff Fellow, CPB, NIA
Andrzej Ziemba, Ph.D.	Visiting Fellow, CPB, NIA
Stephanie Kafonek, M.D.	Medical Staff Fellow, CPB, NIA
Reubin Andres, M.D.	Chief, Metabolism Section, CPB, NIA
Edward Lakatta, M.D.	Chief, Cardiovascular Section, CPB, NIA
Jerome Fleg, M.D.	Scientist, Cardiovascular Section, CPB

COOPERATING UNITS *(if any)*

Francis Scott Key Medical Center, Johns Hopkins Hospital
Department of Medicine, Johns Hopkins University
The Johns Hopkins School of Hygiene and Public Health

LAB/BRANCH

Gerontology Research Center, Clinical Physiology Branch

SECTION

Metabolism Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.5	0.90	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.)*

Endurance exercise training elicits physiological adaptations which increase the functional capacity of various organs. Older, physically well-trained "master" athletes tend to have a cardiovascular functional capacity (VO_2max) which more closely approximates that of much younger individuals than that of their sedentary peers. They also have higher levels of high density lipoprotein (HDL) cholesterol, lower percent body fat and are more insulin sensitive than age-matched sedentary controls.

To examine the interrelationship of age and physical fitness to endocrine-metabolic function, a study was designed to compare lipid profiles and metabolism, glucose metabolic rates and insulin sensitivity, and cardiovascular function in highly trained older men (greater than 50 years of age) with their sedentary peers as well as with highly trained young individuals. The role of training in the highly trained individuals will be examined by de-training them over a 10 day period. Endocrine-metabolic function studies include 1) glucose tolerance, beta cell sensitivity, and insulin sensitivity using oral glucose challenge (OGTT) and hyperglycemic clamp techniques, 2) lipoprotein metabolism and lipoprotein lipase activity, 3) sympathoadrenal response to isometric exercise (handgrip), upright posture and hyperglycemic clamp.

Of 102 regularly exercising men, 50 to 86 years of age, enrolled in the program since June 1985, baseline fasting glucose and lipid profiles have been obtained on 42 of the most highly active participants. Thirteen of these have also undergone an initial treadmill screening test and maximal oxygen consumption (VO_2max) test, 5 have undergone a second VO_2max test and thallium scan, and 4 have undergone oral glucose tolerance (OGTT) and isometric exercise (handgrip) tests. Preliminary lipid profiles confirm high levels of HDL cholesterol in these very active older men.

ANNUAL REPORT OF THE LABORATORY OF BEHAVIORAL SCIENCES

NATIONAL INSTITUTE ON AGING

In view of the detailed summary reports from each LBS section, this report will be limited to a presentation of the major administrative events of the past year, and an identification of some significant research findings.

Administrative Issues

There are two noteworthy administrative events. First is the reorganization of the Laboratory. Based on a set of recommendations proposed by the Chief, LBS, the Stress and Coping Section (SCS) and the Learning and Problem Solving Section (LPSS) will be separated from LBS and will be incorporated into a new Laboratory. In addition, the Psychophysiology Section (PS) will be dissolved. The Laboratory of Behavioral Sciences will be reorganized into two sections: The Behavioral Medicine Section and the Behavioral Physiology Section. These changes will be implemented at the beginning of FY86. The second, major administrative accomplishment of this fiscal year has been the realization of the Inpatient Geriatric Research Project. This project, which has been under discussion for about five years is jointly funded by NIA and by the Health Care Financing Administration (HCFA). It establishes an Inpatient Geriatric Continence Unit at the Mason F. Lord Building of the Francis Scott Key Medical Center. This program will investigate a number of behavioral techniques for treating incontinence among nursing home residents.

Research Findings

Since 1970, the Psychophysiology Section has carried out an extensive series of studies evaluating the effectiveness of behavioral treatment of incontinence (fecal or urinary). As a result of our findings with fecally incontinent patients, our training techniques have become the treatment of choice for many patients with fecal incontinence. Over the last several years we have directed our attention to urinary incontinence, and our findings have been as encouraging as have been our results with fecal incontinence. In a study completed this year, we have shown that the Kegel Exercise treatment for stress incontinence is significantly more likely to be successful if the patients are trained in the laboratory and given feedback on their sphincter, bladder and abdominal responses as they learn to increase the strength and duration of contraction of pelvic floor muscles. An outgrowth of our work on the treatment of incontinence has been the establishment of an Inpatient Geriatric Continence Unit (see section on Administrative Issues). In contrast to community-dwelling elderly, inpatients are likely to be more infirm. Their two major infirmities are mobility limitations and cognitive impairment. A study on these problems indicated that mobility limitations are more prevalent than are cognitive limitations. However, a second study showed that in some patients the mobility limitation can be treated; in a selected group

of patients who were wheel chair dependent at least 50% of the time it was possible to use behavioral strategies to significantly increase walking.

In addition to our extensive research activities on the assessment of behavioral treatments for incontinence, we also are carrying out a controlled study of behavioral treatment of high blood pressure. Previous work in PS had shown that "borderline hypertensives" could learn to lower their blood pressures and could sustain this effect for at least six to nine months post-treatment. In an ongoing study, we are extending these findings to patients with established hypertension who are taking antihypertensive medications. For example, we are finding that many patients can reduce their pressures sufficiently to be able to reduce their medication requirements, and that these effects can be sustained for at least one year following treatment.

In order to be effective, treatments must be rational. From a behavioral perspective, rational treatments are those which are directed at behaviors which are relevant to the illness under study and are based on behaviors which are capable of being performed. Research in the Stress and Coping Section has been looking carefully at the personality characteristics which mediate the Type-A trait. One of these characteristics is "hostility." However, the concept of hostility is ambiguous since hostility is itself based on a number of more fundamental personality traits. Studies this year have shown that many measures of hostility do not adequately separate such traits as neuroticism from measures of disagreeableness which are more likely to reflect the nature of hostility. This finding is especially relevant because a number of earlier studies have shown that neuroticism, per se, is not a predictor of coronary artery disease among persons manifesting the Type-A trait. Pulmonary studies in PS are directed at improving the breathing capacities of patients with chronic obstructive pulmonary disease. However, before one can develop such training methods, he needs first to be able to assess the ability of patients to perform the requisite breathing maneuvers, and to compare their performances with healthy persons. In order to do this, we have developed a technique for evaluating abdominal breathing during a standardized challenge, and we are testing subjects across the age span of 20 to 75 years. Results to date have shown that some healthy persons between 20 and 40 years cannot perform the task although it is seemingly relatively simple and similar to tasks used in other laboratories to train patients with breathing difficulties. Clearly, normative data such as these will facilitate the development of appropriate treatment methods.

There are several issues which are especially important in personality research. Two of these which have been studied in SCS are the taxonomy of personality and the stability of personality. The first question asks whether it is possible to describe an individual using a relatively small number of personality traits; and the second question asks whether personality traits change significantly throughout the lifespan, and if so, whether there are critical periods when such changes can be seen. Previous research on the first question has suggested that a five dimensional model of personality comprising neuroticism, extraversion, openness to experience, agreeableness and conscientiousness may be necessary and

sufficient to provide a comprehensive assessment of personality. Research completed this year has provided further support for this model, and it has extended the scope of personality assessment from traditional psychometric instruments to measures based on clinical views of personality. The second question can only be answered with longitudinal studies. While previous research in this Laboratory based on findings from the Baltimore Longitudinal Study of Aging (BLSA) has shown evidence for stability, those findings were limited by the select character of the sample. However, current research utilizing data derived from a cohort of about 10,000 respondents to the National Health and Nutrition Examination Survey I Epidemiologic Followup Study have supported the notion that personality in the adult is stable throughout the lifespan. Since this cohort has been carefully selected to provide a statistically representative sample of the American population, these findings provide considerable support to the stability hypothesis. Furthermore, these data show that despite the fact that the participants in the BLSA were not selected at random, findings from this cohort still permit one to reach important and general conclusions about personality.

In addition to the clinical studies noted above, LBS also carries out an extensive basic research program using both human and animal models. The human research this year has focused on changes in memory, and on the mechanisms which might mediate these changes. Studies using the Benson Visual Retention Test (BVRT) and based on the BLSA cohort have provided further evidence that there are substantial, age-related declines in nonverbal memory but that these appear only late in life. An experimental analysis of the components of nonverbal memory has shown that visuospatial information can also be encoded verbally and that verbal descriptions provided during acquisition facilitate subsequent recall, especially for older persons. However, findings in the Learning and Problem Solving Section indicate that the verbal descriptions primarily facilitate object recall ("What" information) rather than relative position recall ("Where" information). Additional research in LPSS also has found that different aspects of cognitive performance show different patterns of change with age. While the nonverbal memory, measured by the BVRT, declines with age, verbal memory, measured with the vocabulary subtest of the Wechsler Adult Intelligence Scale, declines very little with age, and these two measures of cognitive performance are poorly correlated. These data provide further evidence against the notion of univocal, immutable declines in cognitive function with age. *

There are two programs of basic animal research in PS. One utilizes nonhuman primates and is concerned with determining the extent to which cardiovascular responses can be trained, and thus, can mediate adaptive changes. One study in this Laboratory has shown that animals can be taught to regulate their systolic blood pressures as well as their heart rates. A second study has shown that animals can be trained to attenuate the tachycardia of exercise. This last finding is especially interesting since it complements findings from this Laboratory which showed that normal people, patients with coronary artery disease and patients with high blood pressure also can learn this skill. It is likely that this animal model will provide a deeper understanding of the mechanisms underlying such learned control of the circulation, and it may also provide an

insight into possible clinical applications of such learning. The second program of basic animal research is directed at an analysis of the age-changes in thermoregulation. Previous research in PS had shown that body temperature falls late in life in C57BL/6J mice. Since this is a highly inbred strain, it is important to determine the generality of this finding. Research completed this year has shown that a decline in body temperature occurs in a variety of mouse species in addition to C57BL/6J; namely, A/J, B6AF1/J (a hybrid line derived from A/J and C57BL/6J) and a wild strain of mice (Mus musculus). Not only does body temperature decline late in life among C57BL/6J mice, but there is now evidence of a brief decline in middle-age as well. This conclusion is based on a series of cross-sectional and longitudinal studies we have carried out over the past several years and confirmed this year. This finding of a brief decline at about 14 months of age, followed by a recovery which is sustained until senescence, is especially interesting since it is one of the few examples of a middle-aged effect in physiological function -- the termination of ovulation is perhaps the only clear-cut case of a middle-age change.

Summary Report, Psychophysiology Section

As noted above (see Administrative Issues) LBS will be reorganized at the beginning of fiscal year 1986; the Psychophysiology Section will be dissolved; and two new sections will be created: the Behavioral Medicine Section and the Behavioral Physiology Section. The common, conceptual theme which will underlie all of the research programs within this Laboratory is that neurally-mediated, physiological responses can be characterized as behavior, and can be analyzed and modified in accordance with behavioral science principles which have been developed over the past 100 years. This conceptualization is based on findings in this Laboratory and others that have shown that physiological responses are conditional in three senses: 1) they are conditional in the sense that reflex responses are not invariant effects which occur independent of the circumstances under which they are elicited; 2) they are conditional in the sense that the stimuli which elicit reflex responses can be acquired through experience; and 3) they are conditional in the sense that the physiological responses can be emitted in anticipation of environmental consequences. The fact that physiological responses are conditional means that they can become adaptive (or maladaptive), and that they can be modified through training. Our programs look at the basic mechanisms which determine the range and limits of such adaptiveness also at the clinical applications implicit in these adaptations.

There have been a number of major scientific accomplishments this year. The single most important of which is the establishment of an Inpatient Geriatric Continence Project. This project will explore the extent to which behavioral interventions can be used to reduce the prevalence of incontinence in nursing home residents. The behavioral techniques will include bowel or bladder/sphincter biofeedback, habit training and staff management procedures emphasizing strategies for enhancing patient independence. Our findings from two studies completed this year are especially relevant to the issue of self-management. One study showed that 58% of the incontinent patients in our institution are cognitively impaired while 95% of the patients have significant mobility limitations. It is especially noteworthy that 41% of the incontinent patients are mobility impaired but are cognitively able: All of these patients have the potential to become independent. This inference is buttressed further by the findings from the second study which showed that when patients who spend at least 50% of their time in wheel chairs are encouraged to try to walk -- e.g., to the dining room table -- they will significantly increase their walking behavior, and they will generalize this performance to other situations as well. This Laboratory is carrying out an extensive series of studies on biofeedback methods for treating incontinent, community-dwelling persons. One study which was completed this year showed that the feedback of bladder and sphincter activity greatly enhanced the effectiveness of the Kegel exercise treatment of urinary incontinence. Among patients who received instructions but no feedback, 6/11 showed >50% reduction in episodes of leaking; however, among patients who also were given feedback training on sphincter and abdominal muscle control, there was significantly greater improvement with 12/13 showing >50% reduction in leaking episodes.

In addition to our clinical studies of incontinence, this Laboratory also has active projects on the application of behavioral techniques to the control of high blood pressure, and on the application of behavioral techniques to the assessment of pulmonary function. In the hypertension project, patients are seen in the outpatient service of a local Health Maintenance Organization. Control patients are monitored for about 20 months whereas patient in the experimental group are trained to control their pressures using behavioral techniques developed in this Laboratory. Although the study is still going on, there is increasing evidence that the behaviorally treated group is attaining and sustaining clinically significant improvements. One index of effectiveness is medication cost reduction. Among patients who were taking diuretic antihypertensive medications at the time of entry into the study, behaviorally treated subjects showed an average cost reduction of $23.00/year/patient while the control patients showed an increase in costs of $34.00/year/patient over comparable time periods; among patients who entered the study on beta-blocker therapy, the treated subjects showed a cost reduction of $110.00/year/patient while the control patients showed a reduction of $21.00/year/patient.

Our research in the pulmonary laboratory is ultimately designed to develop a behavioral technique for training patients with chronic obstructive pulmonary disease to improve the efficiency of their breathing. At this stage, we are assessing the ability of normal persons across the age range of 20 years to 75 years to maintain abdominal breathing during a standardized challenge. Subjects in this study are stratified into groups based on sex, smoking status and exercise habits. Findings are only available for subjects between 20 and 40 years. Of these, 35/40 (87.5%) were able to perform the abdominal breathing task, and 15 of these (42.8%) were able to perform for the full 8 minutes of the task. During the performance of the task, oxygen consumption decreased significantly in the women, the nonexercisers and in the smokers; respiratory frequency decreased in the nonexercisers; the respiratory exchange rate decreased significantly in women; total peripheral vascular resistance increased significantly in smokers; and systolic blood pressure increased significantly in nonexercisers. Clearly, these findings indicate that abdominal breathing is a significant challenge, even for normal, healthy persons, and they indicate further that training procedures for patients with significant pulmonary disease must be carefully designed to operate within the physiological limits of these patients.

There are two basic science programs in this Laboratory. One utilizes non-human primates as experimental models to evaluate the physiological mechanisms mediating learned control of cardiovascular performance; and the second utilizes rodents to evaluate the mechanisms mediating age changes in thermoregulation. Previous research in our non-human primate laboratory has shown that monkeys can learn to control their heart rates. Research during the past year has shown that these animals also can learn to modulate systolic blood pressure. Additional studies have shown that these animals not only can learn to modulate heart rate, but also can learn to attenuate the tachycardia of exercise. Given the ubiquity of exercise, and given the salient role that exercise ability plays in

natural selection, this finding greatly extends our knowledge about the importance of learning in the modulation and regulation of cardiovascular function.

We have carried out an extensive series of longitudinal and cross-sectional studies of body temperature in C57BL/6J mice. In four independent studies we have found evidence for a unique, middle-aged phenomenon: resting body temperature is consistently reduced in these animals between 14 and 15 months after which it rises again until late in life when it falls again. Studies completed this year show that the fall in body temperature in senescent mice, which we reported several years ago, is not specific to the C57BL/6J strain which is our primary animal model. Cross species studies using C57BL/6J mice, A/J animals, B6AF1/J (a hybrid of the first two species) and a wild strain of mice (Mus musculus) all have shown that body temperature falls late in life. Since previous research in this Laboratory has shown that senescent C57BL/6J animals can adapt to repeated exposures of cold by raising their body temperatures (presumably, as a result of increased heat production), future research will be directed at efforts to characterize some of the behavioral strategies and physiological mechanisms which might facilitate this capacity for late-life adaptation.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00062-12 LBS

PERIOD COVERED
October 1, 1984 to September 30, 1985

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Daydreaming and Aging: Normative and Experimental

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

PI: L.M. Giambra, Ph.D. Senior Invetigator LBS, GRC, NIA

COOPERATING UNITS *(if any)*

None

LAB/BRANCH
Laboratory of Behavioral Sciences

SECTION
Learning and Problem Solving Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
.8	.7	.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 purpose of this work is to determine the parameters of task-unrelatedthought-intrusions both spontaneous (daydreams) and otherwise, as well as related mental activity such as insight, intuition, and mindwandering. An additional purpose is to investigate the relation between sustained attention and age. The purposes are accomplished through the use of controlled laboratory studies and retrospective questionnaires. Outcomes derived from these purposes and obtained over the fiscal year were: (a) Three samples of men and women tested in 1962-64 and 1980-84 who ranged in age from 20-92 years and who performed the Mackworth Clock Test, were observed to show no statistically significant age differences in number of spontaneous skin potential responses and a significant age effect for males for skin potential response latency revealing a U-shaped function with a minimum at middle-age; since both measures are taken as indicates of physiological arousal this outcome weakly suggests that that middle-aged males are most highly aroused when performing a sustained attention task. (b) In an 18 year longitudinal study of the Mackworth Clock Test it was determined that only the change in target response time was signficantly affected by the initial age of the men--hit likelihood, false alarms, skin potential latency, and number of spontaneous skin potential responses were unaffected--with young men becoming faster as they approached middle age and middle-aged men becoming slower as they aged; this outcome provides additional support for the notion resulting from cross-sectional studies that age has little effect on overall sustained attention. (c) In a Total Sample of 613 men and women the vigilance decrement in performance as indicated by likelihood of observing a target could be described precisely by a mathematical function comprised of two exponential terms, a negative exponential and an upper bounded term composed of the reciprocal of one plus a negative exponential, multiplied by constant; the simple negative exponential was intrepreted as an effortful control process and the other component was interpreted as an automatic, nonconscious process.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 AG 00063-18 LBS

PERIOD COVERED
October 1, 1984 to September 30, 1985

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

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

Bernard T. Engel, Ph.D.	Chief, LBS	LBS, GRC, NIA
Mark I. Talan, M.D.	Visiting Associate	LBS, GRC, NIA
Gyorgy Bardos, Ph.D.	Visiting Associate	LBS, GRC, NIA

COOPERATING UNITS *(if any)*
Laboratory of Cellular and Molecular Biology

LAB/BRANCH
Laboratory of Behavioral Sciences

SECTION
Psychophysiology

INSTITUTE AND LOCATION
National Institute on Aging, National Institutes of Health, Baltimore, MD 21224

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
5.92	2.18	3.75

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.)*

The purpose of this project is to investigate the role of the central nervous system in behavior. In some experiments non-human primates are used to examine the extent to which the cardiovascular system can be modified by instrumental conditioning. In other experiments we examined age-related changes in thermoregulation.

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

PROJECT NUMBER

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00064-24

PERIOD COVERED
October 1, 1984 to September 30, 1985

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	Section Chief	LBS, NIA
Others:	L.M. Giambra	Senior Investigator	LBS, NIA
	J.D. Sinnott	Towson State University	

COOPERATING UNITS (if any)

Francis Scott Key Medical Center

LAB/BRANCH
Laboratory of Behavioral Sciences

SECTION
Learning and Problem Solving Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL	OTHER
2.0	0.3	1.7

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.)

Among the goals of this project are to describe age differences and changes in reasoning performance and to investigate psychological processes underlying such age-related performance. Data collection continues for the longitudinal study of concept problem solving of men and women. Plans for construction and validation of additional individual models using computer programming are in progress.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00065-25 LBS

PERIOD COVERED

October 1, 1984 to September 30, 1985

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	Section Chief	LBS, NIA
Others:	L.M. Giambra	Senior Investigator	LBS, NIA
	E.A. Robertson-Tchabo	University of MD, College Park	
	J.D. Sinnott	Towson State University	

COOPERATING UNITS *(if any)*

Francis Scott Key Medical Center

LAB/BRANCH

Laboratory of Behavioral Sciences

SECTION

Learning and Problem Solving Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
2.6	0.6	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.)*

Among the goals of this project are to describe adult age differences and changes in memory and learning performance and to investigate psychological processes underlying such age-related performance. This year, the second in a series of aging studies of memory and linguistic integration of related sentences was completed. Preliminary analyses indicate that: (1) the young were able to discriminate somewhat previously presented sentences from congruent sentences not presented, but the elderly were not; (2) the young were able to reject more false sentences than were the old; (3) the age groups did not differ on verification of inferable information, an index of linguistic integration; and (4) only small differences favoring the young were found in two measures of memory for facts.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00066-24 LBS

PERIOD COVERED

October 1, 1984 to September 30, 1985

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 Section Chief LBS, NIA

COOPERATING UNITS *(if any)*

Francis Scott Key Medical Center

LAB/BRANCH

Laboratory of Behavioral Sciences

SECTION

Learning and Problem Solving Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL	OTHER
1.4	.4	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.)*

Among the goals of this project is to describe adult age differences and changes in nonverbal memory performance. Estimates of age change based on regression analyses of 24 years of first-time scores on the Benton Visual Retention Test for men were calculated for ten birth cohorts. The largest estimates of age change were found for the two earliest born cohorts (1877-1884 and 1885-1892), moderate estimates of change for the next four cohorts (born between 1893 and 1924), and virtually no change for the four latest born cohorts. These results are consistent with individual measures of change obtained longitudinally; substantial change in nonverbal memory occurs only late in life.

Similar regression analyses were used to compare estimates of age change in eight pairs of birth cohorts over the same period of life. The pairs of estimates of age change in nonverbal memory were quite similar in magnitude and were highly correlated.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00067-18 LBS

PERIOD COVERED

October 1, 1984 through September 30, 1985

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

Learned Modification of Visceral Function in Man

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

Bernard T. Engel, Ph.D.	Chief, LBS	LBS, GRC, NIA
Kathleen A. McCormick, Ph.D.	Research Nurse	LBS, GRC, NIA
Kathryn L. Burgio, Ph.D.	Staff Fellow	LBS, GRC, NIA
Michael S. Glasgow, Ph.D.	Research Physiologist	LBS, GRC, NIA

COOPERATING UNITS *(if any)*

Francis Scott Key Medical Center; Care First Medical Plan; New York Opera Company; Wolf Trap Farms

LAB/BRANCH

Laboratory of Behavioral Sciences

SECTION

Psychophysiology

INSTITUTE AND LOCATION

National Institute on Aging, National Institutes of Health, Baltimore, MD 21224

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
6.77	2.77	4.0

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 concerned with the application of behavioral methods and principles to clinical medicine. Subjects are patients selected from various medical clinics, or normal subjects who are studied to evaluate potential clinical methods. The main focus of this project is on clinical problems especially relevant to middle aged or elderly persons.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00070-01 LBS

PERIOD COVERED

October 1, 1984 through September 30, 1985

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)*

Bernard T. Engel, Ph.D.	Chief, LBS	LBS, GRC, NIA
Kathleen A. McCormick, Ph.D.	Research Nurse	LBS, GRC, NIA
Louis Burgio, Ph.D.	Psychologist	LBS, GRC, NIA

COOPERATING UNITS *(if any)*

Francis Scott Key Medical Center; Health Care Financing Administration; Office of the Surgeon General of the United States

LAB/BRANCH

Laboratory of Behavioral Sciences

SECTION

Psychophysiology

INSTITUTE AND LOCATION

National Institute on Aging, National Institutes of Health, Baltimore, MD 21224

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
2.83	1.83	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.)*

Incontinence is a major reason for institutionalizing elderly persons, and is widespread in nursing homes. This project is designed to evaluate behavioral intervention techniques for the treatment of these patients.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00075-07 LBS

PERIOD COVERED

October 1, 1984 to September 30, 1985

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)*

Paul T. Costa, Jr., Chief, Stress & Coping Section, LBS,GRC,NIA
Robert R. McCrae, Research Psychologist, Stress Coping, LBS,GRC,NIA
Alan B. Zonderman, Senior Staff Fellow, Stress & Coping, LBS,GRC,NIA
Catherine M. Busch, Staff Fellow, Stress & Coping, LBS,GRC,NIA

COOPERATING UNITS *(if any)*

Division of Digestive Diseases, FSK
Department of Psychology, University of Maryland, Baltimore County
Dept. of Psychiatry, Duke University Medical School

LAB/BRANCH

Laboratory of Behavioral Sciences

SECTION

Stress & Coping Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Md 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.0	3.0	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.)*

This project is concerned with the effects of stressors, coping mechanisms, and enduring personality dispositions on psychological and health outcomes. One study examines the impact of life changes separately and cumulatively on perceptions of health, well-being, and personality in a 10-year followup of a national probability sample; a second collaborative study on the effects of stress following the nuclear accident at Three Mile Island found no evidence of increase in neuroticism attributable to the incident; a third assessed the ability of the MMPI to measure agreeableness and conscientiousness--aspects of personality thought to be relevant to coronary prone behavior--and found that the MMPI must be supplemented with other measures; a fourth examined the Spielberger Anger scale as a potential measure of agreeableness and found that it was more strongly correlated with neuroticism than with agreeableness; a fifth study confirmed the adequacy of the five factor model of personality in analyses comparing factors in the California Q-Set with questionnaire and adjective checklist measures of the five factors; a sixth study provided cross-sectional evidence of stability in the personality dimensions of neuroticism, extraversion, and openness to experience in a national probability sample; a seventh examines relations between physiology, psychological characteristics, and symptom reports associated with irritable bowel syndrome.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 AG 00076-06 LBS

PERIOD COVERED
October 1, 1984 to September 30, 1985

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Openness to Experience and Coping Styles*

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

Robert R. McCrae, Research Psychologist, Stress & Coping, LBS,GRC,NIA

Paul T. Costa, Jr., Chief, Stress & Coping, LBS,GRC,NIA

COOPERATING UNITS *(if any)*

LAB/BRANCH
Laboratory of Behavioral Sciences

SECTION
Stress & Coping Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.3	1.0	.7

CHECK APPROPRIATE BOX(ES)

- [X] (a) Human subjects
  - [ ] (a1) Minors
  - [X] (a2) Interviews
- [ ] (b) Human tissues
- [ ] (c) Neither

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

This project is concerned with the personality disposition of openness to experience and its relation to coping styles. One study examined the relation between openness and Eysencks' measure of psychoticism. Because both openness and psychoticism were originally conceived as complements to the personality dimensions of neuroticism and extraversion, Eysenck hypothesized that openness was the opposite of psychoticism, and that a substantial negative correlation should be found between measures of the two constructs. However, data from 451 men and women, aged 24 to 96, showed no significant correlation between openness and psychoticism, and suggested that psychoticism was better identified as the opposite pole of the two dimensions of agreeableness and conscientiousness. A second study examined major dimensions of coping efforts. Scores for the use of 27 coping mechanisms were factored in two samples of men and women, and two replicated factors were found. The first, labeled Neurotic coping, was defined by such coping mechanisms as hostile reaction and self-blame, and was associated with lower psychological well-being. The second, Mature coping, included rational action, perseverance, and positive thinking, and was associated with increased well-being.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00077-01 LBS

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Relationships between intelligence measures and auditory evoked potential parameters.

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

David L. Robinson, D.Phil., Visiting Associate, LBS,GRC,NIA

COOPERATING UNITS *(if any)*

Learning & Problem Solving section, LBS

LAB/BRANCH

Laboratory of Behavioral Sciences

SECTION

Stress and Coping

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Md 21224

TOTAL MAN-YEARS:	PROFESSIONAL	OTHER:
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.)*

Recent reports by Hendrickson and by Robinson and his associates have suggested substantial correlations between certain EEG evoked potential (EP) parameters and intelligence test scores in young subjects falling in the age range of 15-22 years. The present study involved the investigation of relationships between intelligence measures and auditory EP parameters. In particular, the study was designed to ascertain whether the Hendrickson findings could be generalized to older subjects. EP measures and intelligence test scores were obtained from 99 adult subjects participating in the Baltimore Longitudinal Study of Aging. With the experimental conditions prescribed by Hendrickson, there was a tendency for older subjects to fall asleep during the EEG recording session. Consequently, the data were analyzed separately for subjects who stayed awake and for those who slept. Separate analyses were also performed for male and female subjects. The main finding to be reported is that correlations of the order of magnitude reported in the earlier studies referred to above were only found in the data obtained from subjects who slept during the EEG recording session. These subjects also tended to be older than the subjects who did not sleep. Correlations obtained in the data of the subjects who did not sleep were small in contrast. The results have been interpreted in terms of the Yerkes-Dodson law which postulates that "arousal" is linked to performance and that the relationship takes the form of an "inverted-U" curve. It is suggested that both the very young subjects tested in the earlier studies and the older subjects who slept in the present study are functioning at a lower level of arousal. At this lower level of arousal the relationship between arousal-related EEG parameters and performance is nearly linear since it corresponds to the ascending limb of the inverted-U curve. Subjects falling in the intermediate range of ages are more highly aroused, it is suggested, and as a consequence their data relates to the flat middle section of the arousal/performance curve, if not to the descending high arousal limb.

FY 1985 ANNUAL REPORT AND RESEARCH HIGHLIGHTS
Laboratory of Cellular and Molecular Biology

The Inorganic Biochemistry Section has made considerable progress in studies on the mechanism of RNA synthesis, the importance of conformational changes in DNA, and hemoglobin dynamics, and the techniques are being developed for the study of *in vivo* aging by NMR spectroscopy and imaging.

Active Site of RNA Polymerase. The basic molecular processes responsible for RNA synthesis occur at the active site of the RNA polymerase enzyme, where the DNA template and the nucleoside triphosphate substrates are bound. A major new project is to map out the active site of this enzyme; if this can be done successfully, it will be an important step in the elucidation of the mechanism of RNA synthesis. The active site consists of the initiation site, where the first substrate is bound to an intrinsic zinc(II), and an elongation site, where all succeeding substrates are bound to an activating Mg(II). These two metals can be replaced by paramagnetic ions (Mn), and the distances from these ions to atoms on the substrates can be determined by measuring the paramagnetic effect on the relaxation of the atomic nuclei. Some of these distances at the initiation and elongation sites have been determined by Wu *et al.* and Mildvan *et al.*, respectively. We have determined the remaining distances at the elongation site, and in the presence of template - previously the distances had been determined without DNA present.

Complete knowledge of the active site requires an understanding of the spatial relationships between initiation and elongation sites. The two sites come in contact at the point where the two substrates form an internucleotide bond, i.e., the 3'OH group of the initiation substrate must touch the α-phosphate of the elongation substrate. Complete mapping then requires one more distance - that between the metals at the initiation and elongation sites. Such a metal-metal distance can be determined by EPR measurements, since the EPR spectrum of a paramagnetic metal is affected by another paramagnetic metal in its proximity.

We have been able to place Mn(II) into the initiation site and to determine its EPR spectrum on that site, to place Mn(II) into the elongation site and determine its spectrum there, and finally to place Mn(II) in both sites. In the latter instance there was, in fact, a marked influence of the metals on each other, demonstrating their proximity. We have been able to make preliminary measurements of the distance between them, and using this distance we have constructed a tentative model of the active site.

From the model it appears that the bases of the two nucleoside triphosphate substrates are not parallel, but are oriented at an angle to each other that suggests that the elongation site is at a point on the DNA template between the DNA double helix and the DNA-RNA hybrid that is formed from newly synthesized RNA and the DNA strand it copies, and the initiation site is at the beginning of the hybrid helix.

Z-DNA as a template for RNA Synthesis. The B to Z conformational change occurs only with DNA of certain sequences (e.g. alternating GC) and therefore is

a reflection of the sequence on the surface of the template. The Z conformation is believed to be involved in genetic regulation by helping to make it possible for DNA-binding proteins to recognize specific DNA sites. Our previous finding that the B to Z transition in poly(dGdC)·poly(dGdC) is accompanied by a dramatic decrease in the ability of the DNA to act as a template for RNA synthesis indicates that the B to Z transitions could regulate RNA synthesis. This finding has now been confirmed by work at Harvard.

In order to understand the mechanism by which genetic regulation can occur through conformational change, we have been studying several characteristics of the phenomenon. One of them is the effect of the binding of RNA polymerase to B and Z DNA. We have confirmed that addition of the enzyme to the Z forms of poly(dGdC)·poly(dGdC) and poly(dGdm^{5}C)·poly(dGdm^{5}C) results in a conversion to the B form of DNA. Moreover, we have found that the addition of the enzyme to the B forms before the conversion of B to Z decreases the rate of B to Z conversion. Thus the enzyme inhibits the conversion of B to Z and brings about the conversion of Z to B. Evidently the enzyme preferentially binds to B, and this preference can explain the low RNA synthesis activity when the template is in the Z form.

Mechanism of Conversion of B to Z DNA. Since the transition from B to Z DNA is of great biological interest, it is important to understand the mechanism of the interconversion. We asked the question "Does the conversion involve the breaking of hydrogen bonds between bases, or is the molecule twisted without such breaks?" To answer the question one requires an agent for the conversion and an agent to test for single-stranded-DNA intermediate, and the condition that the transition is long enough so that the intermediate can be detected. The Tb(III) ion was used both as conversion agent and intermediate-detector. It converts the poly(dGdC)·poly(dGdC) from the B to the Z form in 1 hr at 22°, and its fluorescence is enhanced by single-stranded, but not double stranded DNA. The presence of a fluorescence-enhancing intermediate therefore supports the breaking of H-bonds between guanine and cytosine during the transition. Tb(III) produces all of the conformational transitions in the G-C DNA previously observed with $Co(NH_3)_6^{3+}$, so that B → Z → "A" → ψ. It may therefore be useful as a probe to monitor the mechanism of all of these transitions.

Age Change in Methylation of Cytidine in Mouse. There have been reports of age changes in the degree of methylation of DNA in the literature, but these studies have not involved the best analytical procedures. In a collaboration with Ram Singhal and Laura Hoopes, DNA from the livers of C57B1/6J mice was subjected to very careful HPLC analysis of all nucleosides, including 5-methyl-deoxycytidine. Very constant readings for deoxyguanosine, deoxyadenosine, and thymidine were obtained during the lifespan of the animals (e.g. deoxyadenosine varied between 30.1 and 30.3). 5-methyl deoxy-cytidine decreased from 6 to 12 to 18 to 24 months (from 1.67 to 1.02) with a corresponding increase in unmethylated deoxycytidine. There appears to be a significant increase in methylation at 26 and 28 months (1.11 and 1.21), coupled with an insignificant decrease in unmethylated deoxycytidine. Thus methylation clearly decreases to 24 months, and may increase again in the senescent state.

Studies on the Possible Effect of Aluminum on Alzheimer's Disease. There is evidence from brain autopsy studies that aluminum accumulates in localized areas

of the brain of Alzheimer's patients to a much greater extent than in the brain of controls. the correlation between Al and Alzheimer's disease is in controversy. We are engaged in a study designed to test the correlation and to try to understand what may be the effect of the Al. we have previously found that the addition of Al to chromatin produces a second peak in the ^{31}P NMR spectrum of chromatin, which generally contains only one peak (due to DNA phosphate). The second peak is presumably due to DNA whose chemical environment has been changed by Al. We then posed the question whether chromatin from Alzheimer's brain may exhibit this second peak, in contrase with the chromatin from the brains of controls. A comparison of the ^{31}P spectra of 7 Alzheimer brain chromatins and an equal number of controls, leads to the following results: 2 of the controls, but none of the Alzheimer's materials, have only one peak; all the rest have two peaks, but the second peak is generally higher in Alzheimer's than in controls. Moreover, in several jcases it was shwon that the 2nd peak is abolished by desferrioxamine, which removes Al from chromatin, thus indicating that the 2nd peak is indeed the result of metal binding, and probably Al binding. This result is in line with Al involvement in the disease, even though there is no all-or-none effect; but the presence of neurofibrillar tangles and senile plaque also differentiate Alzheimer's from controls by their number, rather than their presence or absence. The case is not yet proved, and we are pursuing these studies further.

Hemoglobin Dynamics. It has been recognized in recent years that proteins in solution undergo conformational fluctuations and that an understanding of these dynamic processes are necessary to explain the functions of proteins. We have previously shown how Mossbauer spectroscopy and electron spin resonance can be used to probe dynamics at the iron site in hemoglobin. By measuring the time course for the formation of a distal histidine bond at different temperatures it has now been possible to show that this process is associated with an energy barrier > 60 K joule $mole^{-1}$ which serves as an index of heme pocket flexibility. The electron spin resonance spectra for these bis-histidine complexes in ferrihemoglobin were shown to be very sensitive to the orientation and position of the distal histidine which is constrained by the structure of the heme pocket. In this way it has been possible to identify an intermediate complex for which the energy barrier is appreciably lower. This complex subsequently relaxes into one of three more stable complexes dependent on the geometry of the ligand pocket.

By extending our previous visible spectroscopy studies to cryogenic temperatures in the range of 173 K - 273 K, it has been possible to demonstrate that these spectra are sensitive to conformational fluctuations. The temperature dependent increase in intensity thus levels off below 200 K where previous x-ray and Mossbauer studies indicate that conformational fluctuations no longer take place. By studying the nature of the change in spectrum it can be concluded that a major portion of the dynamics detected by the visible spectrum is associated with protein constraints on the proximal histidine-iron bond.

The electron spin resonance spectra of various spin label molecules attached to a reactive sulfhydryl group on the proximal side of the heme

has been used to probe conformational dynamics at sites removed from the heme. By changing the size and shape of the spin label it has been possible to delineate two pockets on the proximal side of the heme, both of which change during ligand binding.

By measuring the spin interaction between Cu(II) bound to the amino terminus of the β-chain and this spin label it has been possible to demonstrate long-range conformational fluctuations which bring the amino terminus of one β-chain close to the carboxyl terminus of the other β-chain.

The work of the Macromolecular Chemistry Section continued to center on the development of methods which would make possible in vivo manipulation of the receptors for neurotransmitters in a selective and lasting manner; furthermore significant advances were made in the development of the solubilization and administration of hormones and drugs.

Catecholamine Receptors. Formerly the Macromolecular Chemistry Section was developing probes and studying exclusively beta-adrenoceptors. This is an important receptor which is a target of widely used drugs; nevertheless it was felt that a probe for other catecholamine receptors should also be developed. This enlargement of the field may enable us to create defects in animals which would better model pathological situations observed in some diseases of interest. Thus in Alzheimer's disease both dopamine and beta-adrenergic receptors were reported to be changed, and perhaps selective and lasting destruction of both these receptors in brains of animals may create meaningful animal models of that disease. Consequently an attempt was made to work simultaneously on probes related to beta-blockers, neuroleptics and antihypertensives of proper structures in order to interact with beta-adrenoceptor, dopamine receptor and alpha-adrenoceptor. In the first group, two new probes greatly superior to those previously employed were obtained. The newly developed probes alkylate β-adrenoceptor at 10^{-7} M concentration in vitro and satisfactory destruction of beta-adrenoceptor in vivo with doses of 1 mg/kg in rats were obtained. Furthermore, new probes may be radioiodinated. In the latter two categories the work is in exploratory phases. Various designs were considered and several compounds synthesized and evaluated. These results suggest that the future work should focus on compounds related to benzamide drugs and prazosin.

Solubilizers of Lipophilic Compounds. Due to personnel and laboratory limitations, only a little experimental work has been done in this field. Collaborative schemes were developed in which previously developed and synthesized materials could be consumed. Two of these schemes involving human disease are described in "Selected Research Accomplishments." A collaborative scheme was also used to characterize fully hydroxypropyl-beta-cyclodextrins, which results were required for the above mentioned testing.

The Molecular Physiology and Genetics Section has continued in attempts to explain the physiological and behavioral dysfunctions of aging in molecular

terms. Particular emphasis has been placed on regulatory mechanisms as influenced by environmental and genetic factors and modulated by the endocrine and neuroendocrine systems.

Age Changes in Sensori-Motor and Learning Memory Functions. Deficits in sensori-motor and learning/memory functions are well documented and highly important manifestations of aging. We have improved the methodology for measurement of such functions through automation and computerization. Studies at the molecular level have implicated age changes in the dopaminergic system primarily in sensori-motor deficits and the cholinergic system primarily in learning/memory deficits. Alterations in both neurotransmitter metabolism and receptor transduction mechanisms appear to be responsible for dysfunctions. Receptor loss is probably due to biosynthetic deficits, although cell loss cannot be ruled out. In fact, others have suggested that cell loss in the cholinergic system may be a major factor in deterioration of learning/memory function. Dysfunction in both systems can be retarded by dietary restriction. Such manipulations affect age changes at the molecular level as well, suggesting that fundamental aging mechanisms may be targeted. We are currently establishing a primate model to extend our rodent studies on the effects of dietary restriction on the aging rate.

Endocrine Regulation and Aging. Endocrine regulation of reproductive function and salivary gland secretion have also been examined during aging. We have implicated post receptor changes, such as decreased calcium mobilization in secretory dysfunction and both receptor and post-receptor changes in altered estrogen action, in uterus and pituitary. Further elucidation of the molecular lesions responsible for such alterations is underway. This includes examination of phospholipid metabolizing enzymes (required for calcium mobilization) in parotid cells and specific estrogen dependent gene transcription in the uterus and pituitary. Use of recombinant DNA technology is allowing quantitation of both gene dosage and expression. Preliminary studies suggest that aging may alter both types of processes in various physiological systems.

Oxidation Damage Protective Mechanisms. Recombinant DNA probes are also being employed to assess oncogene expression as a function of age and the role of oxidative damage protective mechanisms in the maintenance of function and longevity. Recent evidence suggests that oxygen radical damage may be partially responsible for various functional deficits and increasing vulnerability with increasing age. Such damage is also being assessed by measurement of modified nucleotides resulting from DNA damage and repair.

In summary, studies employing a wide spectrum of approaches have gained further insight into those molecular changes responsible for altered function during aging, and are seeking ways to delay, halt or reverse such deterioration.

FY 1985 ANNUAL REPORT AND RESEARCH HIGHLIGHTS
Inorganic Biochemistry Section

The Inorganic Biochemistry Section has made considerable progress in studies on the mechanism of RNA synthesis, the importance of conformational changes in DNA, and hemoglobin dynamics, and the techniques are being developed for the study of in vivo aging by NMR spectroscopy and imaging.

Active Site of RNA Polymerase. The basic molecular processes responsible for RNA synthesis occur at the active site of the RNA polymerase enzyme, where the DNA template and the nucleoside triphosphate substrates are bound. A major new project is to map out the active site of this enzyme; if this can be done successfully, it will be an important step in the elucidation of the mechanism of RNA synthesis. The active site consists of the initiation site, where the first substrate is bound to an intrinsic zinc(II), and an elongation site, where all succeeding substrates are bound to an activating Mg(II). These two metals can be replaced by paramagnetic ions (Mn), and the distances from these ions to atoms on the substrates can be determined by measuring the paramagnetic effect on the relaxation of the atomic nuclei. Some of these distances at the initiation and elongation sites have been determined by Wu et al. and Mildvan et al., respectively. We have determined the remaining distances at the elongation site, and in the presence of template - previously the distances had been determined without DNA present.

Complete knowledge of the active site requires an understanding of the spatial relationships between initiation and elongation sites. The two sites come in contact at the point where the two substrates form an internucleotide bond, i.e., the 3'OH group of the initiation substrate must touch the α-phosphate of the elongation substrate. Complete mapping then requires one more distance - that between the metals at the initiation and elongation sites. Such a metal-metal distance can be determined by EPR measurements, since the EPR spectrum of a paramagnetic metal is affected by another paramagnetic metal in its proximity.

We have been able to place Mn(II) into the initiation site and to determine its EPR spectrum on that site, to place Mn(II) into the elongation site and determine its spectrum there, and finally to place Mn(II) in both sites. In the latter instance there was, in fact, a marked influence of the metals on each other, demonstrating their proximity. We have been able to make preliminary measurements of the distance between them, and using this distance we have constructed a tentative model of the active site.

From the model it appears that the bases of the two nucleoside triphosphate substrates are not parallel, but are oriented at an angle to each other that suggests that the elongation site is at a point on the DNA template between the DNA double helix and the DNA-RNA hybrid that is formed from newly synthesized RNA and the DNA strand lt copies, and the initiation site is at the beginning of the hybrid helix.

Z-DNA as a template for RNA Synthesis. The B to Z conformational change occurs only with DNA of certain sequences (e.g. alternating GC) and therefore is

a reflection of the sequence on the surface of the template. The Z conformation is believed to be involved in genetic regulation by helping to make it possible for DNA-binding to proteins recognize specific DNA sites. Our previous finding that the B to Z transition in poly(dGdC)·poly(dGdC) is accompanied by a dramatic decrease in the ability of the DNA to act as a template for RNA synthesis indicates that the B to Z transitions could regulate RNA synthesis. This finding has now been confirmed by work at Harvard.

In order to understand the mechanism by which genetic regulation can occur through conformational change we have been studying several characteristics of the phenomenon. One of them is the effect of the binding of RNA polymerase to B and Z DNA. We have confirmed that addition of the enzyme to the Z forms of poly(dGdC)·poly(dGdC) and poly(dGdm^{5}C)·poly(dGdm^{5}C) results in a conversion to the B form of DNA. Moreover, we have found that the addition of the enzyme to the B forms before the conversion of B to Z decreases the rate of B to Z conversion. Thus the enzyme inhibits the conversion of B to Z and brings about the conversion of Z to B. Evidently the enzyme preferentially binds to B and this preference can explain the low RNA synthesis activity when the template is in the Z form.

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has been used to probe conformational dynamics at sites removed from the heme. By changing the size and shape of the spin label it has been possible to delineate two pockets on the proximal side of the heme, both of which change during ligand binding.

By measuring the spin interaction between Cu(II) bound to the amino terminus of the β-chain and this spin label it has been possible to demonstrate long-range conformational fluctuations which bring the amino terminus of one β-chain close to the carboxyl terminus of the other β-chain.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00045-15 LCMB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Effect of Metals and Proteins on Nucleic Acid, 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:	James J. Butzow	Commissioned Officer	IBS LCMB NIA
	Patricia Clark	Research Chemist	IBS LCMB NIA
	Yong A. Shin	Research Chemist	IBS LCMB NIA
	Rajasekharan P. Pillai	Visiting Associate	IBS LCMB NIA
	*Daniel Waysbort (DOD 7/3/85)	Visiting Associate	IBS LCMB NIA

*On leave from Israel Institute for Biological Research, Ness-Ziona

COOPERATING UNITS *(if any)*

Laboratory of Molecular Biology, NIADDK (E. Charney, I. Levin, S. Zimmerman); Department of Chemistry, Wichita State University (R. Singhal); Purdue University (Arnott); Oregon State Univ. (Johnson); Univ. of New Mexico (Bustamanta)

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:
5.5	4.5	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.)*

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 tranfer, 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 00046-15 LCMB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Medicinal Chemistry Applied to Problems Prominent in Senescence

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	Research Chemist	MCS LCMB NIA
	Jan S. Milecki EOD 1-24-85	Visiting Associate	MCS LCMB NIA
	Wiestaw Buchowiecki EOD 1-1-85	Visiting Fellow	MCS LCMB NIA
	Takashi Ishizu EOD 5-1-85	Visiting Fellow	MCS LCMB NIA
	Lajos Szabo EOD 7-1-85	Visiting Fellow	MCS LCMB NIA

COOPERATING UNITS *(if any)*

University of Florida, J. Hillis Miller Health Center, Gainesville, Florida; University of Minnesota, Minneapolis, Minnesota; NIDR, NIH, Bethesda, Maryland; University of San Francisco, San Francisco, California.

LAB/BRANCH

Laboratory of Cellular and Molecular Biology

SECTION

Macromolecular Chemistry Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
5.4	4.4	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.)*

Two problems which have relevance to aging have been studied. In the field of congeners of catecholamines the following results were obtained: (A) A new series of compounds which selectively destroy beta-adrenoceptors was developed which has indexes about two orders better than previously available compounds. The results suggest that new series will enable selective manipulation of beta-adrenoceptors in brain to be performed in a practical manner. (B) A compound which activates and then attaches itself permanently to beta-adrenoceptors was prepared. Evaluation of this compound indicates that beta-adrenoceptor has intrinsic self-deactivation capacity, i.e. can not be jammed in activated state. (C) Orientation studies of dopamine confiners were initiated. In the field of solubilizers of lipophilic hormones and drugs the previously developed compounds, hydrophilic derivatives of cyclodextrins, were analyzed thoroughly and prepared in quantity to support two clinical evaluation studies.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00047-15 LCMB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Structure-Function Relationships in Hemoglobin and Erthrocytes

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

PI:	J.M. Rifkind	Research Chemist	IBS LCMB NIA
Others:	P. Chuknyiski	Visiting Fellow	IBS LCMB NIA
	A. Levy	Visiting Associate	IBS LCMB NIA
	P.T. Manoharan (DOD 10/5/85)	Visiting Scientist	IBS LCMB NIA
	I.J. Rhee	Guest Researcher	IBS LCMB NIA

COOPERATING UNITS *(if any)*

Johns Hopkins University School of Medicine (J. Glicksen); Benedict College, South Carolina (K. Alston); State University of New York at Buffalo (F. Davis); Medical College of Wisconsin (W.E. Antholine); Sandia Natl. Laboratories (J.A. Shelnutt)

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:
4.1	3.1	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 purpose of this project is to study the mechanisms involved in regulating the binding of oxygen to hemoglobin and the transport of oxygen to the tissues. The project also focuses on ways in which these functions are impaired and change with age. We have therefore studied the mechanisms involved in the oxidation of hemoglobin. Oxidation affects oxygen transport because it produces nonfunctional hemoglobin, which no longer binds oxygen. These studies have been extended to include an investigation of the stability of the entire erythrocyte and the erythrocyte membrane as well as other structure function relationships in membranes.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00113-2 LCMB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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:	Rajasekharan P. Pillai	Visiting Associate	IBS LCMB NIA
	Daniel Waysbort (DOD 7/3/85)	Visiting Associate	IBS LCMB NIA

COOPERATING UNITS *(if any)*

See Page 2 of this Annual Report

LAB/BRANCH

Laboratory of Cellular & Molecular Biology

SECTION

Inorganic Biochemistry Section

INSTITUTE AND LOCATION

National Institute on Aging/NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.4	1.3	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.)*

NMR is used for the non-invasive study of aging in animals and cells, and for the study of age changes in human arms and legs. A biospec spectrometer (300/1.9) is used to study age changes in animals by multinuclear spectroscopy, using 2-dimensional NMR and saturation transfer techniques to study how metabolic rates of exchange change with age. The metabolic changes are compared to morphological changes studied by imaging techniques, which are also useful for studying changes in the distribution of drugs and metabolites. Probes designed for use with a narrow-bore Varian XL-200 spectrometer are employed to perfuse cells such as human fibroblasts of varying passage and from donors of different ages. Metabollsm of the cells is studied by multinuclear NMR techniques.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

PROJECT NUMBER

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01-AG 00301-2 LCMB

PERIOD COVERED: October 1, 1984 to September 30, 1985

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)

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

Other:

R. Chuknyiska	Visiting Fellow	LCMB	NIA
J. Henry	Staff Fellow	LCMB	NIA
Y. Ishikawa	Visiting Fellow	LCMB	NIA
B. Baum	Dental Officer	PCB	NIDR
M. Blackman	Guest Scientist	CPB	NIA

COOPERATING UNITS (if any)

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

LAB/BRANCH

SECTION: ~~Gerontology Research Center,~~

Molecular Physiology and Genetics Section

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

TOTAL MAN-YEARS: PROFESSIONAL: OTHER:

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 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 00302-2 LCMB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Regulation of Physiological Functions During Aging: II. Behavioral Biology

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

Donald K. Ingram, Rsch. Psychologist, Lab. of Cellular & Molecular Biology, NIA

OTHER:

M. Talan	Visiting Scientist	LBS, GRC, NIA
J. Sinnott	Guest Scientist	LBS, GRC, NIA
R. Weindruch	Asst. Prof. of Psychology	LBS, GRC, NIA

COOPERATING UNITS *(if any)*

ADR, NIDA, ADAMHA; Dept. Psychol., JHU; Jackson Lab.; Lafayette Clinic; Essex Community College; Dept. Pathology, UCLA

LAB/BRANCH

Gerontology Research Center

SECTION

Molecular Physiology and Genetics Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 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.)*

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 assays are conducted to determine neurobiological correlates of functional losses. Interventions include dietary restriction, environmental enrichment, and various pharmacologic treatments. 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-00303-2 LCMB

PERIOD COVERED
October 1, 1984 to September 30, 1985

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

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

COOPERATING UNITS *(if any)*
Brookhaven National Lab., Upton, L.I., NY; Dr. Richard Setlow
National Cancer Institute, Lab. of Human Carcinogens; Dr. Vincent Wilson

LAB/BRANCH
Gerontology Research Center

SECTION
Molecular Physiology and Genetics Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, MD

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.)*

Our research objective is the investigation of the biochemical and genetic basis of the variations found in the aging rate and maximum lifespan potential observed among the different mammalian species. Particular emphasis is placed on humans which appear to have the lowest aging rate and longest maximum lifespan potentials of all mammals. Past work of our laboratory has indicated that aging may be a result of the loss of proper gene expression in cells and this has led to formulation of the dysdifferentiative hypothesis of aging. Recent work to further test this hypothesis has involved studies of oncogene expression and methylation patterns of DNA with age in mouse and human tissues. An age-dependent decrease in the amount of 5-methyl cytosine content in DNA of mouse tissues with age has been found. We have also examined the possibility that active oxygen species might be important in destabilizing proper gene expression and that in turn endogenous antioxidants may be gene stabilizing agents. Tissues from longer-lived species were found to have higher levels only of specific types of antioxidants but to be less sensitive to autoxidation. Taken together, these results continue to support the concept that aging is accompanied by cellular dysdifferentiative processes and that longevity may be governed in part by endogenous antioxidants which act to stabilize proper gene expression.

Annual Report of the Laboratory of Molecular Aging
National Institute on Aging

The overall objective of the Laboratory of Molecular Aging is to conduct research on the molecular basis of life processes and to examine the impact of aging on cellular functions. Within this framework of endeavor, the Laboratory's goal is to sustain the best tradition of intramural research at the NIH as a center of excellence for biomedical studies.

In meeting this overall objective, the Laboratory:

(1) investigates the mechanisms of transport of solutes and water across biological membranes, including the chemical nature and sequence of intermediate reactions;

(2) studies how the translocation mechanisms are regulated by hormones, pharmacological agents, diet, and other pathophysiological effectors;

(3) explores the mechanisms by which these systems are modified during the aging process and in age-associated disease.

These investigations characterize biochemically the regulatory mechanisms responsible for maintenance of structure, growth and remodelling, differentiation and replication, intracellular and extracellular environments, metabolism, function and vitality. The physiological systems studied include:

(1) mineral metabolism, as related to post-menopausal and senile forms of osteopenia;

(2) regulation of intracellular pH, as related to acid-base balance and cell differentiation, replication and metabolism in the aging animal;

(3) ion pumps and channels in excitable tissues, as related to excitation-contraction coupling during the aging process;

(4) ion channels and gradients in non-excitable tissues, as related to salt-water balance and ion homeostasis in the aging animal.

This report summarizes the following basic sciences projects:

1. Action of parathyroid hormone (PTH) on Na-Ca exchange in isolated renal cells. Last year we reported that Na-Ca exchange activity in renal cortical basolateral membrane vesicles from PTX rats was decreased and, when bovine PTH (1-84) was infused into these animals, activity was fully restored (JBC 259: 10827, 1984). Now, we examined whether PTH, incubated in vitro with renal cortical cells, modulates Ca flux by regulating the exchange. Cells were isolated by collagenase-hyaluronidase digestion and loaded with ^{45}Ca. Ca efflux was measured after diluting the cells in a EGTA medium containing 140 mM Na or choline. The following results were found: (1) extracellular Na increases the

initial (5s) rate of Ca efflux, 12.3±2.2% vs 3.4±0.9; (2) Vmax for Ca efflux=6.4 nmol·5s^{-1}·mg^{-1} prot, Km(Na)=10 mM; (3) PTH (1-84) 10 U/ml increases Na-dependent rate of Ca efflux 55%, from 17.6±4.6 to 27.3±3.8%, passive Ca efflux (choline) is not changed; (4) PTH stimulates efflux maximally after 1.5 min of preincubation with cells, at which time intracellular cAMP is also maximal; (5) Ca efflux and cAMP generation have similar PTH concentration dependencies; (6) PTH (1-34), forskolin, dibut cAMP, and 8-Br cAMP enhance Na-dependent Ca efflux, PTH (3-34) is inactive; (7) PTH (1-84) and (1-34) and forskolin increase intracellular cAMP, PTH (3-34) does not; (8) Na-dependent Ca efflux in cells from PTX rats is decreased, PTH, in vitro, increases rate 106%; and (9) in cells from aged rats (24 mo), compared to cells from 2,6 and 12 mo old animals, PTH enhancement of Na-dependent Ca efflux is markedly decreased, basal (Na) and passive (choline) efflux rates are not altered. These findings suggest that PTH modulate Ca transport by regulating Na-Ca exchange via a cAMP mechanism and that this system may be altered with age.

2. iPTH increases in the aged female rat. Immunoreactive (mid-molecule) PTH levels in the serum of female rats increase significantly in aging. Values for 6,12 and 24 mo old animals are 19 ± 3, 24 ± 4, and 48 ± 9 pmol/l, respectively. Serum phosphate and calcium concentrations do not differ in these age groups. The values for phosphate are 1.60 ± 0.07, 1.62 ± 0.07 and 1.52 ± 0.06 mM, respectively. Serum calcium concentrations also do not change, being 2.31 ± 0.04, 2.35 ± 0.02, and 2.41 ± 0.03 mM, respectively.

3. Mechanism of transepithelial phosphate transport in the proximal tubule. The reabsorption of phosphate in the nephron requires the anion to be translocated from lumen to cell, crossing the luminal brush border segment of the plasma membrane, and from cell to blood, crossing the basolateral segment of the plasma membrane. Transport across the brush border membrane by a Na^+-phosphate cotransport system is well characterized and has been described previously. The mechanism by which phosphate exits from the cell to complete the reabsorption process is essentially unknown and the subject of much controversy. Our preliminary findings support the view that transport across the basolateral membrane is not coupled to Na^+ flux. The possible involvement of an anion exchange system is suggested from the finding the phosphate transport is inhibited by probenicid.

4. Mechanism of the phosphaturia and hypophosphatemia in the aging rats.

We previously reported the age-related increase in urinary excretion of phosphate in male Wistar-derived rats fed a normal phosphorus diet. These rats are also hypophosphatemic, a condition which may have resulted from the age-related decrease in phosphate reabsorption. The mechanism of the age-related decrement in phosphate conservation has been examined by determining the initial rate of Na^+ gradient-dependent uptake of phosphate by renal brush border membrane vesicles. Phosphate transport kinetics indicate that the decreased phosphate uptake by membrane vesicles from senescent 24 mo rats is due to a significant decrease in maximal velocity of the transport system with no change in affinity for phosphate.

The role of parathyroid hormone (PTH) in the etiology of the age-related phosphaturia has been examined since elevated PTH, or renal hypersensitivity to PTH, could conceivably be the cause of the phosphaturia. Compared to 6 mo adults, immunoreactive PTH was nearly 2.5-fold higher in senescent

24 mo rats. However, removal of endogenous PTH by thyroparathyroidectomy (TPTX) or parathyroidectomy (PTX) does not normalize renal phosphate excretion in vivo or brush border membrane vesicle uptake of phosphate in vitro. Other baseline parameters in intact senescent rats also argue against the involvement of PTH in the age-dependent phosphaturia, and cast doubt on the contribution of the elevated circulating PTH. First, urinary excretion of cyclic AMP, a sensitive marker of PTH activity, is not elevated in intact senescent rats, as would be expected if PTH was the cause of the phosphaturia. Second, plasma alkaline phosphatase was actually reduced (-19%) in 24 mo rats, instead of being elevated as would be expected in a state of hyperparathyroidism. Third, plasma Ca^{2+} is normal in old rats. Down regulation of PTH receptors would explain the apparent decreased renal sensitivity to elevated circulating iPTH in the old rat. We conclude that the age-related phosphaturia is independent of PTH (and probably calcitonin and thyroxine).

5. Age-dependent alteration in the synthesis of the Vitamin D hormone.

Previous studies in man and rat showed declines with age in both intestinal absorption of calcium and in serum levels of the vitamin D metabolites, 1,25-dihydroxycholecalciferol (1,25-$(OH)_2D_3$) and 24,25-dihydroxycholecalciferol (24,25-$(OH)_2D_3$). The hydroxylation of 25-$(OH)D_3$ at either the 1-or 24-positions takes place in kidney mitochondria but the mechanism of regulation of the two mitochondrial hydroxylases is unknown.

Studies have been carried out to determine if there are alterations with age in the mitochondrial systems which hydroxylate 25-$(OH)D_3$. The activities of the 25-$(OH)D_3$-1- and 24-hydroxylases are measured in kidney mitochondria isolated from 2,6,12,18 and 24 mo old rats. Formation of 1,25-$(OH)_2D_3$ and 24,25-$(OH)_2D_3$ are determined by competitive binding assays using a fetal chick intestinal cytosolic receptor specific for 1,25-$(OH)_2D_3$ and a non-specific rat serum binding protein for 24,25-$(OH)_2D_3$, respectively, following separation of metabolites on silica Sep-Pak and High Performance Liquid Chromatography (HPLC). 1-Hydroxylase activities in kidney mitochondria from 2,6,12, and 24 mo old rats are 0.46, 0.15, 0.09, and 0.07 nmol/10min/mg protein, respectively; 24-hydroxylase activities are 3.5, 9.0, 21.2, and 27.9 nmol/10min/mg protein, respectively. These findings demonstrate a specific increase with age, in the activity of the 24-hydroxylase system and a specific decrement with age, in the basal activity of the 1-hydroxylase system in renal mitochondria, which correlate with the age-dependent declines in serum levels of the hormones and in intestinal calcium transport.

The age-dependent changes in hydroxylase activities are not due to general changes in mitochondrial function since the content of cytochromes a,a_3 and $c(+c_1)$ and cytochrome oxidase activity in the isolated mitochondria are unaltered with age. However, there is an age-dependent loss of nearly 50% in the total number and function of mitochondria in the renal cortex. Renal homogenates from 2 and 24 month old rats have less cytochrome oxidase activity, from 190 to 100 ngatom O/min/mg, respectively, and less cytochrome content, cytochrome a decreased from 0.16 to 0.08, cytochrome a_3 from 0.13 to 0.06 and cytochromes c $(+c_1)$ from 0.25 to 0.12 µmol/g, respectively. Thus, the age-dependent decrement in 1-hydroxylase activity in the kidney represents the decrease in specific activity per mitochondrion plus the loss in the number of mitochondria per kidney.

6. Regulation of intestinal calcium absorption by the Vitamin D hormone.

Previous studies demonstrated that there is an age-related decline in calcium absorption by the intestine, a contributory factor to the negative calcium balance seen in the aged. Intestinal calcium absorption is largely regulated by 1,25-dihydroxycholecalciferol ($1,25\text{-}(OH)_2D_3$), the hormonal form of vitamin D. The mechanism by which the hormone regulates calcium transport is unknown. To resolve this question and to determine how the system is altered with age, a model system, calcium uptake in isolated duodenal cells of the vitamin D deficient chick, was established.

We reported last year that in vitro pre-incubation for 1 hr of isolated duodenal cells from D-deficient chicks with physiological concentrations ($< 10^{-13}$ M) of $1,25\text{-}(OH)_2D_3$ stimulated cell calcium uptake and this induction is blocked by inhibitors of RNA and protein synthesis. In continuing studies with this model we have now demonstrated that the vitamin D hormone does not alter the general metabolism or integrity of the cell during the exposure period. This is evident from the findings the ATP content of the cell, the ability to incorporate amino acids into protein, and the retention of lactic dehydrogenase activity are unaffected by the treatment with $1,25\text{-}(OH)_2D_3$.

In studies to identify the cellular site of action of the vitamin D hormone, we find that the hormone increases calcium uptake into duodenal brush border membrane vesicles. The uptake in membrane vesicles from repleted chicks is 1.59 ± 0.11 nmol·min^{-1}·mg^{-1} protein compared to 0.97 ± 0.07 in brush border vesicles from deficient animals. We suggest that the stimulation in cellular calcium uptake by the vitamin D-hormone results, at least in part, from an increase in calcium influx at the luminal membrane of the cell.

In further studies of the hypothesis that the initial response of the enterocytes to $1,25\text{-}(OH)_2D_3$ is to increase calcium entrances by an alteration in the lipids in the brush border membrane of the cell, we find that: (1) there is no difference in phospholipase C activity between cells from D-deficient and $1,25\text{-}(OH)_2D_3$ replete chicks; (2) there is no difference in the incorporation of linoleic acid into the 2-C position of lipids in cells from deficient and replete animals; (3) there are no consistent changes in the phosphatidyl choline, phosphatidyl ethanolamine, phosphatidyl serine, and phosphatidyl inositol contents of the brush border membranes of cells from D-deficient animals and cells incubated in vitro with $1,25\text{-}(OH)_2D_3$.

7. Studies of the effect of $1,25\text{-}(OH)_2D_3$ on renal calcium transport.

The basolateral segment of the rat renal tubular plasma membrane possesses Ca^{2+}-dependent ATPase activity which is independent of Mg^{2+}. Two kinetic forms are found: one, is a high affinity (apparent Km for free Ca^{2+} of 172 nM), low capacity (Vmax of 144 nmol Pi·min^{-1}·mg^{-1} protein) type; the other, has low affinity (apparent Km of 25 μM) and high capacity (896 nmol Pi·min^{-1}·mg^{-1} protein). Mg^{2+} inhibits both Ca^{2+}-ATPases. The high affinity enzyme exhibits positive cooperativity with respect to ATP, with a n value of 1.6. Ca^{2+}-ATPase activity is not affected by calmodulin and is not inhibited by vanadate. Both high and low affinity Ca^{2+}-ATPase activities are increased when $1,25(OH)_2D_3$ is given to vitamin D deficient rats. Kinetically, the enhanced activities are due to an increase in the Vmax values; the apparent affinities for free Ca^{2+} are not changed.

8. Sodium-proton exchange activity in the aging rat.

We previously reported on the properties of the Na^+-H^+ exchange carrier in plasma membranes (luminal) of the proximal tubule and on the regulation of exchange activity by hormonal and pathophysiological effectors. The Na^+-H^+ exchanger couples the flux of sodium from lumen to cell down its electrochemical gradient to a proton flux from cell to lumen against its electrochemical gradient. In the kidney, the exchanger plays a critical role in the regulation of intracellular pH, the transepithelial transport of sodium and bicarbonate, the acidification of the urine, and the urinary excretion of titratable acids and ammonium. We now report that in luminal membrane vesicles isolated from 6,12,18 and 24 mo old male rats, the Na^+-H^+ exchange activity remains constant up to 18 mo, but decreases dramatically (50%) in the 24 mo old rat. The values are: 6 mo, 2.31 ± 0.22; 12 mo, 2.40 ± 0.27; 18 mo, 2.51 ± 0.13; and 24 mo, 1.20 ± 0.19 nmol $Na^+ \cdot 5s^{-1} \cdot mg^{-1}$ protein. Glucose transport activity in the same membrane vesicles is not affected by age, the values remaining constant at about 14 pmol glucose $\cdot 5s^{-1} \cdot mg^{-1}$ protein. Since Na^+-H^+ exchange activity is regulated by a variety of hormonal and pathophysiological inputs, the diminished activity in the aged rat may be the result of alterations in these effectors.

9. Thyroid hormone regulation of sodium-proton exchange activity.

Na^+-H^+ exchange activity, i.e., amiloride-sensitive Na^+ and H^+ flux, in renal proximal tubule brush border (luminal) membrane vesicles was increased in the hyperthyroid rat and decreased in the hypothyroid rat, relative to the euthyroid animal. A positive correlation was found between Na^+-H^+ exchange activity and serum concentrations of thyroxine (T4) and triiodothyronine (T3). The thyroid status of the animal did not alter amiloride-insensitive Na^+ uptake. The rate of passive pH gradient dissipation was higher in membrane vesicles from hyperthyroid rats compared to the rate in vesicles from hypothyroid animals, a result which would tend to limit the increase in Na^+ uptake in vesicles from hyperthyroid animals. Na^+-dependent phosphate uptake was increased in membrane vesicles from hyperthyroid rats; Na^+-dependent D-glucose and L-proline uptakes were not changed by the thyroid status of the animal. The effect of thyroid hormones in increasing the uptake of Na^+ in the brush border membrane vesicle is consistent with the action of the hormones in enhancing renal Na^+ reabsorption. Further, the regulation of transtubular Na^+ flux has now been shown to be concomitant with modulation of the entry of Na^+ into the tubular cell across its luminal membrane, mediated by the exchange reaction, and with the previously reported control of the pumping of Na^+ out of the cell across its basolateral membrane, mediated by the Na^+,K^+-ATPase.

Next, we studied the kinetic mechanism by which hyperthyroidism increased the Na^+-H^+ exchange activity in isolated renal brush border membrane vesicles. Treatment altered the initial rate of Na^+ uptake by increasing V_m (hyperthyroid, 18.9 ± 1.1 nmol $Na^+ \cdot mg^{-1} \cdot 2s^{-1}$; normal, 8.9 ± 0.3 nmol $Na^+ \cdot mg^{-1} \cdot 2s^{-1}$), and not the apparent affinity K_{Na^+} (hyperthyroid, 7.3 ± 1.7 mM; normal, 6.5 ± 0.9 mM). Hyperthyroidism resulted in the proportional increase in 1 mM Na^+ uptake at every intravesicular pH measured. A positive cooperative effect on Na^+ uptake was found with increased intravesicular acidity in vesicles from both normal and hyperthyroid rats. When the data were analyzed by the Hill equation, it was found that hyperthyroidism did not change the n (hyperthyroid, 1.2; normal, 1.2) or the $[H^+]_{0.5}$ (hyperthyroid, 0.39 µM; normal, 0.44 µM) but increased the apparent V_m (hyperthyroid, 1.68 nmol $Na^+ \cdot mg^{-1} \cdot 2s^{-1}$; normal 0.96 nmol

$Na^+ \cdot mg^{-1} \cdot 2s^{-1}$). The uptake of Na^+ in exchange for H^+ in membrane vesicles from normal and hyperthyroid animals was not influenced by membrane potential. H^+ translocation or debinding was rate limiting for Na^+-H^+ exchange since Na^+-Na^+ exchange activity was greater than Na^+-H^+ exchange activity. Hyperthyroidism caused a proportional increase and hypothyroidism caused a proportional decrease in Na^+-Na^+ and Na^+-H^+ exchange. We conclude that hyperthyroidism leads to either an increase in the number of functional exchangers in the membrane or exactly proportional increases in the rate-limiting steps for Na^+-Na^+ and Na^+-H^+ exchange activity.

10. Renal adaption in metabolic acidosis.

We previously reported that acid secretion, mediated by sodium-proton exchange, is stimulated in chronic metabolic acidosis and that this response required an intact adrenal gland or glucocorticoid supplements when the glands are removed. We now find that the initial rate (5s) of Na^+-dependent phosphate uptake in brush border membrane vesicles isolated from rat proximal tubule was decreased in metabolic acidosis, 0.42 ± 0.02 vs 0.59 ± 0.05 nmol/mg protein in vesicles from control animals. The decrement in transport activity required an intact adrenal gland, or glucocorticoid supplements when the adrenals were removed. Ammonium and calcium excretions were increased during acidosis 600% and 56%, respectively. These alterations were also largely dependent on an intact adrenal gland or glucocorticoid supplements. Na^+-dependent glucose cotransport, however, was not altered by acidosis or the glucocorticoid status of the animal. These findings are consistent with glucocorticoids having an important regulatory role in the kidney by orchestrating the proximal tubular adaptation to metabolic acidosis by altering phosphate, calcium, and ammonium excretions.

11. Cell culture systems for the study of the cellular mechanism for hormonal regulation of phosphate transport.

Phosphate uptake by primary cultures of chick renal cells was studied. Uptake was Na^+-dependent; saturable with respect to phosphate, with an apparent Km of 0.14 mM; and with respect to Na^+, with a S_{50} value of 45 mM. Phosphate transport was energy-dependent, altered by changes in extracellular pH; and inhibited by arsenate, ouabain, and sulfhydryl reagents. The phosphate uptake system was responsive to changes in the concentration of phosphate in the growth media. Deprivation of phosphate for only 1 hr increased phosphate uptake. The characteristics of the primary cell phosphate uptake system resembled the properties of phosphate transport in the kidney. The primary cultured chick cells also possessed a Na^+-dependent α-methylglucoside uptake system. Parathyroid hormone, vasopressin, glucagon, dibutyryl cAMP, and forskolin inhibited Na^+-dependent phosphate uptake. Dexamethasone also inhibited the cell phosphate uptake system. Triiodothyronine stimulated phosphate uptake. These findings indicate that glucocorticoids and thyroid hormone have direct effects on the renal cell transport of phosphate.

The regulation by glucocorticoids of phosphate transport in primary cultured chick renal cells was examined in further detail. Dexamethasone inhibited the Na^+-dependent phosphate uptake system. Na^+-independent phosphate uptake and Na^+-dependent uptakes of α-methylglucoside and L-proline were unaffected. The mineralocorticoid aldosterone did not alter phosphate uptake. The inhibition of Na^+-dependent phosphate uptake by dexamethasone was concentration-dependent, exhibited a lag period, was blocked by inhibitors of RNA and protein synthesis,

and was rapidly reversed when the steroid was removed. Following reversal, the cells could respond a second time to the glucocorticoid. However, this time the response was apparently without a lag phase, could occur as late as 24 hours after termination of the initial response, and was prevented by actinomycin D and cycloheximide. These findings demonstrate that glucocorticoids act directly on renal cells to modulate phosphate transport and suggest that the renal cell system provides an attractive model to examine the mechanism by which glucocorticoids control gene expression and regulate plasma membrane transport function.

12. Adrenergic regulation of metabolism.

The effects of norepinephrine on rat proximal tubules isolated by a Percoll gradient technique were studied. Prazosin-inhibitable stimulation of gluconeogenesis and inositol phosphate accumulation was observed, with both processes exhibiting dependence upon extracellular Ca^{2+}. Inositol phosphate accumulation was stimulated 10-fold for IP_1, 5-6 fold for IP_2, and only 50-100% for IP_3. LiCl was required for these increases. Angiotensin II also increased inositol phosphates to approximately 50% of the level obtained with norepinephrine. Parathyroid hormone and vasopressin had no effect. Maximal and half-maximal doses for these increases were 10^{-4} and 3×10^{-6} M for norepinephrine, and 10^{-5} and 3×10^{-7} M for angiotensin II. The levels needed to increase gluconeogenesis were somewhat less for both hormones. The norepinephrine stimulation of inositol phosphate accumulation is due mostly to a decrease in the level of phosphatidylinositol-4,5-bisphosphate.

Approximately 85% of total protein kinase C in proximal tubules is cytosolic. Upon exposure to norepinephrine, this level falls and particulate protein kinase-C increases 2-fold to 30% of total. The dose-response relationship for this effect corresponds closely to stimulation of inositol phosphate accumulation. Similar observations on both inositol phosphate accumulation and protein kinase-C translocation have been made on isolated cardiac myocytes.

13. Identification and characterization of ion channels in non-excitable tissues.

We have continued the investigation of ion channels in kidney cells using the patch clamp technique. The apical membrane from a clonal preparation of cultured medullary thick ascending limb cells from rabbit was characterized using both microelectrodes and cell-attached patch clamp technique. We found a Ba induced depolarization and a furosemide induced hyperpolarization of the apical membrane, two identifying conductive properties of the apical membrane of the thick ascending limb of the mammalian kidney in vivo. We also measured channel activity at the normal resting membrane potential. We have found the presence of a 135 pS channel in the apical membrane. This channel increases the frequency of opening and fractional open time with cell depolarization. The fractional open time increases an e-fold/15 mV an effect which is accounted for by increases in mean open time and decreases in mean closed time. A smaller channel also carrying outward current but with a single channel conductance of 35 pS was observed less frequently.

Using excised patches with a K chemical gradient in the absence of an electrical gradient, we found that current flowed in the direction of the electrochemical gradient for K, thus proving that a K channel exists in this membrane. In

the presence of 5mM K in the pipette and 50-150 mM K in the bath at the intracellular face of the patch, we measured the single channel conductance to be about 125 pS which is the same as the single channel conductance in cell-attached patches. We have also observed smaller conductances of 67 and 35 pS. A substitution of 1 mM Ca++ for 10-7 M Ca++ decreases channel activity; at 10-8 M Ca++ the channel openings are very infrequent. These results suggest that this channel belongs to the class of Ca++ activated K channels. We have observed a similar channel in the apical membrane of chick cells and such a channel has been observed by others in the apical membrane of the cortical collecting tubule. These K channels have been observed in the apical membrane of segments of the kidney known to have K conductive properties.

Most K conductive epithelia show a block of the membrane potential by Ba. Indeed we have found the apical membrane of both the chick cells and the medullary thick ascending limb cells depolarizes in the presence of Ba. We characterized the kinetics of the Ba block of channel activity using excised patches. We found that Ba decreases the mean open time and also increases the mean closed time of the channel.

14. Age-dependent change in mycardial Ca^{2+} pump activity.

Last year we reported that the initial velocity of ATP-dependent Ca^{2+} transport in sarcoplasmic reticulum (SR) vesicles isolated from senescent rat myocardium was diminished (43%, $p < .05$) compared to the activity measured in the young (6-8 mo) population. Increasing the sample size from 6 to 24 paired experiments reduced the average difference in transport activity between the two age groups by 23% (4.28 ± .33 nmol Ca^{2+} /mg protein/sec in the young vs 2.92 ± .31 nmol/mg/sec in the old) but increased the level of significance ($p < .005$). In addition, there were indications that the slow phase of spontaneous Ca^{2+} release which follows the rapid uptake phase decays more rapidly in the old population, suggesting that the diminished initial rate of ATP-dependent Ca^{2+} accumulation may be due to accelerated Ca^{2+} efflux. Comparison of the passive rates of Ca^{2+} efflux by dilution of Ca^{2+}-loaded vesicles into a Ca^{2+}-free (EGTA containing) medium revealed no significant age difference excluding increased passive permeability as the explanation for the decreased Ca^{2+} transport activity. It has recently been shown that Ca^{2+} efflux is significantly enhanced by micromolar levels of Ca^{2+} in the extravesicular medium acting by a channel-mediated mechanism that involves Ca^{2+}-induced Ca^{2+} release. There is also independent evidence showing that the Ca^{2+} pump Ca^{2+} ATPase activity and phosphoenzyme level are unaltered with age. Taken together, these results indicate that as a function of age the Ca^{2+}-activated component of Ca^{2+} release may be increased without a change in pumping rate. Consequently, efforts will be directed in the coming year towards characterizing the quantitative behavior of Ca^{2+}-induced Ca^{2+} release mechanism in different age groups to assess its potential contribution to the decrement in Ca^{2+} transport activity and prolonged contraction duration in cardiac papillary muscle.

15. Calcium release channel in sarcoplasmic reticulum.

The development of tension in muscle following electrical stimulation involves the rapid release of Ca^{2+} from the sarcoplasmic reticulum by a mechanism which is presumed to be mediated by a Ca^{2+} channel. In collaboration with Drs. B. Suarez-Isla and C. Orozco of the Laboratory of Neurosciences, we have initiated studies to test this hypothesis by means of the patch clamp technique which

enables resolution of the current fluctuations that result from the movement of ions through single channels. Skeletal muscle SR vesicles consisting of both heavy and light components were washed extensively to remove K^+ contamination which could interfere with measurement of the current flux Ca^{2+} channels. Gigaseals were formed at the tip of the patch pipette by the double dip method using SR suspensions containing between 50 and 200 mM $CaCl_2$ or $BaCl_2$. Preliminary experiments revealed the presence of a cationic channel of small (~ 1 pA) conductance that preferentially conducts Ca^{2+} and Ba^{2+}, is activated by millimolar concentrations of caffeine (which lengthens the duration of the burst openings), and is blocked by ryanodine, La^{3+} and Cd^{2+}. The channel opens spontaneously and appears to be voltage independent. In addition, we have found that the frequency of forming gigaseals and observing channels substantially exceeds the percent contamination of SR by mitochondrial and sarcolemmal membranes excluding the possibility that these contaminants are the source of the channel activity. Extrapolation of the current vs $[Ca^{2+}]$ curve to a physiologic Ca^{2+} level (5 mM) yields a single channel conductance of .05 pA which is in substantial agreement with the Ca^{2+} channel conductance estimated from the macroscopic Ca^{2+} flux and the approximate density of Ca^{2+} channels. This indicates that this channel is capable of sustaining Ca^{2+} fluxes required for the activation of muscle contraction and thus supports the hypothesis that the observed Ca^{2+} conductance is an obligatory component of the excitation-contraction coupling mechanism.

16. Transient kinetics of the cardiac sarcolemmal Na^+/Ca^{2+} exchanger.

The Na^+/Ca^{2+} exchanger in canine cardiac sarcolemmal (SL) vesicles exhibits a transient burst of Ca^{2+} accumulation that is enhanced by an inside positive membrane potential and inhibited by an inside negative potential. Similar presteady state kinetic measurements carried out this year with a preparation of SL vesicles from beef heart gave an entirely different pattern of behavior consisting of a brief early lag phase followed by a linear rate of Ca^{2+} accumulation. On the other hand, exposure to Ca^{2+} in the absence of internal Na^+ or Ca^{2+} produced a biexponential burst of Ca^{2+} accumulation without evidence of an initial lag. The slow linear phase following the burst was considerably slower than the steady state phase of Na^+-dependent Ca^{2+} uptake and rapidly rose to a plateau. This behavior contrasts with that previously observed in the dog where Ca^{2+} uptake in the absence of internal Na^+ shows a prominent lag and no burst phase. This difference in behavior, which is presumably species specific, can be explained by assuming that in the bovine preparation preincubation with Na^+ prior to mixing with Ca^{2+} stabilizes the formation of a Na^+ binding conformation that undergoes conversion to a Ca^{2+} binding state at a velocity that is rate-limiting for Na^+/Ca^{2+} exchange. In the dog this step is apparently much faster enabling the subsequent Ca^{2+} translocation step to be resolved as an initial burst. The species specific difference observed in the absence of internal Na^+ may reflect a greater tendency of the bovine Na^+/Ca^{2+} exchanger to assume an external orientation as opposed to an occluded or internally-oriented state.

17. Transient kinetics of the Na^+/H^+ exchanger in kidney brush border membranes.

Although recent attention in this laboratory has focused on the regulation of steady state Na^+/H^+ exchange activity by hormones, the effect of hormones on the transient phase of the exchange reaction has not been investigated. This is a potentially interesting area of investigation since information contained in

the transient phase can be used to estimate the carrier site density which may be altered in response to a change in hormonal status. Using low temperature to resolve the initial time course of Na^+ uptake, we observed the presence of an early burst phase that is representative of the first turnover of the system and is proportional to the carrier site density. Further studies have confirmed this behavior and have uncovered new aspects of the exchange mechanism under conditions of varying internal pH. The results show enhancement of the steady state velocity of Na^+ uptake at low internal pH without a significant change in the burst amplitude. Since desaturation of internal H^+ binding sites at alkaline pH should reduce the number of carriers participating in the first turnover for a simultaneous (concerted) exchange mechanism, these results tend to favor a ping-pong mechanism in which the movement of Na^+ to the inside of the vesicle precedes the translocation of H^+ in the opposite direction.

18. Kinetics of the Na^+,K^+-ATPase.

Previous measurements in this laboratory have shown that the time course of K^+ + EDTA-induced dephosphorylation of phosphorylated Na^+,K^+-ATPase does not conform to the simple monoexponential pattern predicted by the Post-Albers mechanism. In an effort to determine the origin of the slow ($k = 20\ s^{-1}$) decay phase that follows the rapid ($k = 300\ s^{-1}$) dephosphorylation produced by K^+, we examined the pattern of phosphoenzyme decay after treating the enzyme with a detergent ($C_{12}E_8$) which is known to dissociate the enzyme into monomers. The presence of the detergent had two major kinetic effects: (1) to eliminate the slow component of the K^+ + EDTA-induced dephosphorylation reaction, and (2) to substantially reduce the level of Na^+-dependent phosphorylation. Parallel experiments using HPLC to determine the state of aggregation of the solubilized enzyme revealed the presence of α_2 dimers and higher molecular weight aggregates indicating failure of the detergent to completely abolish subunit-subunit interactions. The results suggest that detergent increases the susceptibility of the phosphoenzyme bond to attack by water, possibly by mimicking a conformational effect of K^+. They also support the view that the slower component of dephosphorylation arises from an interaction between adjacent catalytic subunits whose interfacial contact area may be partially disrupted by the detergent.

19. Kinetics of dansylgalactoside accumulation by the lactose carrier.

Active lactose accumulation in E. coli membrane vesicles is mediated by a carrier mechanism that derives energy from the electrochemical gradient developed during respiration of lactate. In collaboration with Drs. R. Kaback, J. Lee and J. Bishop, we are attempting to characterize the mechanism of this system using a dansylgalactoside (DG_6) fluorescent substrate analog in combination with stopped-flow mixing. Measurements of the initial time course of lactate-dependent DG_6 accumulation have revealed complex behavior consisting of rapid ($k = 10\ s^{-1}$), intermediate ($k = 2\ s^{-1}$) and slow ($k = .3\ s^{-1}$) phases which presumably correspond to binding and/or partitioning of the fluorophore into hydrophobic regions of the membrane. A similar time course of fluorescence enhancement was observed in the absence of lactate (nonenergized state) and in the uninduced strain (minus the lactose carrier) but with a lower fluorescence intensity in all three phases. The amplitude of the rapid phase of DG_6 accumulation in the absence of energy increased with DG_6 concentration whereas the amplitude of the corresponding phase under energized conditions did not. These results are compatible with a mechanism in which the initial unenergized fluorescence enhancement is due to passive partitioning of the probe into the

outer lipid leaflet of the membrane while the energized enhancement arises from partitioning at the inner membrane surface subsequent to accumulation of the fluorescent substrate inside the vesicle. The slower increase in fluorescence following the rapid phase may correspond to uptake and partitioning of the fluorophore subsequent to the first turnover. Additional experiments with water soluble fluorescence quenchers are planned to determine the origin of the signal and hence binding location of the dye at each stage of the transport cycle.

20. Continuous flow determination of the H^+/O ratio in mitochondria.

In mitochondria, oxidation of succinate leads to the formation of an inside negative membrane potential and alkalinization of the matrix as a consequence of the active extrusion of protons. Although the chemiosmotic hypothesis that Mitchell proposed to explain this phenomenon has gained general acceptance, certain features of the model are still controversial. Among these is the predicted stoichiometry of H^+ ejection to oxygen consumption which has a value of 4 (according to the Mitchell hypothesis) for sites 2 and 3 in the respiratory chain. Although this ratio is supported by measurements made with the O_2 pulse technique, other laboratories using alternative methods have reported higher values ranging from 6 to 8. To explain this discrepancy, models have been proposed that involve proton pumps that are mechanistically distinct from the spatially arranged sequence of redox carriers in the Mitchell hypothesis. Because the observed ratios appear to be strongly dependent on the technique used to measure the rates of H^+ ejection and O_2 consumption, efforts have been directed to improve resolution of the initial phase of these reactions. Quite recently, Drs. R. Hendler and A. Lehninger have observed an interesting start up phenomenon employing a method that involves rapid displacement of CO from O_2 binding sites on the cytochromes by a pulse of laser light. Their measurements have demonstrated the presence of an early H^+ burst that is associated with a lag in O_2 consumption yielding initial H^+/O ratios as high as 30 and 50. An inherent technical difficulty limiting the accuracy of this approach is the relaxation time of the pH and O_2 electrodes which underestimates the true reaction velocity and requires a correction for the H^+ and O_2 levels at reaction times below 300 msec. To eliminate this uncertainty, we are attempting real time measurements of these reaction using the continuous flow method with the electrodes placed at a variable distance from the point of mixing. In this method, anaerobic mitochondria in a succinate-containing medium are mixed with an oxygenated solution and H^+ ejection and O_2 consumption measured at timed intervals ranging from 10 msec to one second. In the past year we have experienced a number of technical difficulties involving rheogenic artifacts, O_2 leaks, and stray electrical noise. Our efforts to date have been successful in eliminating artifacts in the O_2 electrode, but problems persist in the pH measurements. Preliminary results obtained by mixing buffered media with solutions of known H^+ and O_2 composition indicate that this approach has sufficient sensitivity to resolve the minute changes in H^+ and O_2 concentration that are expected to occur in the subsecond time domain.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 AG 00048-11 LMA

PERIOD COVERED
October 1, 1984 to September 30, 1985

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)

Jeffrey P. Froehlich	Medical Officer	LMA GRC NIA
Other:		
Phillip F. Heller	Chemist	LMA GRC NIA
Kinya Otsu	Visiting Fellow (EOD 12/1/84)	LMA GRC NIA
Bertram Sacktor	Chief, Laboratory of Molecular Aging	LMA GRC NIA
James Kinsella	Senior Staff Fellow	LMA GRC NIA
Benjamin Suarez-Isla	Visiting Associate	LNS NIA cont'd

COOPERATING UNITS (if any) Laboratory of Neurosciences, NIA NIH; Laboratory of Neurochemistry, NINCDS, NIH; Laboratory of Cellular Biology, NHLB, NIH; Department of Physiological Chemistry, Johns Hopkins University; Department of Physiology, University of Maryland; cont'd on attached sheet

LAB/BRANCH
Gerontology Research Center, Laboratory of Molecular Aging

SECTION
Intermediary Metabolism Section

INSTITUTE AND LOCATION
NIA, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.8	1.8	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 biochemical mechanisms involved in the formation and maintenance of ionic transport gradients and their dissipation via conductive pathways in excitable tissues. Single channel current fluctuations from Ca^{2+} release channels in isolated membrane vesicles of sarcoplasmic reticulum prepared from skeletal muscle were recorded using the patch clamp technique. The level of Ca^{2+} conductance and pattern of sensitivity to activators and inhibitors of Ca^{2+} release support participation of this channel in the mechanism of activation of muscle contraction. Measurements of ATP-dependent Ca^{2+} uptake, Ca^{2+} ATPase function and passive Ca^{2+} diffusion support the view that reduced active Ca^{2+} uptake rates in cardiac sarcoplasmic reticulum from old rats may be due to an increased Ca^{2+} efflux rate mediated by a Ca^{2+}-activated Ca^{2+} channel. Investigation of the transient phase of Ca^{2+} uptake by the Na^+/Ca^{2+} exchanger in cardiac sarcolemmal vesicles revealed the presence of a biphasic burst phase that was inhibited by intravesicular Na^+. The results are consistent with a mechanism in which Na^+ stabilizes the formation of a Na^+-specific binding conformation that undergoes slow conversion to a Ca^{2+}-specific form upon addition of Ca^{2+}. A transient burst phenomenon was also observed in the time course of Na^+ uptake mediated by the Na^+/H^+ exchanger in kidney brush border membranes. The pH dependence of the burst favors a consecutive as opposed to a concerted movement of Na^+ and H^+ during the first turnover of the system. Solubilization of Na^+,K^+-ATP-ase was shown to activate turnover of the phosphoenzyme in fashion similar to that produced by K^+. Disruption of intersubunit contacts and exposure of the catalytic site to H_2O could account for this behavior. Stopped-flow fluorescent studies of lactose accumulation in E. coli membrane vesicles have demonstrated complex behavior indicative of sequestration followed by partitioning of the substrate into the inner leaflet of the membrane.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00051-05 LMA

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Phosphate and Calcium Homeostasis: Pathophysiology of Osteopenia in Aging

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

Bertram Sacktor	Chief, Laboratory of Molecular Aging	LMA GRC NIA
C. Tony Liang	Research Chemist	LMA GRC NIA
Bernard A. Bulos	Research Chemist	LMA GRC NIA
Linda Cheng	Research Chemist	LMA GRC NIA
Gary Kiebzak	Staff Fellow	LMA GRC NIA
Makoto Ishida	Visiting Associate (DOD 5/23/85)	LMA GRC NIA
Hiroyuki Hanai	Visiting Fellow (EOD 9/01/84)	LMA GRC NIA

COOPERATING UNITS *(if any)*

David Spector	Renal Division, Department of Medicine	JHU
Edward Kraus	Renal Division, Department of Medicine	JHU

Renal Division, Department of Medicine, Johns Hopkins University, Baltimore, MD

LAB/BRANCH

Gerontology Research Center, Laboratory of Molecular Aging

SECTION

Intermediary Metabolism Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
8.8	6.3	2.5

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 report describes studies on the mechansisms of phosphate and calcium homeostasis relevant to changes in mineral metabolism during the aging process. The findings relate to investigations on:

1. Action of parathyroid hormone (PTH) on Na-Ca exchange in isolated renal cells.

2. iPTH increases in the aged female rat.

3. Mechanism of transepithelial phosphate transport in the proximal tubule.

4. Mechanism of the phosphaturia and hypophosphatemia in the aging rats.

5. Age-dependent alteration in the synthesis of the Vitamin D hormone.

6. Regulation of intestinal calcium absorption by the Vitamin D hormone.

7. Studies of the effect of $1,25\text{-}(OH)_2D_3$ on renal calcium transport.

8. Cell culture systems for the study of the cellular mechanism for hormonal regulation of phosphate transport.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

PROJECT NUMBER

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00052-05 LMA

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Pathophysiological and Hormonal Regulation of Membrane Transport Systems.

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

Bertram Sacktor	Chief, Laboratory of Molecular Aging	LMA GRC NIA
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R. Prasad	Visiting Fellow (EOD 4/29/85)	LMA GRC NIA

COOPERATING UNITS *(if any)*

B. Suarez-Isla, Visiting Associate, LN, GRC, NIA
D. Spector, Renal Div, Dept Med, JHU
G. Hill, Dept Pathol., and W. Guggino, Dept of Physiology, JHU

LAB/BRANCH

Gerontology Research Center, Laboratory of Molecular Aging

SECTION

Intermediary Metabolism Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
7.0	4.5	2.5

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 report describes studies on the biochemical, biophysical, and physiological mechanisms of membrane transport in the kidney, the regulation of these transport systems by hormones and various pathophysiological effectors, and the changes which occur in renal function in aging. The findings relate to investigations on:

1. Sodium-proton exchange activity in the aging rat.

2. Thyroid hormone regulation of sodium-proton exchange activity.

3. Renal adaption in metabolic acidosis.

4. Adrenergic regulation of metabolism.

5. Identification and characterization of ion channels in non-excitable tissues.

National Institute on Aging
Report of Chief, Laboratory of Neurosciences
Program Overview

The Laboratory of Neurosciences (LN) at the National Institute on Aging was formed in 1978, and has embarked on a program of research on the central and peripheral nervous systems and muscle, in health, aging and disease, including dementia. In 1982, the Laboratory was divided into two sections -- a Clinical Section on Brain Aging and Dementia, and a Basic Section on Cerebral Physiology and Metabolism. The Clinical Section is located at the Clinical Center in Bethesda and is directed by Dr. Gary Berg. Furthermore, in September 1982, a six bed patient care unit was established for an inpatient program to study patients with Alzheimer's and other dementias as well as normal subjects. The unit has temporary use of the 12E ward in the Clinical Center (Bethesda), and hopefully in the near future will be given a permanent ward appropriate for the program. This issue remains unresolved, however. An Outpatient Dementia Clinic was also started in 1982, as a means to screen subjects for the inpatient protocols and to establish methods for the differential diagnosis and staging of the various dementias. The Basic Section of the Laboratory moved to Bethesda in March 1984, and provides together with the Clinical Section, a concerted program in the neurosciences.

This report summarizes the following projects: (A) brain function in aging and dementia, involving positron emission tomography studies of healthy aging, Alzheimer's disease, Down syndrome and adult autism, (B) functional interactions between brain regions, (C) neuropsychology in aging and dementia, (D) neurological function in aging and dementia, (E) brain anatomy in aging and dementia, (F) cerebrospinal fluid chemistry in aging and dementia, and (G) clinical pharmacokinetics and pharmacodynamics. These projects were conducted primarily by members of the Clinical Section on Brain Aging and Dementia.

Projects conducted mainly by the Basic Section on Cerebral Physiology and Metabolism include: (H) cerebral metabolism, relation to brain function and aging, (I) brain lipid metabolism, relation to function and aging, (J) regulation of gene expression in brain, aging and dementia, (K) blood-brain barrier and central nervous system function (L) transport systems at the blood-brain barrier, (M) drug pharmacokinetics, relation to pharmacodynamics and senescence, (N) pharmacology of central and peripheral catecholaminergic nervous system, (O) assessment of neurochemical markers in relation to age, behavior and dementia, (P) synapse development, specificity and mechanism in culture, and (Q) function of peripheral nerve and muscle.

A. Brain Function in Aging and Dementia.

In order to examine brain function during healthy aging and in disease states, the major thrust of the clinical program has been to measure cerebral metabolism by means of a new procedure recently introduced to the

Clinical Center, positron emission tomography (PET). In the last four years, the LN has established and validated the PET procedure so as to obtain accurate and consistent measures of regional cerebral metabolic rates for glucose ($rCMR_{glc}$) under standardized and reproducible experimental conditions in humans.

1. Methodology. B. Horowitz developed an analytic procedure to reconstruct plasma radioactivity curves in PET studies from only several measurements, so as to recover data from PET studies in which plasma radioactivity curves are incomplete.

2. Healthy aging. 18F-2-deoxy-D-glucose (FDG) was injected intravenously in 40 healthy men between the ages of 21 and 83 years, as a positron-emitting analogue of glucose, to examine regional cerebral metabolic rates for glucose ($rCMR_{glc}$). PET scanning was performed under resting conditions, when the subjects' eyes were closed and ears plugged with cotton. $rCMR_{glc}$ was not correlated significantly with age in 31 pairs of bilaterally symmetrical and in 3 midline brain regions, and mean hemispheric glucose utilization also was not correlated significantly with age. No metabolic parameter was correlated with scores on subtests of the Wechsler Adult Intelligence Scale and the Revised Benton Visual Retention Test. These findings demonstrate that brain oxidative metabolism is age invariant in the resting state in healthy humans and is unrelated to neuropsychological performance. The age invariance indicates that, in the absence of disease, compensatory mechanisms exist in the senescent human brain to counteract effects of many of the morphological and neurochemical age changes which have been reported.

3. Alzheimer's disease. $rCMR_{glc}$ was examined with PET in patients with Alzheimer's disease (AD) of differing severity, as measured by scores on the Folstein Mini-Mental Test and Wechsler Adult Intelligence and Memory Scales. Absolute values for $rCMR_{glc}$ in the frontal, parietal, temporal and occipital lobes did not differ from values in healthy controls in AD patients with mild and moderate dementia. The severely demented group showed metabolic deficits in the left frontal and bilateral parietal and temporal regions. However, ratios of $rCMR_{glc}$ to sensorimotor $rCMR_{glc}$ revealed significant decrements in both parietal lobes in the mild and moderately demented patients, whereas the severely demented patients had decrements in the temporal and frontal cortices as well. Our findings suggest that memory and cognitive deficits in mild-moderate AD patients are accompanied by reduced metabolism in association areas of the parietal lobes.

We studied $rCMR_{glc}$ in 17 patients with AD and in 17 healthy controls, using a method of analysis which separates subjects into groups on the basis of similar patterns of metabolism, rather than diagnosis (Q component analysis). Three groups were identified, two composed mainly of control subjects, and one of AD patients. The AD pattern consisted of an anterior to posterior gradient of decreasing metabolic activity, with relative sparing of anterior medial frontal, primary visual and subcortical regions. The pattern was not related to severity of dementia, and corresponded to independent findings of parietal lobe deficits in AD (see above). It remains to be seen whether the pattern is unique to patients with AD, in which case it may be of diagnostic use. This work was done by Dr. C. Grady.

4. Adult Down syndrome. At least 150 developmental abnormalities and diseases may affect the human brain at an early age and cause mental retardation. Of these, Down syndrome (DS) is the most common with an established etiology. Brains of young adult DS subjects show no consistent morphological abnormalities, but brains of older DS subjects have pathological and neurochemical changes that also characterize Alzheimer's disease. M. B. Schapiro used PET and FDG to measure $rCMR_{glc}$ in 13 young adult DS subjects aged 19-33 years, and in four old DS subjects aged 47 to 63 years, who showed evidence of cognitive reductions. Hemispheric and many regional metabolic rates in young DS subjects were 20-30% higher than in age matched controls, whereas metabolic rates in the older DS subjects were less than in the younger DS subjects and did not differ from values in age-matched controls. This study demonstrated that DS is associated with an elevated brain oxidative metabolism, possibly reflecting excessive and inefficient use of glucose. Aging in DS is accompanied by a decline in metabolism, corresponding to the decline in cognitive function and to reported evidence of neuropathology.

5. Adult autism. Autism is an irreversible psychiatric disorder with onset in infancy and with a suspected neurological basis. Patients with infantile autism fail to develop emotional relationships, have delayed language development and frequently are retarded. We employed PET and FDG in 10 adult, high-functioning autistic men (aged 18 to 39 years) who had been diagnosed in childhood prior to the age of 3 years by Dr. Leo Kanner (who defined the syndrome), and compared the results with data from 10 age-matched controls. $rCMR_{glc}$ was 13-21% higher in the autistics than in the controls in all the hemispheric lobes and in subcortical regions. Metabolism for the brain as a whole also was elevated. There were no significant hemispheric or lobar lateral metabolic asymmetries, nor local defects that could be identified with the ECAT II scanner. Values for $rCMR_{glc}$ were intermediate between values in controls and the higher (by as much as 30%) values in Down syndrome (see above). Like Down syndrome, there appeared to be a general excessive rate of glucose utilization in autism. This work was performed in collaboration with J. Rapoport and J. Rumsey of the NIMH, and directed by R. Duara at the LN.

B. Functional Interactions Between Brain Regions.

Patterns of brain metabolism in healthy men. A matrix method was developed to examine functional interactions between brain regions, by correlating regional cerebral metabolic rates for glucose ($rCMR_{glc}$), as determined with PET, in the 40 healthy men, under reduced visual and auditory stimulation. Brain regions in one cerebral hemisphere were metabolically correlated with homologous regions in the other, reflecting functional connections via the corpus callosum. Regions and subcortical nuclei in the frontal and parietal lobes were closely coupled with each other, but not with regions in the temporal and occipital lobes, which formed an independent coupled unit. Furthermore, metabolic interactions were more frequent in the right than in the left cerebral hemisphere. At rest in healthy men, the brain demonstrates left-right regional metabolic coupling and, within each hemisphere, two independent interacting units, the frontal-parietal

and occipital-temporal areas. Pattern analysis provides another parameter in addition to absolute metabolic rates to examine brain functional activity. This work was directed by B. Horwitz and R. Duara.

C. Neuropsychology in Aging and Dementia

1. Healthy aging. J. V. Haxby demonstrated, in 40 healthy men aged 21 to 83 years, that age differences in performance on tests of general intelligence (Wechsler Adult Intelligence Scale) and of visual memory (Benton Visual Retention Test) were significantly less than differences reported in normative studies with these tests, suggesting that the increasing incidence of illness in the elderly contributes to age-related differences in normative standards for neuropsychological tests. Performance was not correlated significantly with regional cerebral metabolic rates for glucose ($rCMR_{glc}$), as measured with PET (see Section A). This lack of correlation supports the hypothesis that physiological and psychological cerebral functions are coupled only when both are under the limiting influence of disease.

2. Alzheimer's Disease. J. Haxby examined 27 patients with Alzheimer's disease (AD) with mild, moderate or severe dementia, as indicated by a standardized Mini-Mental State examination. The mild and moderate groups demonstrated marked impairment of recent memory and of learning ability. In individual patients, language and visuospatial impairments were often of markedly disproportionate relative severity, suggesting that, aside from memory impairment, neuropsychological deficits associated with AD are heterogeneous.

In patients with moderate AD, the relative disproportion of language and visuospatial impairments, as measured by subtests of the Wechsler Adult Intelligence Scale and experimental tests of drawing and syntax comprehension, was significantly correlated with asymmetry of $rCMR_{glc}$ consistent with functional neuroanatomy. In patients with mild AD, such a correlation did not hold. However, all patients with mild and moderate AD demonstrated a larger range of right-left asymmetries of individual values for $rCMR_{glc}$. In mildly demented AD patients with memory defects, metabolic asymmetries as measured with PET appear to precede measurable asymmetries of cognitive function controlled by the neocortex.

J. V. Haxby also showed that patients with mild-moderate AD demonstrated a larger range of right-left asymmetries of individual values for $rCMR_{glc}$ as determined with PET than did healthy age-matched controls, and a larger coefficient of variation of the difference between right and left $rCMR_{glc}$, divided by their sum, than did age-matched controls. Furthermore, he employed tests of visuoconstructive and of language ability, and showed that the metabolic asymmetries were not related to asymmetrical cognitive performance in healthy controls or in mildly demented AD patients, but were so related in moderately demented AD patients. Those patients with lesser right-sided as compared with left-sided $rCMR_{glc}$ also had lesser visuoconstructive competence as compared to language competence and vice versa. Thus, moderate AD is associated with asymmetrical metabolic deficits which have functional significance and correspond to asymmetric cognitive deficits, consistent with known functional neuroanatomy.

C. L. Grady demonstrated that the clinical, factor and localization scales of the Luria-Nebraska Neuropsychological Battery, when applied to control and AD patients in whom $rCMR_{glc}$ also was measured, were correlated significantly with metabolic deficits in the disease group but not in the control group. The correlation held most strongly with parietal lobe metabolism, and was consistent with our findings with PET that the parietal lobes are particularly vulnerable to the neuropathological process in AD.

D. Neurological Function and Behavior in Aging and Dementia.

1. Audiology. Studies of central auditory functions using the staggered spondaic word (SSW) test, showed that AD patients performed worse on this dichotic hearing test than did age-matched controls. It also was demonstrated, using computer assisted tomography (CT) of the brain, that increased atrophy of both temporal lobes was associated with poorer SSW performance. A unilateral SSW ear deficit was associated with more atrophy in the contralateral hemisphere. These findings are consistent with evidence that this type of auditory processing is sensitive mainly to temporal lobe deficits in Alzheimer's disease. This work is done in collaboration with A. Grimes of the Outpatient Department of the Clinical Center.

2. Motor activity and aging. J. W. Renfrew employed patient activity monitors (PAM) attached to the nondominant wrist, and self-report diaries, to examine hourly motor activity and sleep in 14 healthy men, aged 27 to 84 years, over 10 day periods, in their natural work and home environments. Counts/hour on the PAM were divided into high and low activity periods per day. The mean duration of low activity per day equaled 7.2 hr in the 14 subjects, as compared to 8.0 hr for sleep time, as estimated from the diaries; neither parameter was correlated with age. Net counts per day, on the other hand, fell by 5% per decade, suggesting that motor activity but not sleep duration declines with age in healthy individuals. This work was performed in collaboration with T. R. Colburn (NIMH).

3. Outpatient dementia clinic. An Outpatient Dementia Clinic was established at the Ambulatory Care Research Facility in Bethesda in 1982. Since that time, 225 patients with dementia have been evaluated, and have either been allocated to inpatient protocols or followed in the clinic to evaluate the course of dementia. Family pedigrees are being gathered and evaluated.

E. Brain Anatomy in Aging and Dementia.

1. Quantitative analysis of CT data. A computerized procedure was developed to quantify the volumes of cerebral cortical structures from data obtained with computerized transverse axial tomography (CT). By means of an image processing procedure (DMORPH), the means and standard deviations of CT numbers of representative regions of cerebrospinal fluid, white matter and gray matter were determined for each CT scan. A CATSEG program used these means to define ranges for each tissue type, and to assign to each pixel in a scan one of the three categories. Volumetric estimates were obtained by summing over seven consecutive scans in a 49 mm brain segment. Methods to evaluate surface areas of CT structures also were developed. This work was performed by J. DeLeo, H. Creasey, and M. Schwartz.

2. Healthy aging. CT was employed to examine brain anatomy in vivo in 30 healthy men, aged 21 to 81 years. Seven consecutive CT slices, 30 to 80 mm above the inferior orbitomeatal line, were analyzed. CT numbers (Hounsfield units) in gray and white matter regions were not correlated significantly with age. The volume of gray matter was correlated negatively with age, and the volume of cerebrospinal fluid rose with age. The volumes of the lateral and third ventricles were elevated in the elderly, and volumes of the thalamus and lenticular nucleus were reduced. The results demonstrate that brain atrophy occurs in the healthy elderly, and provide baseline CT-derived measures for healthy men in relation to age. This work was directed by H. Creasey.

3. Alzheimer's disease. In 19 patients with AD (age range 45 to 81 years), quantitative analysis of CT data demonstrated that the percentage of intracranial space occupied by gray matter was reduced, and that occupied by cerebrospinal fluid was increased, as compared to values in age-matched healthy controls. Furthermore, with respect to the severity of dementia as measured by the Mini-Mental Examination, the percentage of gray matter declined and the percentage of white matter increased. The relations were statistically significant after partialing out age. The findings demonstrate that brain atrophy can be quantitatively demonstrated with CT scans in AD patients, and be used in the differential diagnosis of this disease. This work was done by H. Creasey.

4. Down syndrome. Adult Down syndrome (DS) subjects with trisomy 21 karyotype were examined by quantitative CT scanning, in relation to age matched healthy controls, by M. Schapiro. In young DS subjects (21 to 35 years), reductions were present in total intracranial volume and gray matter volume. However, when the volumes of gray matter and of individual intracerebral structures were normalized to height, no significant differences were observed from controls. When young and old DS subjects were compared (older than 35 years), an increased CSF volume was demonstrable, indicative of brain atrophy. Thus, no gross differences exist between brains of young DS subjects and controls, after normalization for the established relation between brain size and height. Aging in DS, which is associated with reduced cognitive capacity and neuropathology, is associated with evidence of brain atrophy.

F. Cerebrospinal Fluid Chemistry in Aging and Dementia.

1. Markers of catecholamine metabolism. A. D. Kay examined concentrations of homovanillic acid (HVA), 5-hydroxyindole acetic acid (5-HIAA), norepinephrine (NE), and MHPG in cerebrospinal fluid and plasma from 30 patients with AD and from 15 age-matched healthy controls. No statistically significant differences were found between the patients and controls in any of these metabolite concentrations. In addition, no consistent relation was demonstrated between metabolite concentrations and the severity of dementia, or between age and metabolite concentrations. Thus, lumbar cerebrospinal fluid concentrations of these markers of brain catecholamine metabolism are not good indices of brain function in relation to age or to AD.

2. Choline in Down syndrome. J. Hodes and A. D. Kay measured cerebrospinal fluid concentrations of choline in young adults with Down syndrome, and in age-matched healthy controls. The young Down syndrome subjects had significantly higher choline values, which could not be accounted for by differences in plasma choline levels. Increased spinal fluid choline suggests increases in the activity of the central cholinergic system in Down syndrome, and is not inconsistent with a report, from this laboratory that the cerebral metabolic rate for glucose is elevated in Down syndrome. This work was done in collaboration with I. Hanin.

3. Corticotropin releasing factor (CRF) in Alzheimer's disease. CRF is a 41-amino acid peptide which is present in brain regions, including the hypothalamus, amygdala and substantia innominata, which are reported to be affected in AD. CSF samples from 23 AD patients and from 11 healthy age-matched controls were assayed for CRF. In 11 of the 23 patients, and in one of the controls, CRF was below 12.5 pg/ml. CRF levels were significantly reduced in the CSF of AD patients, indicating that this disease may be associated with selective loss of CRF-containing neurons. This work was directed by C. May.

4. Peptidyl-a-amidation activity in Alzheimer's disease. The peptidyl-a-amidation enzyme (PAM) is thought to be coreleased from secretory granules with amidated peptides, including CRF. PAM activity was significantly reduced in the CSF of AD patients as compared to the CSF of controls, consistent with the reported reduction in CRF, and suggesting that there is a selective loss or dysfunction in AD of brain neurons which produce amidated neuropeptides. This work was directed by C. May.

5. Blood-brain barrier in Alzheimer's disease. Distruption of the blood-brain barrier and immunologically-mediated injury to the brain have been proposed as pathogenic mechanisms in AD. These hypotheses were investigated by measuring concurrent CSF and serum concentrations of albumin and of immunoglobulin G (IgG) in 31 AD patients and in 20 controls. There were no significant differences in the CSF/serum ratios of albumin and of IgG between AD patients and controls, nor between the ratios of the ratios (IgG) index. Therefore, there was no evidence of blood-brain barrier breakdown or of abnormal central nervous system production of immunoglobulins in the AD patients.

G. Clinical Pharmacokinetics and Pharmacodynamics.

N. R. Cutler examined the effect of a serotonergic reuptake blocker, Zimelidine, in AD patients. The drug significantly reduced, by up to 38%, the concentration of 5-hydoxyindole acetic acid in the cerebrospinal fluid of patients, but did not, however, modify memory function. The data do not support a serotonergic mechanism in the dementia of AD.

N. R. Cutler examined the pharmacokinetics of vancomycin, an anticancer drug, in man in relation to age. The half-life of the terminal phase of loss from plasma of vancomycin was significantly prolonged in the elderly as compared to the younger subjects, but there was no age change in the volume

of distribution of the drug. The data provide information for adjusting the recommended dosage of vancomycin in the elderly. The data also support evidence that vancomycin is lost from the body solely via glomerular filtration.

H. Cerebral Metabolism, Relation to Brain Function and Aging.

1. Regional cerebral blood flow in Beagle dogs of different ages. Regional cerebral blood flow (rCBF), as a measure of brain functional activity, was measured in Beagles by the i.v. infusion of ^{14}C-iodoantipyrine, in relation to age. Reductions between 1 and 12 years of age were statistically significant only in 9 of 35 brain regions, and ranged from 11 to 25%. The majority of brain regions showed reductions by an average of 29% in 14-15 year old dogs, which also had cardiovascular and sensory-motor problems. The results demonstrate that cerebral functional activity is minimally reduced during most of the adult life of the dog, but falls in extreme senescence in relation to disease. These studies correspond in part to our findings in humans with PET (see above).

2. Effects of cholinergic agonist on cerebral metabolism in rat. We measured $rCMR_{glc}$ with ^{14}C-DG in 3 month old Fischer-344 rats in response to various doses of the cholinergic agonist, arecoline. Animals were pretreated with methylatropine to prevent parasympathomimetic side effects. $rCMR_{glc}$ increased in a dose-dependent manner in most brain regions, including those which mediated the tremor which also was produced. At low doses, $rCMR_{glc}$ was stimulated in the hippocampus and layers IV and VB of the cerebral cortex, which have high concentrations of muscarinic receptors. The results demonstrate where and to what extent brain metabolism is stimulated with a clinically used cholinergic agonist.

3. Cholinergic function in relation to age. Male Fischer-344 rats, aged 3 or 24 months, were administered arecoline and $rCMR_{glc}$ was measured as noted above. Cerebral metabolic responses did not differ significantly between the two age groups, indicating that muscarinic post-synaptic receptor responses are intact in the senescent rat brain.

4. Metabolic responses of rat brain to a dopaminergic antagonist. Haloperidol, a neuroleptic dopaminergic antagonist, was given to 3 month old male Fischer-344 rats, at a high and low dose, following which $rCMR_{glc}$ was measured at different times. The time course of the $rCMR_{glc}$ response differed in relation to dose, and showed delayed decreases between 30 and 90 minutes after haloperidol. The onset of the responses correlated with the time course of catalepsy, and corresponded to known pharmacokinetics of the drug. The results identify where and when haloperidol, a clinically used drug, acts within the brain.

5. Development of tolerance to the cerebral metabolic effects of haloperidol. Fischer-344 rats that received daily injections of haloperidol for 3 weeks showed reduced values for $rCMR_{glc}$ in regions of the mesolimbic dopaminergic system, but no catalepsy as noted in acutely treated rats. The general metabolic response was less than after acute administration. These results show that a reduced $rCMR_{glc}$ response corresponds to the tolerance that develops after continuous haloperidol treatment.

6. Age-associated decline in effect of haloperidol on $rCMR_{glc}$. Peak effects on cerebral metabolism to haloperidol were significantly less in 33 month old Fischer-344 rats than in 3 and 12 month old animals. Furthermore, catalepsy was less in response to haloperidol in old than in young rats. On the other hand, brain concentrations of haloperidol were higher in old than in young rats, due to a slower rate of elimination of the drug. These age differences correlate with known age-dependent structural and biochemical deficits of central dopaminergic function in the brain of the senescent rat, and suggest an imbalance between dopaminergic and cholinergic activity (see 3 above).

7. Effect of phenobarbital on brain metabolism in the rat. The anesthetic, phenobarbital, was administered to rats at different doses, and $rCMR_{glc}$ was measured after one hour by the 2-DG technique. Lower doses of phenobarbital, which affected performance on a rotating cylinder, reduced $rCMR_{glc}$ significantly in brain regions involved with motor performance but not in cerebral cortical regions. Higher doses affected cerebral metabolism generally. The results demonstrate regional specificity of the phenobarbital metabolic effect at low doses, and indicate specific actions on the motor system.

8. Effects of nicotine on brain metabolism in rats. Nicotine, a cholinergic agonist, was administered to awake rats and $rCMR_{glc}$ was measured with the 2-DG technique. The rats were pretreated with hexamethonium bromide. Nicotine, 1 mg/kg, elevated $rCMR_{glc}$ by an average of 25%, primarily at sites of central nicotinic receptors. Higher doses produced tremor and elevated $rCMR_{glc}$ generally throughout the brain. Unlike many other drugs, the regional responses to nicotine corresponded to specific central nicotinic receptors.

9. Effects of methiothepin on brain metabolism. Methiothepin, a serotonergic antagonist, reduced $rCMR_{glc}$ in relation to dose administered to awake rats. The effects at low doses were interpreted in terms of serotonergic autoreceptor blockage, which increases serotonin release and thereby enhances indirectly post-synaptic inhibitory effects of serotonin. The changes were accompanied by reduced spontaneous motor activity, demonstrating a link between regional energy metabolism and functional brain activity.

I. Brain Lipid Metabolism, Relation to Function and Aging.

1. Method to measure brain palmitate incorporation. A quantitative method was developed by A. Kimes to examine the uptake of an intravascular fatty acid, palmitate, into individual brain regions of awake rats. ^{14}C-palmitate was injected intravenously, and plasma concentrations of cold and radiolabeled palmitate were measured to decapitation at 4 hours. The transfer constant for radiotracer, equal to brain radioactivity divided by the integrated plasma palmitate radioactivity, was multiplied by the cold plasma palmitate concentration to give the flux of palmitate into brain, Jpalm. Brain radioactivity was determined by quantitative autoradiography, and

remained unchanged between 4 and 24 hours, indicating that 14C-palmitate was incorporated into stable brain structures. Jpalm was found to be proportional, within individual brain regions, to $rCMR_{glc}$ as measured with the 2-DG technique (see above). Palmitate uptake in gray matter exceeded uptake in white matter. The palmitate method should make it possible to relate turnover of brain lipid structures to brain oxidative metabolism and function.

2. Mathematical model for brain incorporation of plasma palmitate. A three compartment 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 can be used to determine values of transfer constants between brain and blood, and to interpret time-dependent changes in brain radioactivity following the i.v. injection of 14-C-palmitate.

3. Effect of aging of the rat on Jpalm. H. Tabata demonstrated that Jpalm was age invariant in rats, aged 3 to 24 months. As the rate of incorporation of palmitate into brain represents the lower limit for turnover of brain lipids, the results demonstrate that brain structural integrity is maintained throughout aging of the rat.

4. Uptake of palmitate by the brain of the developing rat. Jpalm was measured in awake Fischer-344 rats between the ages of 15 days and 3 months. Jpalm rose between 15 and 20 days of age in gray and white matter regions, then declined 4-5 fold in gray matter and 7-10 fold in white matter by 38 days, and reached adult levels by 3 months of age. The white/gray ratio for Jpalm declined significantly between 20 days and adulthood. The time course of Jpalm corresponded to the time course of myelination during development of the rat brain, when there are parallel changes in the rates of palmitate incorporation into gray and white matter regions. Jpalm clearly is a measure of brain lipid turnover and synthesis. This work was performed by H. Tabata.

J. Regulation of Gene Expression in Brain, Aging and Dementia.

1. Cell-free protein synthesis system from rat brain. A cell-free protein synthesis system, capable of initiating protein synthesis, was derived from the rat brain and characterized by J. Cosgrove. Optimal conditions were identified, and both 40S and 80S initiation complexes could be labeled using 35S-methionine.

2. Aging and brain protein synthesis. J. Cosgrove, using the cell-free system, demonstrated age invariance of brain protein synthesis capacity, and no age difference in the aggregation state of polyribosome profiles obtained from brains of 3 and 34 month old Fischer-344 rats. These results agree with other studies in this laboratory that brain oxidative metabolism and palmitate incorporation generally are age invariant in the Fischer-344 rat, and point to compensatory mechanisms that maintain cerebral functional activity during aging and in the absence of disease.

K. Blood-Brain Barrier and Central Nervous System Function.

1. Reversible osmotic opening of the blood-brain barrier.

a. Method and clinical application. In 1972, we first demonstrated that the blood-brain barrier (BBB) could be reversibly opened in animals by infusion of a hypertonic solution of a water soluble nonelectrolyte (e.g., urea, mannitol, arabinose) into the internal carotid artery. The effect later was shown to be caused by osmotic shrinkage of cerebrovascular endothelial cells, with consequent widening of interendothelial tight junctions. In later years, we experimentally refined the osmotic method, and quantified changes of cerebrovascular permeability in relation to infusate concentration and infusion time, and demonstrated the reversibility of the osmotic effect. We showed that, when the BBB is opened osmotically, brain metabolism is transiently stimulated, brain edema occurs and metabolism is uncoupled temporarily from cerebral blood flow. Thus BBB integrity must be maintained continuously for normal cerebral function. In diseases which affect BBB integrity in man, changes in consciousness may be related to these central effects of BBB disruption.

On the basis of the animal studies, we initiated a Phase I clinical protocol with E. A. Neuwelt (Oregon Health Sciences Center) to apply the osmotic procedure in patients with metastatic brain tumors, so as to allow methotrexate or other antineoplastic drugs into the brain. We demonstrated with computer assisted tomography that the BBB can be opened reversibly in humans without producing apparent neurological damage. The clinical study is being continued to see whether the osmotic procedure will be efficacious for prolonging survival of patients with brain tumors.

b. Pore mechanism for BBB opening. To further support the tight junctional as compared to the transcellular channel or vesicular mechanism, Y. Z. Ziylan and P. J. Robinson examined the time course of cerebrovascular permeability to nonelectrolytes of different size, ^{14}C-sucrose (mol. wt. = 340 daltons), ^{3}H-inulin (mol. wt. = 5200) and ^{3}H-dextrans (mol. wt. = 79000 or 200,000), following osmotic barrier opening. Whereas the barrier was opened markedly to all of the radiotracers immediately following the intracarotid injection of 1.8 molal arabinose solution in rats, the rate of closure was faster the larger the molecule. Size differentiation during recovery supports the tight junctional mechanism rather than the vesicular mechanism, as vesicles are much larger than any of the tracers and would not be selectively permanent to smaller as compared to larger molecules. Furthermore, the differential rate of barrier reclosure suggests that, if drugs are to be used with the osmotic procedure, they should be administered within a few minutes after hypertonic arabinose infusion.

c. Drug loss from the loaded brain. Rates of loss of ^{3}H-methotrexate (an anticancer agent) and of ^{14}C-sucrose were examined following loading of both tracers into the rat brain in association with osmotic BBB opening. Brain ^{3}H-methotrexate concentration fell with a mean half-time of 4.8 hours, as compared to 4.5 minutes for ^{14}C-sucrose loss. The slower rate indicates that the drug is bound to brain cells. The rate can be used to calculate the net dose and administration regimen for methotrexate following osmotic opening, for treatment of certain brain tumors.

d. Dimethyl sulfoxide and BBB. Dimethyl sulfoxide (DMSO) has come into vogue as a means of enhancing drug entry into the brain in humans, in treating brain malignancies. N. H. Greig demonstrated, however, with the technique developed in this laboratory, that DMSO does not increase cerebrovascular permeability to proteins, nor to small water soluble anticancer drugs such as melphalan, in rats or mice. On the basis of his work, it is likely that the previous reports are erroneous. Because DMSO is potentially toxic, it should not be used to enhance drug entry into the brain in humans.

2. Cerebrovascular permeability and transport.

a. Positron emission tomography and BBB integrity. Positron emission tomography was employed to examine time-dependent changes in blood-brain barrier permeability to [68Ga]EDTA in the Rhesus monkey, following reversible barrier opening by intracarotid infusion of a hypertonic mannitol solution. The PET technique, when combined with measurements of plasma radioactivity, provided a quantitative measure of the cerebrovascular permeability-area product (PA) at different times after mannitol treatment. On the basis of these findings, the PET technique is being employed in patients with Alzheimer's disease and in age-matched controls to examine blood-brain barrier integrity.

b. Pharmacokinetics of anticancer agent, melphalan. A high pressure liquid chromatography technique was developed by D. Sweeney and N. Greig to measure brain and plasma concentrations of melphalan, an anticancer alkylating agent of wide clinical use. The pharmacokinetics of melphalan were determined in the rat, and parameters of protein binding were analyzed in terms of whole blood melphalan and plasma protein concentrations.

The cerebrovascular-permeability area product, PA, was determined for melphalan in awake rats by N. Greig. It was shown that this drug is transported by the carrier system that transports large neutral amino acids at the BBB, consistent with melphalan being a derivative of phenylalanine. Transport demonstrated saturation and competitive inhibition. Although the affinity of melphalan for the carrier is low, this study suggests that drug design may allow facilitated entry of amino acid analogues that are therapeutically effective.

c. Regulation of brain uptake of morphine. D. Schulman demonstrated that morphine entry into the brain of rats is augmented by an alkaline blood pH, and reduced by an acidic blood pH. The results are consistent with the pH-partition hypothesis of entry of weak basic drugs into the brain. Alterations in blood pH frequently occur in the elderly, and should be taken into account when inducing analgesia with morphine or with its base analogue meperidine.

d. Glucose transport at BBB. P. Robinson developed a theoretical model that describes steady-state glucose transport into and utilization by the brain. The model takes into account cerebral blood flow, saturable transport of glucose across the BBB, and Michaelis-Menten kinetics for incorporation of glucose into the brain metabolic pool. The role of capillary

heterogeneity is explicitly taken into account, and its effect on transport during hypoglycemia is analyzed. The model represents a quantitative analysis of glucose transport under normal and low flow or hypoglycemic conditions.

L. Transport Systems at the Blood-Brain Barrier.

1. Method of analysis. A new in vivo brain perfusion method was developed by Q. R. Smith to quantitatively determine rates of regulated and passive transfer of various solutes at the BBB. Unlike other current procedures, the method is free of errors caused by biotransformation in tissues other than brain, and makes it possible to accurately control the exact contents of the brain intravascular space. The method was employed to accurately measure maximum velocities of transport, and transport affinities, of a number of large neutral amino acids, and to further understand their role as precursors of neurotransmitters and protein synthesis in the brain.

2. Relation of cerebrovascular permeability to solute lipid solubility. The brain perfusion method demonstrated a linear relation between cerebrovascular permeability of 22 nonelectrolytes and their octanol-water partition coefficients. Solute molecular weights ranged from 18 to 609 daltons. The relation is consistent with simple diffusion through an aporous lipid membrane and with the proposal of this laboratory that the endothelial layer of the blood-brain barrier corresponds to an extended lipid membrane with respect to drug penetration.

3. Facilitated transport of large neutral amino acids. Concentration-dependent uptakes into brain of eight large neutral amino acids were measured in anesthetized rats with the brain perfusion technique. Each uptake was sterospecific, saturable and sodium independent, and followed Michaelis-Menten kinetics with different affinities (1/Km) and maximum velocities for the different amino acids. There were no regional differences in Km for a given amino acid. The values of Km for the 8 amino acids differed by 10-100 fold from values published by prior techniques. The correct calculation of affinities should make it possible to characterize the chemical structure of the amino acid carrier, for understanding regulation of transport into the brain.

4. Brain uptake of amino acids and aging in rats. The concentration-dependent brain uptake of cycloleucine, a model nonmetabolizable large neutral amino acid, did not differ significantly between Fischer-344 rats aged 3 and 24 months. The values for the Michaelis-Menten constants, Km and Vmax, also showed no significant difference. Lastly, the plasma concentrations of each of nine neutral amino acids did not vary with age, except for a 50% increase in threonine in the old rats. Thus, contrary to previous reports, cerebrovascular transport of large neutral amino acids is age-invariant in rats. As transport is coupled to brain protein synthesis, these findings support the finding by J. Cosgrove (see above) that brain protein synthesis is age-invariant in the rat. The work was done by Q. R. Smith.

5. Protein binding and brain uptake of erythrocin B. Although food colors have been held responsible for several behavioral disorders, there is no information about whether they can enter the brain. H. Levitan demonstrated that the food dye, erythrocin B, is not taken up significantly by the brain of the rat when in the peripheral circulation, due to very tight binding to plasma protein. However, if infused into the brain by the technique of Smith and Takasato, free of plasma protein, measurable brain uptake occurs. Thus, the absence of a central effect of the dye is related to its tight binding to plasma proteins and to a blood-brain barrier to the protein-dye complex.

6. Ion uptake into the central nervous system.

a. Cerebrovascular permeability to ions. Homeostasis of ionic composition within the central nervous system is poorly understood in relation to aging and altered cerebral function. The transfer constants of a number of monovalent and divalent ions were measured at the blood-brain barrier of anesthetized rats by Q. Smith. Most rapid uptake from blood occurs by ion passage through the choroid plexus into cerebrospinal fluid, and not at the cerebral capillaries and directly into brain. Cerebrovascular permeabilities to ions are low, consistent with the continuous structure of the vascular endothelium. The study demonstrates multiple sites for ion exchange among brain, spinal fluid and blood.

b. Cerebrospinal fluid and capillary integrity in aging rats. Q. Smith showed that the rate of formation of cerebrospinal fluid (CSF) could be measured in rats by measuring CSF uptake of plasma 22Na. No significant change in the rate occurred between 3 and 24 months of age in awake Fischer-344 rats, and a decrease of only 18% occurred by 34 months. Furthermore, a low capillary permeability to Na was maintained during aging of the rat. Therefore, with aging, the blood-brain barrier remains intact, and the rate of formation and turnover of CSF are unchanged in the rat.

M. Drug Pharmacokinetics, Relation to Pharmacodynamics and Senescence.

1. Determination of the cholinergic agonist, arecoline. A method using gas-liquid chromatography with nitrogen-phosphorus detection was developed by J. N. Schreiber for the quantitative estimation of arecoline, a cholinergic agonist used clinically in the treatment of Alzheimer's disease, in plasma and tissue samples. The method involves extraction of the compound from the biological matrix, followed by quantitation using the corresponding n-propyl ester as an internal standard.

2. Protein binding of drugs as affecting brain uptake. The BBB is impermeant to proteins, so that binding of a drug or other biologically active substance to plasma proteins may hinder its entry into the brain. Changes in protein content and binding occur in aging and disease states. P. Robinson developed a mathematical model that describes the binding of drugs to proteins, and that allows the prediction of brain uptake rates of

protein-bound drugs. The model incorporates association and dissociation rate constants for the drug/protein complex, and relates them to regional cerebral blood flow and capillary transit time. The key factor determining drug uptake is the dissociation rate constant as compared to brain capillary transit time.

N. Pharmacology of Central and Peripheral Catecholaminergic Nervous System.

1. Age differences and relevance of extra-adrenal chromaffin tissue in rats. The LN previously demonstrated increased plasma concentrations of catecholamines in senescent Fischer-344 rats, but reduced responsivity of the cardiovascular and other systems to catecholamines. Increased concentrations may derive from paraganglia, extra-adrenal chromaffin tissue which are found in the para-aortic region of the rat and are abundant in the fetus and at birth but degenerate postnatally. M. Partanen demonstrated that paraganglia proliferate in senescent Fischer-344 rats, and contain large quantities of catecholamines that probably contribute to high plasma levels. Growth of paraganglia may be an overall response of the sympathetic nervous system to reduced end organ sensitivity.

2. Age changes in human sympathetic ganglia. Sympathetic ganglia from human subjects aged 16 to 94 years, without neurodegenerative disorders, were obtained from sympathectomies or from autopsy. The lower cervical and upper thoracic (stellate) ganglia were processed for histochemistry and electron microscopy. Major age differences included: (1) decreased neuronal catecholamine histofluorescence, (2) increased autofluorescent lipopigment and heterogeneity of lipopigments, and (3) dendritic hypertrophy. Some neurons demonstrated increased numbers of neurofilaments and neuropathological changes. These findings establish baseline age changes in human sympathetic ganglia, for comparison with changes in disease states. The work was conducted by A. Hervonen.

3. Neuropeptides in adult human sympathetic ganglia. Immunoreactivities to the following peptides were localized in human sympathetic ganglia by indirect immunofluorescent methods: (Met5)-enkephalin, (Met5)-enkephalin-Arg6-Phe7, bombesin-gastrin-releasing peptide, and substance P. These immunoreactivities indicate that the peptides modulate the functions of subpopulations of neurons in sympathetic ganglia. Similar immunoreactivities were found in sympathetic ganglia (superior cervical, hypogastric) of the rat.

O. Assessment of Neurochemical Markers in Relation to Age and Behavior.

Effect of diabetes. Rats made diabetic by administration of streptozotocin were shown by M. Bitar to have decreased activity of tryosine hydroxylase, and increased concentrations of norepinephrine, in various brain regions which included the thalamus and hypothalamus. These results suggest that diabetes can alter brain monoamine metabolism and behaviors subserved by monamine neurotransmitters.

P. Synapse Development, Specificity and Mechanism in Culture.

J. W. Cosgrove and B. A. Suarez-Isla identified a protein fraction from medium conditioned from spinal cord neurons of chick embryos, which significantly decreases the percentage of muscle cells with slow hyperpolarizing after potentials. These potentials also are decreased during synapse formation between muscle cells and spinal cord neurons. The results suggest that the protein fraction contains a critical element to the formation of long-lasting correct synapses. Further work is in progress to identify the component of the fraction and its mechanism of action on the muscle membrane.

B. A. Suarez-Isla examined the effect of inorganic blockers of calcium permeability, such as cobalt and manganese, on the ability of retina neurons from chick embryos to extend processes critical for synapse formation. He concluded that calcium fluxes through specific channels are required for competent synapse formation during development, and suggested that interference with calcium entry into cells during aging might contribute to neuronal death.

B. A. Suarez-Isla developed a double-dip method, involving patch clamping and microelectrodes, to examine specific acetylcholine channels in resubstituted lipid bilayers from Torpedo Californica. Single channel currents were demonstrated in response to activation by three cholinergic ligands: acetylcholine, carbamylcholine and suberyldicholine, all of which gave an identical single channel conductance. The method is being applied to cell membranes from neurons in tissue culture.

B. Horwitz proposed a model which indicates how dendritic spines on central nervous system neurons, during neuronal activity, might reduce competition between neighboring afferent inputs and help to organize the local integration of nerve-nerve interactions. He calculated that electrical fields generated during neuronal activity can promote electrophoretic migration of charged metabolites within the cell or on the cell membrane, sufficient for synaptic stabilization and accumulation within dendritic spines.

Q. Function of Peripheral Nerve and Muscle.

The blood-nerve barrier consists of the perineurium, which surrounds the nerve, and the endoneurial capillaries which are comparable to continuous capillaries in the central nervous system. Little is known about how these barrier sites affect nerve growth and function.

1. Blood-nerve barrier and hypertension. The effect of experimental hypertension on capillary structure in the endoneurium of the perfused frog sciatic nerve was examined by M. E. Michel. At flow rates exceeding the normal rate of blood flow, the vascular endothelium demonstrated, under electron microscopy, blebs and blisters and penetration of the intravascular tracer, microperoxidase. Systemic hypertension may damage the blood-nerve barrier by a similar mechanism, resulting possibly in nerve edema and peripheral neuropathy.

2. Alkaline phosphatase in nerve and brain. C. Latker demonstrated alkaline phosphatase in different tissues of the blood-nerve barrier in frogs and rats, as well as in capillaries of the central nervous sytem of the rat. Within the perineurium of the frog sciatic nerve, for example, the enzyme is localized to caveoli or vesicular indentations, suggesting that these structures establish a restricted environment for transport regulated by this enzyme.

3. Permeability of nerve capillaries. Permeability and transport of endoneurial capillaries were examined by a vascular perfusion technique developed by A. Weerasuriya. In the frog sciatic nerve, permeability to 14C-sucrose at capillaries was low, but somewhat larger than at the perineurium. Permeabilities for 24K, 36Cl, and 22Na in relation to each other suggested that their movement across nerve capillaries is passive, via a paracellular route that is somewhat selective for cations as compared to anions. The absence of active capillary transport of Na or K is remarkable, as the concentrations of these ions presumably are regulated within the nerve environment.

4. Glucose transport into nerve. Glucose is the major substrate for nerve metabolism, but its mode of entry into nerve from blood is poorly understood. E. Rechthand, using a nerve perfusion technique, demonstrated for the rat tibial nerve that glucose influx into the nerve, at the vasculature, is by a saturable, stereospecific facilitated diffusion mechanism, with a Km equal to 42 μmol. ml $^{-1}$. This is the first time that transport of glucose has been demonstrated at the nerve, and shows that the blood-nerve barrier is a regulatory as well as a permeability interface.

5. Nerve blood flow. I. Rundquist used a laser method to examine nerve blood flow in the sciatic nerve of the anesthetized rat. A flow signal was recorded continuously for 15 to 90 minutes. Absolute values of flow also were measured by infusion of 14C-iodoantipyrine into the femoral vein. Nerve blood flow ranged from 0.09 to 0.51 ml/min/g, with a mean of 0.27 ml/min/g, comparable to flow in brain white matter of anesthetized rats. Intensity of flow was correlated with the laser Doppler output. The laser method is suited for monitoring nerve blood flow in relation to pharmacological or physiological manipulation, and may eventually be of use in humans.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00120-08 LN

PERIOD COVERED
October 1, 1984 to September 31, 1985

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Blood-Brain Barrier and entral Nervous System Function

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

PI:	S.I. Rapoport	Chief	LN, NIA
	N.H. Greig	Visiting Fellow	LN, NIA
Others:	D.J. Sweeney	Chemist	LN, NIA
	P.J. Robinson	Visiting Associate	LN, NIA
	W.R. Fredericks	Biologist	LN, NIA
	Y.Z. Ziylan	Visiting Fellow	LN, NIA
	E.A. Neuwelt	Neurosurgeon	Univ. Oregon

COOPERATING UNITS *(if any)*
Department of Chemistry, Johns Hopkins University
Department of Nuclear Medicine, Clinical Center, NIH

LAB/BRANCH
Laboratory of Neurosciences

SECTION
Cerebral Physiology and Metabolism

INSTITUTE AND LOCATION
NIA, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.25	2.0	2.25

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.)*

Brain uptake of morphine was shown to be elevated in rats by alkalosis, due to increased plasma concentrations of uncharged morphine and penetration at the blood brain barrier. Melphalan, an anticancer alkylating agent, could be measured in the blood of animals and its pharmakinetics determined. It was shown to enter the brain of rats via an amino acid transport system at the blood-brain barrier; its entry also was related to plasma protein binding.

Glucose transport into the brain was characterized by a multicompartmental model involving capillary profiles of glucose.

The blood-brain barrier was not affected by dimethylsulfoxide, but could be opened in rats by intracarotid infusion of a hypertonic arabinose solution. The rate of reclosure was related to the size of intravascular tracer, indicating that tight junctions between cerebrovascular endothelial cells were modified. Positron emission tomography in monkeys, using [Ga68] EDTA, was used to examine barrier function. The rate of loss of methotrexate from the brain, following loading in association with osmotic barrier opening, indicated intracellular uptake.

Chemical modification of water-soluble drugs was used to enhance drug entry into the brain.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00121-08

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Peripheral Nerve and Blood-Nerve Barrier

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

PI:	E. Rechthand	Medical Staff Fellow	LN, NIA
Others:	S. Sato	Visiting Fellow	LN, NIA
	K. Wadhwani	Student Investigator	LN, NIA
	C. Latker	Senior Staff Fellow	LN, NIA

COOPERATING UNITS *(if any)*

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Department of Medicine, State University of New York, Stonybrook
Department of Biology, University of Maryland

LAB/BRANCH

Laboratory of Neurosciences

SECTION

Cerebral Physiology and Metabolism

INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
5.0	4.5	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.)*

Glucose transport into the rat sciatic nerve from blood, across blood vessels of the nerve endoneurium, is by a facilitated transport system that demonstrates stereospecificty and saturation, and allows matching of transport and nerve metabolism.

The permeabilities of nerve capillaries and of the perineurium to ions are low, but do not demonstrate active or regulated transport of ions. Calcium is not transported at the perineurium of frog nerve, but is accumulated by perineurial cells.

Blood flow in the nerve of the anesthetized rat was measured continously by laser Doppler flowmetry, and shown to be proportional to flow as measured with 14C-iodoantipyrine at discrete times. Autoradiography demonstrated heterogeneous flow distribution within the nerve.

Endoneurial blood vessels of the frog sciatic nerve remained intact during normal rates of perfusion, but were damaged by hypertension. Vesicular profiles could be demonstrated in the perineurium of frog nerve and in endothelial cells of pial blood vessels, using rapid freezing and freeze-substitution. These tissues are diffusion barriers, so that the profiles do not contribute to transcellular channel-mediated or vesicular transport. Alkaline phosphatase was distributed in some vesicles, suggesting that they are microdomains for enzyme activity.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00122-07 LN

PERIOD COVERED
October 1, 1984 to September 30, 1985

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Pharmacology of Central and Peripheral Catecholaminergic Nervous Systems

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

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Others:	J. E. Johnson, Jr.	Expert	EM, NIA
	M. Partanen	Visiting Fellow	LN, NIA
	P. Helen	Visiting Fellow	LN, NIA
	I. Linnoila	Staff Fellow	DCDD, NCI
	H. Alho	Visiting Fellow	LPP, NIMH

COOPERATING UNITS *(if any)* Section of Gerontology, Departments of Biomedical Sciences and Public Health, University of Tampere, Finland; Department of Neurology, Cornell University Medical School

LAB/BRANCH
Laboratory of Neurosciences

SECTION
Cerebral Physiology and Metabolism

INSTITUTE AND LOCATION
NIA, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.5	1.5	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.)*

Indirect immunofluorescent methods were used to localize [Met5]enkephalin, [Met5]enkephalin-Arg6-Phe7 and bombesin-gastrin-releasing-like immunoreactivities in human paravertebral sympathetic ganglia. Peptides were found within nerve fibers and terminals, but not cell bodies.

Immunoreactivities were demonstrated to bombesin-gastrin releasing peptide and Met5-Enkephalin-Arg6-Gly7-Leu8- in small intensely fluorescent (SIF) cells and nerve fibers of rat sympathetic ganglia, suggesting an endocrine function for these cells.

Aging of Fischer-344 rats was shown to be associated with an increased cell number and catecholamine histofluorescence in paraganglia cells in the retroperitoneal area and the abdomen. These number of SIF cells increased in the hypogastric ganglion with age. The changes suggest that paraganglia contribute to increased levels of circulating catecholamines in the aged rat. Consistent with these findings are observations that catecholamine storing cells in paraganglia of old rats showed structural characteristics common to adrenomedullary and paraganglionic cells of young animals. Immunohistochemistry reveals increased levels of catecholamine synthesizing enzymes, tyrosine hydroxylase, dopamine-B-hydroxylase and phenylethanolamine-N-methyltransferase, demonstrating increased catecholamine synthesizing capacity.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00123-07

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Synapse Development, Specificity and Mechanism in Culture

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

PI:	B.A. Suarez-Isla	Visiting Associate	LN, NIA
Others:	J. W. Cosgrove	Senior Staff Fellow	LN, NIA
	B. Horwitz	Senior Staff Fellow	LN, NIA
	C. Orozco	Visiting Fellow	LN, NIA
	K. Niemenin	Visiting Fellow	LN, NIA

COOPERATING UNITS *(if any)*

Salk Institute, LaJolla, CA
Department of Neurobiology, University of Illinois
Department of Pediatrics, University of California

LAB/BRANCH

Laboratory of Neurosciences

SECTION

Cerebral Physiology and Metabolism

INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20205

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.)*

Synapse formation, synapse stabilization and neurotrophic effects on ionic channels were studied using neurons and muscle cells in culture. Synapses were detected and investigated by electrophysiological recording. Single ionic conductances were studied with the extracellular patch clamp technique on cultured neurons and muscle cells and on bilayers formed at the tip of patch pipets. Neurons from chick spinal cord form stable cholinergic synapses with muscle cells in culture, eliciting changes that resemble maturation in vivo. In vitro innervation blocked an apamin-sensitive Ca2+ dependent K+ conductance, an effect that can be elicited in the absence of innervation by a low molecular weight fraction (<4,000 D) obtained from chick spinal cord conditioned medium but not from a spinal cord extract.

Calcium channel blockers impair the ability of dissociated neurons to form synapses with muscle cells in culture, and inhibit neurite extension. The degree of inhibition depends on the age in ovo and is more marked in neurons dissociated from older embryos.

Conditions were established for maintaining fetal dorsal root ganglion neurons in primary culture for up to two months. Electrophysiological recording from a large number of neurons from normal tissues generated a control data base of passive and active electrical membrane properties. Electric fields generated during neuronal activity can promote electrophoretic migration of charge substances within the cell of cell membranes, sufficient to enhance synapse stabilization within dendritic spines.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00125-07 LN

PERIOD COVERED

October 1, 1984 to September 30, 1985

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	Staff Fellow	LN, NIA
	G. Ricchieri	Visiting Fellow	LN, NIA
	E. McCann	Medical Staff Fellow	LN, NIA
Others:	S. I. Rapoport	Chief	LN, NIA
	H. W. Holloway	Biologist	LN, NIA
	S. Carlson	Biologist	LN, NIA
	W. R. Fredericks	Biologist	LN, NIA

COOPERATING UNITS *(if any)*

Department of Neuropathology, University of Western Ontario

LAB/BRANCH

Laboratory of Neurosciences

SECTION

Cerebral Physiology and Metabolism

INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20205

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 ($rCMR_{glc}$) was examined in awake Fischer-344 rats in relation to age, pharmacological stimulation and behavior. The lumped constant used to calculate $rCMR_{glc}$ was shown to decline with age in Fischer-344 rats.

Arecoline, a cholinergic agonist, stimulated $rCMR_{glc}$ in a number of brain regions, including those with muscarinic receptors. Cerebral metabolic responses were not reduced in senescent animals, indicating maintenance of postsynaptic cholinergic function. Metabolic responses to nicotine, another cholinergic agonist, were consistent with the distribution of nicotinic receptors within the rat brain.

Dopaminergic function in the rat brain was examined by measuring $rCMR_{glc}$ in response to haloperidol (a dopaminergic antagonist), bromocriptine (an agonist) and sulpiride (a specific antagonist). The response to haloperidol was reduced in senescent as compared to younger rats, despite higher brain concentrations of haloperidol in the older animals, suggesting a reduced central dopaminergic function, and an imbalance between the cholinergic and dopaminergic systems in the brain of the senescent rat. Metabolic responses to haloperidol depended on time after treatment, and demonstrated tolerance after long-term administration.

Regional cerebral blood flow (rCBF) was age invariant in awake Beagles between 1 and 12 years, and declined only in extreme senescence in relation to systemic disease, suggesting that cerebral functional activity is maintained during the life span of the healthy Beagle.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00126-06 LN

PERIOD COVERED

October 1, 1984 to September 30, 1985

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:	G. Berg	Medical Staff Fellow	LN, NIA
	C.L. Grady	Psychologist	LN, NIA
	N.L. Schlageter	Medical Staff Fellow	LN, NIA
	B. Horwitz	Senior Staff Fellow	LN, NIA
	M. Schapiro	Medical Staff Fellow	LN, NIA
Others:	S.I. Rapoport	Chief	LN, NIA
	J. Haxby	Staff Fellow	LN, NIA
	M. Sundaram	Computer Aid	LN; NIA

COOPERATING UNITS *(if any)*

Child Psychiatry Branch, NIMH
Nuclear Medicine Department, Clinical Center, NIH
University of Lund, Department of Clinical Neurophysiology, Lund, Sweden

LAB/BRANCH

Laboratory of Neurosciences

SECTION

Brain Aging and Dementia

INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.5	4.0	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 regional cerebral metabolic rate for glucose (rCMRglc) was examined, as a measure of cerebral functional activity in 40 healthy men between the ages of 21 and 83 years. rCMRglc was determined by means of positron emission tomography (PET) with 18-F-2-fluoro-deoxy-D-glucose, under resting conditions, when the subject's eyes were covered and his ears plugged to reduce sensory input. Average hemispheric glucose utilization and glucose utilization in individual regions of the right and left hemispheres, did not decline significantly with age ($p > 0.05$).

In young adult subjects with Down syndrome (19-27 yr.), rCMRglc was elevated by 20-40% as compared with age-matched healthy controls, indicating that brains of young adult Down syndrome subjects use glucose excessively despite retardation. In older adults with Down syndrome (> 35 yr.), rCMRglc was reduced as compared to its value in younger patients, associated with a decline in cognitive function suggestive of dementia. Similarly, adult patients with autism, an irreversible psychiatric disorder with onset in infancy and with a suspected neurological basis, showed elevated values of rCMRglc, to values between those in normal and Down syndrome subjects, but no change in the pattern of brain metabolism.

Adult patients with Alzheimer's disease showed variable reductions in rCMRglc, depending on the cognitive deficits. In mild-moderate Alzheimer's disease, relative rCMRglc was reduced in the parietal lobe as compared to other lobes. In severe Alzheimer's disease, rCMRglc was reduced throughout the cerebral hemispheres. The reductions were correlated with cognitive deficits, as determined by neuropsychological testing.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00127-05 LN

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Assessment of Neurochemical Markers in Relation to Age, Behavior and Dementia

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

PI:	J. W. Ferkany	Senior Staff Fellow	LN, NIA
	M. Bitar	Staff Fellow	LN, NIA

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Neurosciences

SECTION

Cerebral Physiology and Metabolism

INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.2	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.)*

Binding of receptors for excitory amino acid neurotransmitters in the rat brain was evaluated in relation to treatment with the modulator, phenylalanyl-L-glutamate. This modulator increased the number of binding sites, to a greater extent in the striatum of brains of 34-month old rats than of 3-month old mature rats.

Rats made diabetic by administration of streptozotocin showed decreases in the activity of tyrosine hydroxylase, and increased concentrations of norepinephrine, in various brain regions, including the thalamus and hypothalamus. These results suggest that diabetes can alter brain monoamine metabolism and behavior subserved by monoamine neurotransmitters.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00128-05 LN

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Drug Pharmacokinetics, Relation to Pharmacodynamics and Senescence

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

PI:	P. Robinson	Visiting Associate	LN, NIA
	J.M. Schreiber	Chemist	LN, NIA
Others:	D. Sweeney	Chemist	LN, NIA
	T. Soncrat	Staff Fellow	LN, NIA

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Neurosciences

SECTION

Cerebral Physiology and Metabolism

INSTITUTE AND LOCATION

NIA, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.5	1	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.)*

A new analytical assay was developed, using gas liquid chromatography with nitrogen phosphorus detection, for the cholinergic agonist arecoline (1, 2, 5, 6-tetrahydro-1methyl-3-pyridinecarboxylic acid methyl ester). The assay was applied to plasma and tissue samples of animals and to plasma samples of humans.

A model was developed for interpretation of the role of drug binding to plasma proteins in determining brain uptake of highly-bound drugs. The model took into account cerebral blood flow and the kinetics of protein binding.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00129-05 LN

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Transport Systems at the Blood-Brain Barrier

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

PI:	Q. Smith	Senior Staff Fellow	LN, NIA
	V. Murphy	Staff Fellow	LN, NIA
	S. Momma	Visiting Fellow	LN, NIA
Others:	S.I. Rapoport	Chief	LN, NIA
	Y. Takasato	Visiting Fellow	LN, NIA
	H. Levitan	Professor, Dept. Biology	University of MD
	Z. Ziylan	Visiting Fellow	LN, NIA

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Neurosciences

SECTION

Cerebral Physiology and Metabolism

INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.3	2.8	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.)*

Transport mechanisms at the blood-brain barrier were studied in the rat. An in situ brain perfusion technique was developed to examine carrier-mediated transport at the cerebral capillary endothelium. Brain perfusion with physiological saline solution or with blood did not alter cerebrovascular permeability to sucrose. Barrier permeability to nonelectrolytes was linearly related to lipid solubility. Plasma protein binding prevents the brain uptake of erythrosin B. Large neutral amino acids cross the blood-brain barrier by facilitated diffusion. Cerebrovascular transport of large neutral amino acids did not change significantly in the Fischer-344 rat between 3 and 24 months of age. The cerebrovascular permeability to inorganic ions was low, comparable to a cell membrane, and followed the sequence K > Mg > Na > Cl > Ca. Calcium influx into the brain was directly proportional to the plasma concentration of ionized calcium. The low permeability of the cerebrovascular endothelium to Na was maintained with age in the rat, and the cerebrospinal fluid transfer constant for Na fell by only 18%.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00130-03 LN

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Neuropsychology Parameters in Aging and Dementia

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

PI:	C. V. Haxby	Staff Fellow	LN, NIA
	C. L. Grady	Psychologist	LN, NIA
Others:	B. Sonies	Speech Pathologist	RM, CC
	A. Cheng	Statistician	LN, NIA
	M. Rice	Psychology Technician	LN, NIA

COOPERATING UNITS *(if any)*

Rehabilitation Medicine Department, Clinical Center

LAB/BRANCH

Laboratory of Neurosciences

SECTION

Brain Aging and Dementia Section

INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.75	2.75	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.)*

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 visuconstructive ability and perceptual-motor speed. Age-related differences in general intelligence and visual memory in our sample of healthy men, ranging in age from 20 to 83 yrs, were found to be smaller than the differences reported in normative studies of non-healthy-screened 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 positron emission tomography (PET) and 18-Flurodeoxyglucose. This discrepancy between verbal and visuospatial abilities was found to be correlated with lateral asymmetry of cortical rCMRglc in patients with moderate Alzheimer's disease, but not in patients with mild Alzheimer's disease. Asymmetry of visual attention to the right and left sides of extrapersonal space was also related to lateral cerebral metabolic asymmetry in moderate Alzheimer's disease. Older Down syndrome adults perform worse on mental abilities tests than do younger subjects. Immediate verbal memory appears to be less affected by age in Down syndrome than are other abilities.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00131-03 LN

PERIOD COVERED

October 1, 1984 to September 30, 1985

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. L. Grady	Psychologist	LN, NIA
Others:	J. W. Renfrew	Psychologist	LN, NIA
	A. Moore	Social Worker	LN, NIA

COOPERATING UNITS (if any)

Research Services Branch, NIMH
Outpatient Department, Clinical Center

LAB/BRANCH

Laboratory of Neurosciences

SECTION

Brain Aging and Dementia

INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL	OTHER
2.25	1.25	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.)

Research was carried out on motor function in man in relation to aging and disease. With the use of a patient activity monitor worn on the non-dominant wrist in 14 healthy men for a period of 10 days, it was demonstrated that average wrist motor activity was lower in older individuals, primarily as a result of low activity during daytime hours. Sleep duration could be estimated from the analysis, and was not correlated with age.

A quantitative neurological examination was standardized in healthy men between 20 and 80 years of age, and established curves for age related declines in coordination, speed and accuracy of movement.

A dementia clinic was established to evaluate dementia patients for in-patient and out-patient protocols. At present, 225 patients have been screened, 32 of which have been diagnosed as having dementia of the Alzheimer type. The subjects were studied with positron emission tomography (PET).

In patients with DAT, studies of central auditory function using the staggered spondaic word (SSW) test indicated that a unilateral deficit was associated with temporal lobe atrophy on the contralateral cerebral hemisphere, as measured with CT scans, but not with asymmetry of cerebral glucose utilization.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00132-03 LN

PERIOD COVERED

October 1, 1984 to September 30, 1985

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)*

PI:	M. Schapiro	Medical Staff Fellow	LN, NIA
	J. Luxenberg	Medical Staff Fellow	LN, NIA
Others:	H. Creasey	Visiting Associate	LN, NIA
	S. Rapoport	Laboratory Chief	LN, NIA
	J. DeLeo	Computer System Analyst	LN, NIA
	H. Frederickson	Electrical Engineer	CSL, DCRT
	J. Rumsey	Psychologist	LCP, NIMH

COOPERATING UNITS *(if any)*

Computer Systems Laboratory, Division of Computer Research Technology
Laboratory of Child Psychiatry, NIMH

LAB/BRANCH

Laboratory of Neurosciences

SECTION

Brain Aging and Dementia

INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.85	2.85	

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.)*

A computer assisted method was employed to estimate the amounts of cerebrospinal fluid, white matter and gray matter in individual computerized (CT) scans of brain. Imaging processing procedures including DMORPH and CATSEG were applied to CT scans.

Computer assisted tomography (CT), together with three dimensional image reconstruction procedures, demonstrated in healthy men between the ages of 21 and 81 years, that the volume of cerebrospinal fluid increased in relation to age and that the volume of gray matter was correlated negatively with age, whereas the volume of white matter in the brain was age invariant. Volumes of lateral and third ventricles were elevated with advancing aging, while volumes of the thalamus and lenticular nucleus were reduced. Volumetric CT analysis showed reductions in young Down syndrome subjects, as compared to young controls, in intracranial volume and gray matter volume. However, the differences were not evidenced when the results were normalized to subject height, indicating that brain changes were proportional to height in Down syndrome. Left ventricular dilatation was noted by CT analysis in brains of autistic adults.

Even in healthy subjects, brain atrophy occurs with aging. The volumetric analysis technique also demonstrated brain atrophy, above and beyond that noted with respect to healthy aging, in subjects with Alzheimer's disease as well as dilatation of cerebrospinal fluid spaces. The degree of atrophy was related to psychometric scores for dementia and mental competence.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00133-03 LN

PERIOD COVERED
October 1, 1984 to September 30, 1985

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)*

PI:	N.R. Cutler	Section Chief	LN, NIA
	A.D. Kay	Medical Staff Fellow	LN, NIA
Others:	P.K. Narang	Staff Fellow	PHARM, CC
	L. Lesko	Consultant to NIH, CC Pharm	PHARM, CC
	M. Power	Staff Nurse	Nursing, CC
	M. Ninos	Staff Nurse	Nursing, CC

COOPERATING UNITS *(if any)*
Pharmacy Department, Clinical Center

LAB/BRANCH
Laboratory of Neurosciences

SECTION
Brain Aging and Dementia

INSTITUTE AND LOCATION
NIA, NIH, Bethesda, Maryland 20205

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.)*

Vancomycin's half life of the terminal phase is significantly prolonged in the elderly from young normals. No significant change was observed in volume of distribution which could be accounted for by altered tissue binding.

Zimelidine, a serotonergic reuptake blocker, was evaluated in Alzheimer's disease patients. Pharmacokinetic, neurochemical and neuropsychological effects were examined. The drug significantly reduced (by up to 38%) 5-hydroxy-indolacetic acid concentrations in cerebrospinal fluid (CSF). CSF concentrations of 3-methoxy-4-hydroxy-phenylglycol, a major metabolite of norepinephrine, tended to increase slightly. Overall, there was no effect of Zimelidine on memory function.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00134-02 LN

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Brain Lipid Metabolism, Relation to Function and Aging

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

PI:	J. Gnaedinger	Staff Fellow	LN, NIA
	J. Miller	Staff Fellow	LN, NIA
	P. Robinson	Visiting Associate	LN, NIA
	O. Tone	Visiting Fellow	LN, NIA
Others:	J. Bell	Chemist	LN, NIA
	D. Sweeney	Chemist	LN, NIA
	D. Larson	Biologist	LN, NIA

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Neurosciences

SECTION

Cerebral Physiology and Metabolism

INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.75	3.5	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 rate of incorporation of palmitate from plasma into different brain regions in the awake rat, Jpalm. Furthermore, a theoretical model was developed to calculate Jpalm from data, and to interpret the results.

Jpalm did not change with aging in Fischer-344 rats between 3 and 34 months of age, indicating that the rate of turnover of palmitate-containing brain lipids was unchanged. During development of the rat, Jpalm increased between 15 and 20 days, then fell more than 8 fold to maturity. The time course corresponded to the time course of myelination in the developing brain.

Jpalm was found to fall in the pituitary and pineal glands of Brattleboro rats as compared to controls, and to fall in central auditory pathways following damage to the cochlea of rats.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00135-02 LN

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Regulation of Gene Expression in Brain; Aging and Dementia

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

PI:	J.W. Cosgrove	Senior Staff Fellow	LN, NIA
Others:	J.R. Atack	Visiting Fellow	LN, NIA
	M. Matocha	Staff Fellow	LN, NIA

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Neurosciences

SECTION

Cerebral Physiology and Metabolism

INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2	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.)*

Amino acid incorporation was measured in a cell-free protein synthesis system derived from the brains of male Fischer-344 rats of different ages. This system has the capacity to initiate protein synthesis in vitro. There was no significant correlation between protein synthesis and age.

A procedure for isolating neurofilament proteins from the rat central nervous system was developed. Analysis of neurofilament proteins by two dimensional gel electrophoresis revealed the three neurofilament proteins of 210K, 160K, and 68K daltons molecular weight. This technique revealed heterogeneity in the neurofilament protein pattern, especially in the 68K dalton polypeptide.

Analysis of gene expression in 11 individual regions of the rat brain at the level of protein end-product was conducted using two dimensional gel electrophoresis in conjunction with a sensitive silver stain protein detection procedure. Differential gene expression was observed for a number of brain proteins. Regulation at the level of protein end-product was not observed for a significant number of brain proteins.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00136-02 LN

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Functional Interactions Among Brain Regions

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

PI:	B. Horwitz	Senior Staff Fellow	LN, NIA
	T. Sonerant	Senior Staff Fellow	LN, NIA
Others:	C. Grady	Psychologist	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 20205

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 the cerebral metabolic rates for glucose as determined by positron emission tomography in humans. The method was applied to regional metabolic data from 40 healthy men at rest, and demonstrated correlations among homologous regions between the cerebral hemispheres, and between the frontal and the parietal lobes on the one hand and the temporal and occipital lobes on the other. Furthermore, right-hemispheric regional interactions exceeded those in the left hemisphere. The method also showed clear evidence of age differences between 15 young and 15 older men. The older subjects had fewer significant correlations in parietal and frontal regions, indicative of reduced integrated activity in these regions with age.

The matrix method was applied to analyze glucose metabolism in Fischer-344 rats, and showed patterns of correlations similar to those in humans.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00140-01 LN

PERIOD COVERED

October 1, 1984 to September 30, 1985

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)*

PI: C. May Medical Staff Fellow LN, NIA

COOPERATING UNITS *(if any)*

Laboratory of Neurochemistry, NIMH
Department of Pharmacology, University of Pittsburgh, School of Medicine
Department of Endocrinology, Johns Hopkins School of Medicine
Biological Psychiatry Branch, NIMH - Clinical Pathology Department, CC

LAB/BRANCH

Laboratory of Neurosciences

SECTION

Brain Aging and Dementia

INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL:	OTHER:
1.5	1.5	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.)*

Cerebrospinal fluid concentrations of homovanillic acid, 5-hydroxyindoleacetic acid, norepinephrine and 3-methoxy 4-hydroxyphenylethylene glycol did not differ significantly between patients with Alzheimer's disease and age matched controls, and were not correlated with age in healthy men. Spinal fluid concentrations of choline increased with age in healthy men, and were higher in young adults with Down syndrome than in age matched controls. CSF biopterin, a coenzyme for tyrosine and tryptophan hydroxylase, was lower in patients with Alzheimer's disease that in controls, and was correlated with concentrations of 5-hydroxy- indoleacetic acid and homovanillic acid.

Corticotropin releasing factor, a neuropeptide, was significantly reduced in the cerebrospinal fluid of patients with Alzheimer's disease as compared to controls, as was peptidyl-alpha-amidation activity, suggesting a loss of neurons which produce amidated neuropeptides.

Ratios of albumin and immunoglobulin between cerebrospinal fluid and plasma were normal in Alzheimer's patients, suggesting that the blood brain barrier is intact.

Overview of Epidemiology, Demography, and Biometry Program
National Institute on Aging

Dr. Jacob A. Brody, Director of the Epidemiology, Demography, and Biometry Program, since its origin in 1978, retired from an illustrious career in the Public Health Service to become the Dean of the School of Public Health at the University of Illinois at Chicago.

Since 1978 the EDB Program has progressed from initially recognizing the lack of population estimates of prevalence and incidence of health problems and impairments of the elderly to meeting this deficiency by initiating several population studies of the elderly. These studies have now been established and are accumulating valuable prospective data. The direction and efforts of the EDB Program must now turn to the analysis of this vast amount of data to provide much needed information on the leading health problems of the elderly. These analyses should identify associated factors for further investigation. They should generate hypotheses to define the actual risk factors of developing the health problems. The ultimate goals of this research are the transfer of knowledge to the implementation of programs for prevention, and the provision of solutions for maintaining persons at their optimal ability for independent living and life satisfaction in the later years.

While the staff has turned its attention to analyses of the accumulated data, effort has also been focused on continuing the data collection on the major research projects, the Established Populations for Epidemiologic Studies of the Elderly (EPESE), the National Health and Nutrition Examination Survey (NHANES I) Epidemiologic Followup Survey, the Survey of the Last Days of Life, the various aspects of the Framingham Study, and initiation of a few new projects. Although this is a logical and potentially profitable direction for the Program to take, the ability to be successful is severely handicapped by the limited number of full-time permanent professional employees within the Program. An example is the NHANES Followup Project which was initiated by NIA, and for which NIA provided the major support. The other eight institutes which have participated in the NHANES Followup have initiated a large number of analytic investigations, whereas the EDB/NIA may not be able to produce equivalent analyses, since there are so few people to do them. The Program has dedicated a considerable effort to the NHANES Followup and would like to have the visability derivable from the publication of results, but the current staffing situation may prohibit that outcome.

The EPESE is proceeding with the analysis of data being collected prospectively. The major endpoints were defined as mortality, hospitalization, admission to nursing home, and disabilities. Analyses related to these endpoints have been labeled "core analyses." The definitions and responsibilities for studies of related demographic characteristics and exposure variables have been assigned during FY 1985. A fourth EPESE project has been initiated in Durham, North Carolina to study a predominantly black population of elderly persons. The first year, a planning year, included pretesting the baseline survey instruments and developing field procedures. The staff of this project has been integrated into the administrative scheme of the other three EPESE projects, a representative having been assigned to each of the major EPESE working committees.

The EPESE Resource Data Book is nearing completion and publication is anticipated during this fiscal year. A paper on the methodologic issues and preliminary findings on the epidemiology of disability in the oldest old was published in the Milbank Quarterly. This publication was developed from the collaboration of the researchers at the three original EPESE locations and EDB staff. The three original EPESE projects, which were to end on June 30, 1985, were awarded an extension of 3 years (to fiscal year 1988). The contracts included support for adding into the East Boston cohort all persons who have become 65 since the study began. This is the only site that is continuing to admit participants into the study population as they become 65 years of age. Also, the extension contract for the University of Iowa included continued followup of the nursing home population which the Iowa investigators interviewed at the time of the baseline survey.

Plans are being developed for specific research aimed at the oldest old participants of all four EPESE sites. These plans include indepth studies of nursing home admissions and clinical evaluation of specific health problems. The field work for the NHANES I Epidemiologic Followup was completed in 1984 and the final data tapes have become available to the participating institutes. A committee to organize publications from this data set has been functioning. Several writing committees with representation from multiple institutes are progressing on specific analyses. The EDB staff is involved with analyses in the areas of hypertension, disability, cognitive functioning, osteoarthritis, hearing, sleep complaints, height/weight, and other subjects. A major area of investigation is nutrition and dietary behavior. The EDB staff is working with experts through professional services contracts to describe eating patterns of the elderly and relate these to morbidity and mortality.

Studies of dementing diseases continue to be a major focus of activities during FY 1985. Preliminary data from the study in East Boston (The Natural History of Senile Dementia) suggests the rates of Alzheimer's disease are substantially higher than expected among the East Boston elderly population. Analyses of these data are in progress and are expected to be published in the final quarter of this fiscal year. Analysis of the data from the Framingham Dementia Study will be initiated early in FY 86. These analyses will include the clinical diagnosis of dementia.

Dr. Mary Farmer has completed an analysis of the Framingham data on the relationship of concurrent and prior blood pressure with levels of cognitive functioning which fails to confirm an association between elevated blood pressure and poor cognitive functioning.

The EDB staff has published several papers from the ongoing studies. Dr. Farmer and other investigators published an important paper in the American Journal of Public Health on the incidence of hip fractures by age, sex, and race. Papers are being developed by other members of the staff on the occurrence of digitalis use among the EPESE subjects, and studies of self assessment of hearing vs. pure

tone audiometry, the relationship between sleep problems and dementia, the relationship of hearing ability and bone density, and correlates, predictors, and prognostic significance of varicose veins in later life from the NHANES I Epidemiologic Followup Survey data.

The pretest of the Survey of the Last Days of Life was completed and the results analyzed. Revisions were made to the questionnaire and the main study went into the field in January 1985. Data collection is proceeding satisfactorily with a high degree of cooperation from respondents, physicians, and health facilities and low rates of item nonresponse and missing data. The Program has supported and assisted in the development of the National Mortality Followback Survey. This is an appropriate investment of time since the study is strongly related to the EDB project entitled, "Survey of the Last Days of Life" and will provide national norms to which we may compare our data.

The pretest results from the NCHS study of nursing home admissions in the National Nursing Home Survey (NNHS) have been received. The results of the study indicated that it was not feasible to include an admissions cohort in the NNHS. Instead, a sample of nursing home residents and a next of kin for each sample resident will be interviewed concerning the resident's history of nursing home admissions up to the time of the NNHS. This retrospective design is to replace the original prospective approach in describing paterns of admission, discharge, and length of stay of a representative sample of persons admitted to nursing homes. The EDB Program continues to work with NCHS on the planning and support of this study.

An important responsibility of the Biometry Office is the development of statistical methodology. A study completed through a professional services contract examined nonrandom item nonresponse for the Iowa EPESE baseline survey. The results showed that many of the CES-D depression scale questions had item nonresponse rates characterized by age, sex interactions and virtually all responses from females were affected by the age of the respondent. The nonrandom associations of other items were also reported. It is concluded that imputation for missing values is a viable technique for remedying the incomplete data due to item nonresponse in the Iowa study. These results may apply to the other locations as well. Methodology is also being developed for the analysis of the NHANES Followup data as well as other methods for analyzing longitudinal data.

The EDB staff have used other national data sets, primarily integrating the data into ongoing EDB research. In particular, the macroeconomic demographic model has coordinated data from the Health Care Financing Administration, the Social Security Administration, the National Center for Health Statistics and the National Center for Health Services Research. Types of health expenditures and sources of funding have been studied by age and sex. A project entitled "Household Formation, Housing, and Aging Population" was initiated to study the rapidly changing patterns of household formation and housing tenure among the elderly. The study entitled, "Aging, Health and Consumer Expenditures," was extended this year for the purpose of re-estimating data which underly the consumer expenditures model. Simultaneously, the "Health Expenditures and Aging

Population" contract was extended to permit the estimation of the health expenditures model in conjunction with the consumer expenditures model. Microeconomic research is now being developed within the section focusing on studies of wealth. Work has begun to study the wealth-age profile with the inclusion of rights to private pensions and social security.

The project entitled, "The Evaluation of Senile Dementia Costs," has resulted in several manuscripts describing the cost of dementia in the elderly and related methodological issues for estimating cost of illness in the elderly. Efforts have been developed for international collaborative work. Plans for collaborative work are being established by Dr. Cornoni-Huntley with the United Kingdom which may allow for the collection of statistics comparable with the EPESE projects. Also, Dr. White has established ties with Japan which may lead to comparative studies related to dementia. There are also possibilities of collaborative work with Sweden and Italy. Such projects could provide not only comparison of prevalence and incidence data but a test of replication of identified associated factors.

The EDB Ad Hoc Scientific Advisory Committee, constituted in fiscal year 1982, continues to review our Program and is assuming an increasing role in our planning process. The primary purpose of the April 16, 1985, meeting was to review the current status and progress of ongoing research and to review concept clearance for two proposed projects: Microeconomics and Hip Fracture Risk Factor Study in the Breast Cancer Demonstration and Detection Program Followup. Reports describing the major research projects were favorably received. Both proposed projects were unanimously approved. It was decided that because of budget constraints we would hold one meeting each year. The next meeting is scheduled for April 8, 1986.

The EDB Program continues to be alert to the benefit of training programs for the staff. Ms. Paulette Campbell is currently completing her year as a Trainee Program Analyst. She has been reclassified as a Program Analyst and has taken over a substantial part of the administrative burden previously born by the scientific staff. As the training period is completed, she will assume an even greater responsibility for the EDB contract administration.

The EDB Program has benefitted greatly from the enthusiastic assistance of part-time employees: Ms. Katherine Dorton, University of Maryland, Mr. Thang Le, George Washington University, and Mr. Bao Loc Le, high school student from Dalton, Ohio.

The progression of the Program is on target but the current ability to attain the results is highly questionable. The lack of professional staff and associated support staff severely limits the output, in particular, the analysis of the vast data library accumulated through thoughtfully developed and well designed projects. These projects were initiated with the anticipation of a growing intramural program in epidemiology, demography, and biometry. The current size of the Program staff is unable to meet the demand for analysis of the vast amount of existing and accumulating data.

Meetings to develop and exploit the research potentials of the four Established Populations for Epidemiologic Studies of the Elderly (EPESE) (AG-0-2105; AG-0-2106; AG-0-2107; and AG-4-2110) were held in Bethesda, December 17, 1984; March 14, April 23, July 8-9, 1985; and in Chicago, October 1984. Meetings were also held in conjunction with the American Statistical Association meeting in Philadelphia, and the American Public Health Association meeting in Anaheim. These were focused on conjoint analysis of specific data, planning for continuation of the interval of surveillance for an additional 3 years, resolution of methodologic issues, and review of proposed analyses and reports. The fourth EPESE project (Piedmont Health Survey of the Elderly - PHSE), in a predominantly black population in North Carolina, got under way during this fiscal year. Instruments were developed and pretested, specific research goals were defined, and coordination with the three existing EPESE projects developed. The smooth start of this new EPESE and its integration into the NIA-EPESE research program was largely the result of Dr. Mary Farmer's able management. A considerable effort was required to complete planning for extensions of the three primary EPESE projects, and to plan for specific research aimed at the "oldest old" participants at all four sites. It was decided that certain analyses must be undertaken in a systematic and coordinated fashion (the core analyses), to be certain that these are promptly and appropriately published. The definitions and assignments for these analytic tasks were accomplished during fiscal year 1985. They include fundamental descriptive and analytic studies relative to deaths, hospitalizations, nursing home events, and physical and cognitive disabilities. In addition, the work on the EDB Program EPESE Resource Data Book continued, with completion of all tables, graphs, and narrative components of that document. Other reports and presentations based on EPESE data were generated at each of the three sites as well as from the EDB staff.

The following publications are a result of the research at the EPESE centers in fiscal year 1985:

Branch, L.G., Scherr, P.A., Cook, N.R., and Taylor, J.O.: Functional status and service use among a community sample of elderly veterans. In: Wetle, T, and Rowe, J.W. (Eds.): Older Veterans: Linking VA and Community Resources. Cambridge, Harvard University Press, 1984, pp. 26-320.

Lavsky-Shulan, M., Wallace, R.B., Kohout, F.J., Lemke, J.H., Morris, M.C., and Smith, I.M.: Prevalence and functional correlates of low back pain in the elderly: The Iowa 65+ Rural Health Study. J Am Geriatr Soc. 33(1)23-28, 1985.

Loening-Baucke, V. and Anuras, S.: Effects of age and sex on anorectal manometry. Am J Gastroenterology. 80(1)50-53, 1985.

Mobily, K.E., Leslie, D.K., Wallace, R.B., Lemke, J.H., Kohout, F.J., and Morris, M.C.: Factors associated with the aging leisure repertoire: The Iowa 65+ Rural Health Study. J Leisure Research. 16(4)338-43, 1984.

Wallace, R.B.: Drug utilization in the rural elderly: Perspectives from a population study. In: Moore, S.R. and Teal, T.W. (Eds.): Geriatric Drug Use--Clinical & Social Perspectives. New York, Pergamon Press, 1985, pp. 79-85.

Wallace, R.B., Lemke, J.H., Morris, M.C., Goodenberger, M., Kohout, F., and Hinrichs, J.V.: Relationship of free-recall memory to hypertension in the elderly. The Iowa 65+ Rural Health Study. J Chron Dis. 38(6)475-81, 1985.

Excellent progress has been accomplished at all three of the primary EPESE sites with regard to: collection and coding of mortality data; acquisition and coding of hospitalization data using HCFA tapes; identification of nursing home events; continued participation of subjects through a second telephone contact and into the second cycle of household interviews; and comparable coding of prescription drugs identified during the household interview. Substudies are well under way at each site relating to a diversity of topics. The process of registering and interviewing "new" participants who have become 65 since the study began (i.e., the successive cohort component of the East Boston study) is progressing well. Information concerning nursing home events beginning to accrue at each site is especially interesting and promises to provide unexpected insights into this aspect of health care. The fourth EPESE got under way during this year with development and pretesting of interview instruments, further definition of the target population, and completion of OMB clearance tasks.

During this fiscal year the final data tapes from the NHANES I Epidemiologic Followup Survey (YO1-AG-9-0018) became available and analyses began. Several committees with representation from all of the involved institutions met to discuss specific analyses, and several of these began. EDB staff are guiding or are involved in analyses related to mortality, hypertension, disability, weight, cognitive functioning, arthritis, hearing, sleep complaints, and other subjects. The EDB Program has initiated plans to publish a book which will summarize findings from the NHANES I Epidemiologic Followup Survey. This book will provide new information on the epidemiology of problems of aging and will inform the scientific community about the contents of the data set in order to facilitate its use by other investigators. A workshop for all of the authors is planned for September 10, 1985. Authors will meet with Dr. Huntley and present the anticipated contents of their respective chapters. Small group discussions will be arranged for those authors whose chapters appear to overlap in content. Professional services contracts will be used to pay travel, per diem, and fees for six of the authors who are working in various universities around the country and who are familiar with the NHANES I data set. Several more workshops are planned for FY 1986. A conference is planned for the end of 1986, when the book will be presented to the public.

In the first and second quarter of FY 1985, EDB staff were actively involved in the planning of a National Cancer Institute (NCI) study which would involve the followback of approximately 60,000 women seen several years earlier as part of a breast cancer demonstration program. Specific studies were planned by EDB staff related to the determinants and predictors of osteoporosis and hip fracture. In the third quarter of the fiscal year the National Cancer Institute announced

that it was deferring this study because of unexpectedly high costs and limited personnel. We hope that the investigation may be revived at some future date so that the NIA studies can be carried out as originally planned.

Dementing diseases continued to be a major focus of activity during FY 1985. The study in East Boston (Natural History of Senile Dementia, AG-1-2106) has produced rather startling results. Based on the approximately 500 subjects examined as part of the study, the prevalence of moderate to severe cognitive impairment in the noninstitutionalized East Boston population over 65 is substantially higher than has been reported in other studies. In addition, approximately 80 percent of the persons identified as suffering from moderate or severe cognitive impairment were also identified as having Alzheimer's disease (definite or probable on the basis of the clinical evaluation). Overall, these data suggest that rates of Alzheimer's disease are substantially higher than expected among East Boston's elderly. Further analyses of these data are currently under way and are expected to result in the generation of manuscripts for publication in the final quarter of this fiscal year.

The Framingham Dementia Study (YO2-AG-2-0040) is now entering a phase when analyses related to the clinical diagnosis of dementia are becoming possible. An initial examination of the performance of study participants on a dementia screening test was presented at a national neurology meeting in Texas. In March, the involved investigators from Boston University, NHLBI, and NIA met in Bethesda to review progress to date and to plan the course of future investigations. A specific series of tasks and investigative goals have now been defined. In addition to a methodologic paper in press in the Journal of Chronic Diseases, three other analyses are now nearing completion: a presentation of neuropsychological test data from cycle 14/15 (first author is Dr. Mary Farmer); a related paper which focuses on the relative effects of education and age, and uses a composite score based on the eight tests given in cycle 14/15 (first author is Dr. Lon White); and a manuscript relating concurrent and prior blood pressures with level of cognitive function functioning at cycles 14 and 15 (first author is Dr. Farmer). This last mentioned paper is especially important in that it fails to confirm an association between elevated blood pressure and poor cognitive functioning.

In October 1984, Dr. White was invited to a meeting in Tokyo, the purpose of which was to encourage and facilitate collaborative and cooperative studies on aging between the United States and Japan. During that visit Dr. White met with a number of prominent Japanese scientists involved in studies on dementia. Contact was also made with representatives of the Tokyo Metropolitan Institute of Gerontology, an institution with which the NIA has established an agreement for reciprocal scientific activities. Also on this trip Dr. White discussed international epidemiologic research on dementia and the possibility of initiating comparative studies among Japanese subjects residing in the continental United States, Japan, and Hawaii. The possibility of NIA support for such studies is currently being considered, with NIA extramural staff members playing a prominent role.

A landmark paper by Dr. Farmer and other investigators was published in the American Journal of Public Health and has provided information on the incidence of hip fractures by age, sex, and race with a precision previously unavailable.

Dr. Guralnik, an EDB Program staff member who is also a PHS Epidemiology Trainee, is now completing his formal training at the School of Public Health in Berkeley, California. His doctoral thesis involves the predictors of disability, poor health, and good health in the Alameda County Study population. At the EDB Program these efforts will be extended to similar studies using the data sets available in Bethesda, and will result in publications comparing the predictors of both ill health and good health in several different populations.

A study collaboratively designed and executed by Dr. White and Dr. Andrea LaCroix defined the occurrence and correlates of digitalis use among EPESE subjects. A manuscript resulting from these analyses is currently in preparation, and results will be presented at the APHA meeting in November 1985.

A study based on NHANES I data related to hearing (pure-tone audiometry and self-assessment of hearing) was carried out to examine the sensitivity and specificity of self-assessment. These investigations, directed by Dr. Tatiana Kudrjavcev (on detail from NINCDS from August 1984 to July 1, 1985), are of additional interest because of their presentation of data related to pure-tone hearing thresholds by age, sex, education, and degree of self-perceived hearing impairment.

The EDB Program provided a special training opportunity for several individuals at various phases in their professional careers. Dr. Mary Farmer, continuing her staff fellowship with the EDB Program, has become an indispensable member of our research team and has continued to carry out her work at the highest level of excellence. Ms. Debbie Moritz (Ph.D. candidate from Yale) spent considerable time with us as a guest worker involved in the analysis and planning of studies on sleep problems and dementia. Ms. Toni Miles, a senior medical student from Howard University, spent one month working on anthropometric data of utility for evaluating the nutritional status of elderly persons. Dr. Roberta Bergman (a medical intern from Bellevue Hospital, New York) spent one month with us working on item non-response in survey questionnaires, and on the planning of studies related to superior health. Ms. Yuko Palesch, a doctoral candidate in statistics at George Washington University, has been a guest worker over a period of some months and has generated some very interesting data related to the occurrence of varicose veins. These initial observations now serve as the foundation of a planned study on the correlates, predictors, and prognostic significance of varicose veins in later life. Ms. Dorly Deeg, an epidemiologic researcher and doctoral candidate from Erasmus University (Rotterdam, the Netherlands), spent one week visiting our Program, during which she presented the results of her own research on the predictors of longevity. Dr. Andrea LaCroix (RN, cardiovascular fellow, and recent Ph.D. in epidemiology from the University of North Carolina) spent a time with us as a guest worker becoming familiar with EDB research and approaches, and later was able to complete a

series of specific tasks related to an epidemiologic study on digitalis, the development of new investigations of the EPESE "oldest old," and epidemiologic analysis of NHANES data. Dr. Tamara Harris (NRSA candidate) was also a guest worker with EDB at intervals during the year.

Epidemiology Office Research Highlights, FY 1985

- EPESE - new study established at Duke University in a predominantly black community--design, instruments, clearances, and pretesting all completed

- EPESE - 3-year extensions of surveillance period approved

- EPESE - plans begin for in-depth studies of the "oldest old" participants

- EPESE - many analyses completed or under way; Resource Data Book expected to go to press in final quarter this fiscal year

- NHANES I Epidemiologic Followup Survey - plans for book formalized, authors working on assigned components

- NHANES I Epidemiologic Followup Survey - all data tapes received and analyses for many studies begin

- Natural History Of Senile Dementia - first wave (approximately 500) of clinical evaluations completed, second wave begins. Analyses show unexpectedly high prevalence of presumptive Alzheimer's disease

- Framingham Dementia - first wave of clinical evaluations of screening test failures nearly complete. Survival and performance on the MMSE screening test both predicted by scores on the neuropsychologic tests given 5 years earlier

- Hip Fracture - report on incidence by age, sex, and race published in the American Journal of Public Health, (Farmer, et al.)

- International Ties - Dr. Cornoni-Huntley established ties with the United Kingdom which may allow comparative studies with EPESE. Dr. White established ties with Japan which may allow comparative studies related to dementia

CONTRACT

Name and Number: YALE UNIVERSITY (NOI-AG-0-2105)

Title: Established Populations for Epidemiologic Studies of the Elderly (EPESE)

Date Contract Initiated: June 30, 1980

Current Annual Level: $600,000

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. Studies are to be completed on problems of pain, vision, hearing, sleep, drug use, constipation, social support and other pertinent areas.

Methods Employed: The project shall include cross-sectional and prospective studies in a carefully defined and accessible population using standard field and analytical techniques. Yearly surveillance of the population will be included.

Major Findings: Participants at each site have been monitored for deaths, hospitalizations, and nursing home events by community surveillance and yearly telephone interviews. EDB staff and the investigators at each locality worked in close cooperation to develop the methods and instruments for these tasks.

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. 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. High priority short term studies will be encouraged.

Proposed Course: The contract was extended through FY87. Extensive work has been accomplished on coding of hospitalization data using HCFA tapes; and identification of nursing home events. Participation of subjects continues through a second followup (telephone interview) and into the third contact (household interviews). Substudies are well underway relating to a diversity of each site is especially interesting and promises to provide unexpected insights into this aspect of health care.

Publication: Cornoni-Huntley, J.C., Foley, D.J., White, L.R., Suzman, R., Berkman, L.F., Evans, D.A., and Wallace. R.B.: Epidemiology of disability in the oldest old: Methodologic issues and preliminary findings. Milbank Memorial Fund Quarterly/Health and Society. 63(2)350-76, 1985.

CONTRACT

Name and Number: UNIVERSITY OF IOWA (NO1-AG-0-2106)

Title: Established Populations for Epidemiologic Studies of the Elderly (EPESE)

Date Contract Initiated: June 30, 1980

Current Annual Level: $700,000

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. Studies are to be completed on problems of pain, vision, hearing, sleep, drug use, constipation, social support and other pertinent areas.

Methods Employed: The project shall include cross-sectional and prospective studies in a carefully defined and accessible population using standard field and analytical techniques. Yearly surveillance of the population will be included.

Major Findings: Participants at each site have been monitored for deaths, hospitalizations, and nursing home events by community surveillance and yearly telephone interviews. EDB staff and the investigators at each locality worked in close cooperation to develop the methods and instruments for these tasks.

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. 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. High priority short term studies will be encouraged.

Proposed Course: The contract was extended through FY87. Extensive work has been accomplished on coding of hospitalization data using HCFA tapes; and identification of nursing home events. Participation of subjects continues through a second followup (telephone interview) and into the third contact (household interviews). Substudies are well underway relating to a diversity of each site is especially interesting and promises to provide unexpected insights into this aspect of health care.

Publication: Cornoni-Huntley, J.C., Foley, D.J., White, L.R., Suzman, R., Berkman, L.F., Evans, D.A., and Wallace. R.B.: Epidemiology of disability in the oldest old: Methodologic issues and preliminary findings. Milbank Memorial Fund Quarterly/Health and Society. 63(2)350-76, 1985.

CONTRACT

Name and Number: PETER BENT BRIGHAM HOSPITAL (NO1-AG-0-2107)

Title: Established Populations for Epidemiologic Studies of the Elderly (EPESE)

Date Contract Initiated: June 30, 1980

Current Annual Level: $900,000

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. Studies are to be completed on problems of pain, vision, hearing, sleep, drug use, constipation, social support and other pertinent areas.

Methods Employed: The project shall include cross-sectional and prospective studies in a carefully defined and accessible population using standard field and analytical techniques. Yearly surveillance of the population will be included.

Major Findings: Participants at each site have been monitored for deaths, hospitalizations, and nursing home events by community surveillance and yearly telephone interviews. EDB staff and the investigators at each locality worked in close cooperation to develop the methods and instruments for these tasks.

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. 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. High priority short term studies will be encouraged.

Proposed Course: The contract was extended through FY87. Extensive work has been accomplished on coding of hospitalization data using HCFA tapes; and identification of nursing home events. Participation of subjects continues through a second followup (telephone interview) and into the third contact (household interviews). Substudies are well underway relating to a diversity of each site is especially interesting and promises to provide unexpected insights into this aspect of health care.

Publication: Cornoni-Huntley, J.C., Foley, D.J., White, L.R., Suzman, R., Berkman, L.F., Evans, D.A., and Wallace. R.B.: Epidemiology of disability in the oldest old: Methodologic issues and preliminary findings. Milbank Memorial Fund Quarterly/Health and Society. 63(2)350-76, 1985.

CONTRACT

Name and Number: DUKE UNIVERSITY MEDICAL CENTER (NO1-AG-4-2110)

Title: Established Populations for Epidemiologic Studies of the Elderly (EPESE)

Date Contract Initiated: September 30, 1984

Current Annual Level: -0-

Objectives: Duke University Medical Center will study an elderly population of at least 4500 noninstitutionalized persons, 65 years of age or older, and of which at least 50 percent is black and approximately 30 percent to 40 percent is white. The population shall be 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 will be conducted. Investigators will conduct 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. During the first year the population shall be defined ecologically in terms of social, political, and demographic characteristics; it shall also be necessary during this first year to establish working relationships with the public and professional groups within this population.

Major Findings: Instruments were developed and pretested, specific research goals were defined, and coordination with the three existing population studies developed.

Significance to Biomedical Research: The NIA is at present 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, are not fully representative of the U.S. elderly, specifically, they do 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: A baseline survey of the population shall be planned during the first year and conducted in the second year to obtain baseline data and an estimate of the participation rate for the specific problem-related studies. The 2nd through the 6th years shall be devoted to continual surveillance of the population, analysis of data, and development and completion of problem-related studies. A final household interview shall be conducted in the 5th year.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 AG 02010 07 EDBP

PERIOD COVERED
October 1, 1984 to September 30, 1985

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Followup of National Health and Nutrition Examination Survey I (NHANES I)

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*
PI: Joan Cornoni-Huntley, Ph.D., M.P.H.
Acting Deputy Associate Director, EDBP, NIA

COOPERATING UNITS *(if any)*
National Center for Health Statistics, Division of Analysis; NCI; NHLBI; NIADDK, NIMH; NIAAA; NIAID; and NINCDS.

LAB/BRANCH
Epidemiology Office

SECTION
Epidemiology, Demography, and Biometry Program

INSTITUTE AND LOCATION
NIA, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.40	.20	.20

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 design and complete a followup of persons examined in the HANES I to study how factors previously measured relate to the health conditions that have developed since the survey. The three major areas for prediction of outcome are 1) nutrition 2) risk factors for chronic disease and 3) health care utilization. The survey will have a household interview including self-reporting of health conditions, utilization of health servics and behaviorial and social status plus some physical measurements as blood pressure, height, and weight.

The field work for the NHANES I Epidemiologic Followup was completed in 1984 and the final data tapes have become available to the cooperating units. NIA/EDB staff are involved in analyses in the areas of hypertension, disability, cognitive functioning, osteoarthritis, hearing, sleep complaints, height/weight, and other subjects. A major area of investigation is nutrition and dietary behavior. The EDB Program is involved in publishing a book which will summarize findings from the NHANES I Epidemiologic Followup Survey.

Continued Followup of the Elderly 1986 is underway. The first half of the pretest of the telephone interview is completed. The continued followup telephone interviews will be completed in fiscal year 1986. The response rate continues to be very high.

PHS 6040 (Rev. 1/84) GPO 914-918

CONTRACT

Name and Number: PETER BENT BRIGHAM HOSPITAL / EAST BOSTON NEIGHBORHOOD HEALTH CENTER (N01-AG-1-2106)

Title: Senile Dementia: Natural History in a Noninstitutionalized Population

Date Contract Initiated: June 16, 1981

Current Annual Level: $400,000.

Objectives: The objective of this study is to describe the course of general health and cognitive decline in a group of SDAT victims and controls.

Methods Employed: Persons suspected of being demented because of performance on a screening examination will receive a neurological and neuropsychological evaluation. SDAT cases and a number of matched controls will then be reexamined at yearly intervals over a period of approximately 3 years; thereafter the cases and controls will be followed as defined by their participation in another EDBP study (EPESE)--for death, hospitalization, and institutionalization end points.

Major Findings: Based on the approximately 500 subjects examined as part of the study, the prevalence of moderate to severe cognitive impairment in the noninstitutionalized East Boston population over 65 is substantially higher than has been reported in other studies. In addition, approximately 80 percent of the persons identified as having Alzheimer's disease (definite or probable on the basis of the clinical evaluation). Overall, these data suggest that rates of Alzheimer's disease are substantially higher than expected among East Boston's elderly.

Significance to Biomedical Research/Justification: This study will provide a better understanding of the prognosis and clinical course of SDAT.

Proposed Course: Further analyses of these data are currently under way and are expected to result in the generation of manuscripts for publication in the final quarter of this fiscal year.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 04003 04 EDBP

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Dementing Illnesses in the Framingham Heart Study

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

Lon R. White, M.D., M.P.H.
Chief, Epidemiology Office, EDBP, NIA
Mary E. Farmer, M.D., M.P.H.
Senior Staff Fellow, Epidemiology Office, EDBP, NIA

COOPERATING UNITS *(if any)*

NHLBI

LAB/BRANCH

Epidemiology Office

SECTION

Epidemiology, Demography, and Biometry Program

INSTITUTE AND LOCATION

NIA, NIH, Bethesda, MD 20892

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.)*

Demented subjects are currently being identified by a two-phase evaluation: administration of the screening test as part of the regular biennial examination, coupled with neurological and neuropsychological evaluations of participants who fail the screening test. A second group of dementia cases will be identified from among recently deceased study participants based on: (a) poor perfromance on neuropsychological tests administered approximately 5 years ago, (b) review of medical records, and (c) telephone interviews with a surviving family member. Approximately 300 deceased, poor performers, and matched controls (prior testing) have been identified for record review and telephone interview followup; this will begin in fiscal year 1986. A third group of dementia cases will be generated as a result of reevaluation during the current (cycle 18) examination. Current funding supports the continuing neuropsychological and neurological evaluations of all study participants suspected of dementia, the gathering of information related to the diagnosis of dementia from family members of possible cases, data managing, and statistical analysis related to the information generated by these examinations and interviews, and coordination of the dementia/aging disability components of the study.

PHS 6040 (Rev. 1/84)

GPO 914-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 04004-03 EDBP

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Healthy Aged--Honolulu Heart Study

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

PI: Lon R. White, M.D., M.P.H.
Chief, Epidemiology Office, EDBP, NIA

COOPERATING UNITS *(if any)*

Honolulu Heart Program, NHLBI

LAB/BRANCH

Epidemiology 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 unreduced type. Do not exceed the space provided.)*

A professional services contract was awarded to Dr. Benfante to carry out research using the data and facilities of the Honolulu Heart Study. The objective of this study is to define the correlates and predictors of survival and good health in later life. From more than 30 variables examined in multivariate analyses, blood pressure, obesity, cigarette smoking, alcohol consumption, serum glucose, uric acid, and triglyceride were inversely associated with staying healthy while forced vital capacity and birthplace in Japan were directly associated with health. Of these nine variables, blood pressure was the strongest discriminator between healthy status and all categories of disease while cigarette smoking and alcohol consumption were the next most important factors. This study suggests that the use of individuals who remain free of disease as a "standard" for health can facilitate the evaluation of risk factors for both total illness and a broad range of specific chronic diseases in a single population.

Publication: Benfante, R., Reed, D., and Brody, JA. Biological and social predictors of health in an aging cohort. J Chron Dis 38(5)385-95, 1985.

PHS 6040 (Rev. 1/84) GPO 914-918

Overview of the Demography and Economics Office

The Demography and Economics Office has emphasized work in population aging with the continual development of the Macroeconomic-Demographic Model (MDM). This model focuses on the current and future trends of population whose mean age is rising or whose population is made up of an increasing proportion of older individuals. This research is closely associated with the concept of demographic transition to a stable and older population structure. We have also begun to focus on the aged population per se through our wealth studies, NHANES studies, and a new project on the microeconomics of aging that examines the health expenditures and health status of the elderly.

A major enhancement to the MDM continues under a contract to ICF, Incorporated (AG-2-2138) for "Health Expenditures and the Aging Population." This effort involved briefings and coordination with such agencies as the Health Care Financing Administration, Social Security Administration, DHHS Assistant Secretary for Planning and Evaluation, National Center for Health Statistics, and the National Center for Health Services Research in order to avoid duplication and waste. Analysis of these data has been started with the generation of numerous age- sex-expenditure breakdowns for type of health expenditures and source of funding and a paper was presented at the International Health Economics and Management Association in Rome, Italy. The contract was extended a year to allow revisions to the Model's data base. The National Health Accounts were recently revised, thus making the Model's data obsolete. A paper was written by the investigators to compare National Health Account payments to their counterparts in the National Medical Care Utilization and Expenditures Survey (NMCUES).

An RFP, No. NIH-AG-84-19, had its deadline extended into FY85. This project is entitled "Household Formation, Housing, and an Aging Population." Of great concern are the rapidly changing patterns of household formation and housing tenure among the elderly. A contract award was made to ICF, Incorporated.

The contract "Aging, Health and Consumer Expenditures" (AG-3-2117) was also extended a year along with the health expenditures modeling contract. The purpose of this research is to disaggregate consumption by age in the (MDM) so that the effects of the aging population may be examined with particular attention to the aggregate share going to health care services. We shall examine the effects of public policy on the welfare of the elderly, using the latest cost-benefit techniques. This contract is also being supported under an interagency agreement with the Assistant Secretary of Planning and Evaluation, DHHS. The Health Expenditures Model shall be estimated simultaneously with the Consumer Expenditures Model to provide one consistent demand system.

A contract entitled "Update and Revision of the Macroeconomic-Demographic Model" (AG-84-05) was awarded in September 1984. It has also been extended to FY86 in order to coordinate its activity with the consumer and health expenditure modeling. The original NIA/MDM was completed in 1981 and is obsolete because of new data and changes in social security and private pension legislation. This proposed contract has been coordinated with the Office of the Assistant Secretary for Planning and Evaluation, DHHS, who is particularly interested in

the analysis of social security. We shall also update and rewrite a previously planned publication on the future of the retirement income system.

Microeconomic research has focused on wealth studies. Dr. Cartwright and Dr. Robert Friedland, Health Economist at Employee Benefits Research Institute (former temporary Demography and Economics staff member), are publishing in the September issue of the Review of Income and Wealth an article entitled "The President's Commission on Pension Policy Household Survey 1979: Net Wealth Distribution by Type and Age." George Washington University has accepted the dissertation research proposal of Mr. Alfred Drummond, Assistant Professor at Goucher College and temporary Demography and Economics staff member. Dr. Cartwright and Mr. Drummond have initiated work to study the wealth-age profile with the inclusion of rights to private pensions and social security.

A pilot study entitled "Evaluation of Senile Dementia Costs" (AG-3-2123) has been completed. This is a pilot study that led to the preparation of the following papers:

- Economic Costs of Senile Dementia: Issues and Recommendations (Cartwright, Hu, and Huang)

- Evaluation of the Costs of Caring for the Senile Demented Elderly: A Pilot Study (Hu, Huang, and Cartwright)

- Cost of Illness and the Elderly (Cartwright, Hu, and Huang)

- The Economic Cost of Senile Dementia in the United States, 1983 (Huang, Hu, and Cartwright)

- A Review of Prevalence and Incidence of Senile Dementia Among the Elderly Population (McDonnell, Hu, and White)

These have been provided to the Senate Select Committee on Aging and to the Office of Technology Assessment. We are attempting to publish the papers. Two of the papers are under review.

Professor Karen Davis from Johns Hopkins delivered a computer model for the EDB IBM/XT under professional services contract No. 263-MD-504549. The computer model provides an interactive graphical display of trends in the elderly which will be useful to depict long-term trends on future health needs, health conditions, and economic factors. European trends may be examined and compared to U.S. trends.

Demography and Economics Office Research Highlights, FY 1985

° Contract AG-4-2107 "Update and Revision of the Macroeconomic-Demographic Model" has been awarded to ICF, Incorporated. This project will lead to a number of important publications on the future of the retirement income system and social security.

- An RFP No. NIH-AG-84-19 "Household Formation, Housing, and the Aging Population" was completed and issued. An award was made to ICF, Incorporated.

- The article "The President's Commission on Pension Policy Household Survey 1979: Net Wealth Distributions by Type and Age" is published. Net wealth for those 65 and over was $61,957 which includes imputed value of employer-based pensions, but no social security values.

- An evaluation of the costs of senile dementia has been completed. Total direct costs are estimated to be 38.4 billion dollars. Of this, community home care costs were 26.7 billion dollars.

- An RFP No. NIH-AG-85-12 "Microeconomics of Aging, Health Status and Conditions, and Health Expenditures" was completed and issued.

- Joseph Anderson and Emmanuel Thorne, investigators on "Health Expenditures and the Aging Population" (AG-2-2138), presented a research paper entitled "Estimates of Aggregate Personal Health Care Expenditures in 1980--Comparisons of the National Health Accounts and the National Medical Care Utilization and Expenditures Survey Data" to the National Center for Health Statistics. The National Medical Care Utilization and Expenditures Survey (NMCUES) accurately captured household sector payments, but differences exist in government payments in comparing the two data sources.

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 and integrated 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. The contractor is required to acquire existing data bases for utilization in the modeling.

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 must be continually studied. For example, the health and welfare of the elderly will be affected both by the evolution of the economy and the income security system. The current NIA model has previously focused on retirement income issues and is now being developed in the area of a detailed health expenditures model.

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 model shall permit an examination of the implications of an aging population in the United States.

CONTRACT

Name and Number: ICF Incorporated (NO1-AG-3-2117)

Title: Aging, Health, and Consumer Expenditures

Date Contract Initiated: September 13, 1984

Current Annual Level: $20,363

Objectives: This research shall investigate the determinates of consumer behavior and the interrelationship between health and other consumer expenditures. The research shall represent an expansion of the NIA Macroeconomic-Demographic Model (MDM) (Contract No. NO1-AG-0-0024) that projects the U.S. economy and details of the retirement income system. The research shall be useful for investigating population aging and other economic phenomena directly related to aging research issues.

Methods Employed: Within the new consumer model, prices, income, family size, age of household head, region of residence, race, and type of residence will be among the determinants of consumer expenditure shares. The model shall be implemented from the latest available data and shall include both cross-section and time-series data. Particular attention shall be placed on the allocation of expenditures by households with different ages for household head and other demographic characteristics. In addition, the determination of health expenditure shares shall consider cost-sharing arrangements that include governmental programs, private insurance, and out-of-pocket expenses. The consumer expenditure model shall be integrated with the NIA MDM and the detailed model being developed of health expenditures. A base case consistent with the NIA model shall be established for the simulation model and used for investigating such effects as population and policy change on the welfare of the elderly and a comparison of such effects to other nonelderly groups.

Major Findings:

Significance to Biomedical Research: The NIA supports a unique MDM that 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 must be continually studied. For example, the health and welfare of the elderly will be affected both by the evolution of the economy and the income security system.

Proposed Course: This contract was extended for one year. The purpose of this research is to dissaggregate consumption by age in the MDM so that the effects of the aging population may be examined with particular attention to the aggregate share going to health care services. We shall examine the effects of public policy on the welfare of the elderly, using the latest cost-benefit techniques. This contract is also being supported under an interagency agreement with the Assistant Secretary of Planning and Evaluation, DHHS. The Health Expenditures Model shall be estimated simultaneously with the Consumer Expenditures Model to provide one consistent demand system.

CONTRACT

Name and Number: ICF, Incorporated (AG-4-2107)

Title: Updating and Revising the Macroeconomic-Demographic Model

Date Contract Initiated: September 26, 1984

Total Cost of Contract: $250,000

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. There are ongoing contracts to develop health and consumption expenditures modeling that shall add equations to the computer simulation model.

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 civil service retirement system.

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.

CONTRACT

Name and Number: Applied Systems Inst., Inc. (NO1-AG-5-2107)

Title: Microeconomics of Aging, Health Status and Conditions, and Health Expenditures

Date Contract Initiated: September 23, 1985

Current Annual Level: $100,000

Objectives: The specific objective of this contract is to focus on the microeconomic analysis of aging and health, i.e., the health status and condition of the elderly and their health care demand. This work will involve reviewing the relevant litreature on aging and health economics, estimating the effect of health status and health conditions, as well as other independent variables on health utilization, and analyzing the results with regard to the elderly population and their health needs.

Methods Employed: The work performed under this contract is of a scientific and technical nature and directed to understanding health expenditures in the elderly population. An important aspect of health expenditures is understanding the role of health status and health conditions in the demand for health care by the elderly. Therefore, a careful development of the joint demand for insurance and health care must be done along with consideration of such aspects as Medicare, Medicaid, and Private Supplemental Insurance. The simulation model will be developed to explore the various aspects of health expenditures with respect to prices, income, private insurance programs, Medicaid, and demographic groups. Such notions as risk spreading and resource allocation are particularly important as well as the implications of elderly welfare and the role of private and governmental insurance markets. In addition, an empiracal model of elderly health expenditures will be developed and estimated with data available from cross sectional surveys such as the National Medical Care Expenditure Survey, National Medical Care Utilization and Expenditure Survey, and National Health Interview Survey. Thus, analysis will be done on publicly available data resources and no primary collection of household survey data will be made. The results of the simulation modeling and econometric modeling shall be presented in final reports.

Significance to Biomedical Research: The NIA/EDB Program is already supporting the development of a health expenditures model for the NIA Macroeconomic-Demographic Model of the U.S. economy. This work emphasizes a population aging focus within a macroeconomic framework. The current work requested focuses on microeconomic considerations in the health market for the elderly.

Proposed Course: The contractor will review the literature in aging and health economics in order to evaluate the state-of-the-art and current aging issues and will provide a literature search and a report systhesizing the various issues. The contractor will also develop and supply a theoretical model of the demand and supply for health services. The model will focus on both societal and individual distinctions. The theoretical model will examine risk and health attributes for individuals identified as belonging to various demographic groups, but with particular attention to elderly groups.

CONTRACT

Name and Number: Applied Systems Inst., Inc. (NO1-AG-3-2123)

Title: Evaluation of Senile Dementia Costs

Date Contract Initiated: June 1, 1983

Total Cost of Contract: $74,283

Objectives: The purpose of this evaluation is to examine the NIA's program for senile dementia research in the context of determining the cost of this disease and the implications for the nation's overall commitment to biomedical research on this disease.

Methods Employed: The investigator shall evaluate the cost of illness methodology and in particular the general problems involved in application to the population, 65 years of age and older. The investigator shall identify unique cost elements of senile dementia that distinguish it from other diseases. This shall involve examining such costs as those that are incurred by the health delivery system, the patients, the family, and society. In this stage, specific case studies shall be used to highlight problems for policymaking in settling research priorities. Based on this research, and also other sources of national and community data on senile dementia, the investigator shall estimate a national cost of senile dementia. Finally, the investigator shall report recommendations with regards to the cost of illness methodology, the NIA research program, and the extent and quality of data.

Major Findings: An evaluation of the cost of senile dementia has been completed. Total direct costs are estimated to be 38.4 billion dollars. Of this, community home care costs were 26.7 billion dollars.

Significance to Biomedical Research: The NIA is deeply involved in stimulating and actively doing research in senile dementia. This disease is tragic as it proceeds through stages to severe memory loss, disorientation, general decline in mental functions, and finally death. Currently, there is no thorough evaluation of the cost of this illness, and data often is not sufficiently detailed to create easily cost elements.

Proposed Course: This pilot study led to the preparation of the following papers. These have been provided to the Senate Select Committee on Aging and to the Office of Technology Assessment. Publication of the papers is planned. Two are under review.

Cartwright, W.S., Hu, T., and Huang, L. Economic Costs of Senile Dementia: Issues and Recommendations
Hu, T., Huang, L., and Cartwright, W.S. Evaluation of the Costs of Caring for the Senile Demented Elderly: A Pilot Study
Cartwright, W.S., Hu, T., and Huant, L. Cost of Illness and the Elderly
Huang, L., Hu, T., and Cartwright, W.S. The Economic Cost of Senile Dementia in the United States, 1983

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 01055 04 EDBP

PERIOD COVERED
October 1, 1984 to September 30, 1985

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Retirement Income System Research with MDM

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

William S. Cartwright, Ph.D., Chief,
Demography and Economics Office, EDBP, NIA

COOPERATING UNITS *(if any)*

LAB/BRANCH
Demography and Economics Office

SECTION
Epidemiology, Demography, and Biometry Program

INSTITUTE AND LOCATION
NIA, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.10	.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.)*

The NIA enters into an agreement with the Assistant Secretary for Planning and Evaluation (ASPE) for the purpose of research on pensions, retirement, and labor force as well as issues involved in integration of micro and macroeconomic models. We have supported the revision and reestimation of the labor market model and simulation studies of the labor supply of the elderly.

We have received a detailed proposal specifying the work to be undertaken. A new version of the Pension Model has been prepared and delivered to NIA's MDM.

PHS 6040 (Rev. 1/84)

GPO 914-918

Overview of Biometry Office

The FY 1985 activities and achievements of the Biometry Office parallel those of previous years, including initiation and maintenance of intramural and contract-supported research, as well as continued methodological consultation and statistical support for research programs conducted by other EDB offices, other NIA programs, and organizations outside the Institute. An increasingly large share of Biometry Office resources (staff and budget) is consumed with a variety of data management activities and statistical computing in support of the EPESE and NHANES I Epidemiologic Followup projects, the two largest data-producing projects of the Program. In recognition of the importance of these latter functions, we have recruited a computer programmer, Ms. Bette Pollard, to replace Ms. Mary Beth Grigson who left the Program in FY 1984. Ms. Pollard is working as an assistant to Ms. Mary Lafferty, our Data Manager, in the preparation of much of our data for analysis. In addition, Ms. Pollard has been named the EDB lead user for the IBM PC/XT and is performing a variety of tasks involving novel applications of the PC to the work of the Program as well as training EDB staff in its use. Aside from this one change in personnel, the Biometry Office staff has remained the same.

As mentioned above, our involvement in data management and statistical analysis of data from the EPESE projects continues at a high level. The EPESE Resource Data Book is now nearing completion, with all tabular and graphical material having been finalized. Draft texts for all the chapters have been completed and all but one chapter have been reviewed by the EDB review group (Dr. Huntley, Dr. Brock, and Ms. Lafferty) and approved for publication by the EPESE Principal Investigators. The remaining chapter is being reviewed, and the technical appendices, including fitting of generalized variance functions to the Yale data by Mr. Everett, are underway. As work on the baseline survey data book winds down, activity is beginning to pick up in other aspects of the EPESE projects. We have received data tapes from each of the three centers containing the first and second telephone followup interview data. In addition, we have also begun to receive endpoint data tapes from the three locations, including data on hospitalizations, nursing home admissions, and mortality. Cause-of-death information was included on the mortality tape, having been coded by the nosologist for the state of Iowa under a professional services contract initiated by the Biometry Office. The coding activity will continue as deaths occur in the three populations. This will require further EDB support through additional professional services contracts with the nosologist.

The arrival of the first endpoint data marks the beginning of another activity with the EPESE data, namely "core" analyses to be done collaboratively by the investigative teams and EDB staff. Several committees have been appointed to conduct these core analyses in the areas of mortality, hospitalization, nursing home utilization, and disability. For each endpoint topic an overall coordinating committee has been appointed, with subcommittees established for analyses relating various exposure data for the particular endpoint of interest. Dr. Brock has been named chairman of the mortality endpoint coordinating committee which also has responsibility for analyses relating demographic

characteristics to mortality. This group will oversee the work of five subcommittees relating various exposure characteristics to mortality. The committee met in July 1985, to make plans for the analysis of demographic characteristics and outline steps to be taken in completing the analysis. Mr. Foley is a member of the coordinating committee for core analysis of disability as an endpoint. He is currently developing an index of disability for possible use in the core analysis.

The Biometry Office staff continues its involvement in several other aspects of the EPESE projects. Dr. Brock continues as chairman of the Documentation Committee which met twice during the year. This group, with considerable work and input from Ms. Lafferty, has developed common specifications for formatting the baseline survey, telephone followup surveys, mortality, hospitalization, and nursing home data sets. With the award of a contract to Duke University for a fourth center, it will be necessary to orient that group to the activities of this committee and work closely with them to insure standardization of procedures, documentation, formatting, and data management across all the centers. In other areas of EPESE, Ms. Cruz continues as staff liaison to the Publications Committee, and Mr. Foley continues to apply his expertise in the means and methods of obtaining Office of Management and Budget (OMB) clearance of survey forms and documents, although Ms. Campbell is gradually assuming those responsibilities. Finally, Dr. Brock has been Project Officer for a professional services contract to study patterns of incomplete responses in the Iowa baseline survey, and he has been asked to participate in a study of the characteristics of refusals in the East Boston location.

In early 1985, the EDB Program received the data tapes for the full data collection of the NHANES I Epidemiologic Followup Survey. Since that time, data management and analytic activities have increased substantially. Many of the working groups formed earlier (with receipt more than a year ago of the data from the Northeast Region) have begun to meet and divide up the work involved in carrying out literally dozens of analyses on these data. National Cancer Institute staff have generously offered to share computer files they created from the raw data to help save expenses of on-line storage. Ms. Lafferty is working closely with NCI staff in this effort. Analyses already under way span a wide variety of topics including height, weight, other anthropometry, functional ability, blood pressure, arthritis, and a host of other exposure and endpoint variables. Data analysis for drafts of two papers on hearing loss has been completed by Ms. Losonczy. Working with a group from the University of Iowa, she has conducted analysis to relate hearing loss and bone density. In the other paper, methodological comparisons between pure tone audiometry and self-assessment hearing scales were made. Mr. Everett has been involved in analyses of weight and weight history, arthritis, and blood pressure. A group headed by Dr. Brock is beginning an analysis of the circumstances of death as ascertained from proxies of individuals in the original NHANES I who died before the followup study was done. Many of the questions in this latter analysis were included in the Survey of the Last Days of Life which will be discussed below. As in the past, Ms. Cruz continues to serve as the EDB staff person responsible for tracking abstracts for the NHANES I Followup Publications Committee. This is similar to the work she does for the

EPESE Publications Committee. The topic of nutrition, one of the most unique aspects of this study, is the subject of a professional services contract initiated by Mr. Everett of our staff. The purpose of this first project is to achieve commonality between the NHANES I and Followup food groupings and to examine eating patterns in the elderly. We anticipate a good deal of further work in this area after the completion of this beginning effort.

As mentioned above, the Survey of the Last Days of Life (AG-2-2137) has continued throughout FY 1985. After a lengthy delay in obtaining OMB clearance of the questionnaire in 1984, a pretest was conducted in the study area (Fairfield County, Connecticut) in the summer of 1984. Analysis of the pretest results showed that the basic methodology of approaching the informant 3 months after the death of the decedent would elicit the response required for successful conduct of the study. Further results of the pretest showed that some changes in the questionnaire would be necessary to eliminate awkward sequencing and high incompletion rates for some questions. After revisions were made the study went into the field in January 1985. At a recent site visit to DMH Associates, the fieldwork contractor in New York City, it was learned that excellent progress is being made in the data collection phase of the study. Close examination of the first two months' data showed that response rates are continuing at an 85 percent level and the data are showing the same kinds of patterns expected based on the pretest data. We anticipate that the fieldwork will continue until March 1986, and that data will be available for analysis in the fall of 1986.

Dr. Brock continues to serve as a member of the interagency consulting group for the National Mortality Followback Survey (NMFS) being conducted by the National Center for Health Statistics (NCHS). This survey, based on a national probability sample of 20,000 deaths, is designed to collect information from the next of kin listed on the death certificate. Topics for the survey include health care in the last year of life, lifestyle factors and the risk of "premature" death, socioeconomic differentials in mortality, and the quality and reliability of non-cause-of-death items on the death certificate. Because of the similarity between this study and the Survey of the Last Days of Life (see paragraph above), we executed an interagency agreement with NCHS this year to support the study (AG-5-0057). As a result, questions on nursing home utilization and cognitive function taken from our Last Days of Life questionnaire are included in the NMFS and will be available for providing national norms to which we may compare our data. At this time, a pretest has been conducted and, although final results will not be available for some time, preliminary indications are that the methodology and questionnaire appear to work well. Plans call for the analysis of the pretest and revision of procedures to be completed in the fall and the main study to begin in January 1986.

Our interest in the National Nursing Home Survey (NNHS) has continued in FY 1985. Following the pretest in 1984, it was decided to be infeasible to implement a full admissions cohort to be followed over time as part of the 1985 NNHS. Instead, NCHS is implementing collection of information on the next of kin component to be used to describe the nursing home utilization patterns of

persons admitted to nursing homes in a specific time window. As with the NMFS, we have supported this study with an interagency agreement (AG-5-0062).

Our previous work in analysis of national mortality data for U.S. elderly is currently being updated. Dr. Brody presented the latest available mortality and morbidity data on cancer in the elderly at a recent meeting in Israel. Mr. Everett is continuing to work on the analysis of those data. In addition, Dr. Brock has been asked to update two chapters recently published on epidemiologic and statistical characteristics of the U.S. elderly population. Further, we are developing a professional services contract to reopen the topic of climatic extremes and mortality in the elderly, a subject which was being actively pursued by Dennis Cosmatos until his leaving the Program in 1983.

Two other topics deserve mention in this report. As clearly indicated earlier in this narrative, a great deal of effort is going into analyses and studies based on the NHANES I and its associated Followup Survey. Since this study was originally designed as a complex sample survey, the assumptions required for standard statistical analysis techniques are not met or, in some cases, even approximately met. Therefore, to make optimum use of these data, considerable work in methodology development needs to be done. The National Institute of Child Health and Human Development (NICHHD) has recently signed a contract with Research Triangle Institute, an experienced and reputable firm in survey research, to study and develop methods for performing regression analyses on complex survey data. Since this topic is highly relevant to our needs in analyzing NHANES, and since one of the products of this work will be software to be applied to these data, we are proposing to join with NICHHD through an interagency agreement to support this research and extend the scope to topics highly relevant to NIA interests. The other topic of interest in this area is longitudinal data analysis, especially as it may apply to our EPESE data. We are developing a professional services contract to evaluate specific ways of analyzing longitudinal data, specifically to assess the "bootstrap" as a tool for the study of longitudinal data in estimating the degree of a polynomial, in finding simultaneous confidence bands for a repeated response at all time points, and to estimate the distribution of a new test for trend. It is our belief that these developments, while mathematically complicated, will make our data even more useful.

Biometry Office Research Highlights, FY 1985

- Developmental work on the Survey of the Last Days of Life (Contract No. NO1-AG-2-2137) was completed early in FY 1985. Analysis of pretest results demonstrated the feasibility of contacting the death certificate informant and obtaining satisfactory responses to interviews to learn about the decedent's last days of life. Numerous revisions to the questionnaire were made following the pretest, and they have proven to be valuable modifications to the main study which went into the field in January 1985. To date, the data collection has gone very well and preliminary results from the main study corroborate what was found in the pretest, namely, the ability to locate a knowledgeable respondent for virtually all cases; a high degree of cooperation from respondents, physicians, and health facilities; and low rates of item nonresponse and missing data.

- Data management activities have been completed for the EPESE baseline survey Resource Data Book. All tabulations and graphical materials have been finalized and approved for publication by the principal investigators. All text chapters, save one, have been completed and approved for publication. With the completion of this work, data management activities will be shifted to the two telephone followup surveys, the hospitalization and nursing home data, and the mortality surveillance data.

- Biometry Office staff have been named to two coordinating committees for "core" analysis of EPESE endpoint data, one on mortality and the other, disability. The mortality committee has met and made assignments for a group of papers to be written on the relation between demographic factors and mortality for the first 2 years' surveillance data. We anticipate completion of this work in FY 1986.

- The first collaborative analysis of EPESE baseline data was published in FY 1985. This paper discusses methodologic issues and preliminary findings on the epidemiology of disability in the oldest old for the first three EPESE locations. Biometry Office staff provided the analysis and discussion on physical functioning.

- A professional services contract (No. 263-MD-432151) was completed to examine nonrandom item nonresponse for the Iowa EPESE baseline survey. The investigator adapted weighted least squares (WLS) analyses for categorical data to identify factors related to the probabilities of nonresponse for bowel and bladder problems, the CES-D Depression scale, and cognitive recall data. For the bowel and bladder questions, nonresponses were explained as separate functions of age, education, and marital status, depending on which questions were examined. Many of the CES-D questions had item nonresponse rates characterized by age-sex interactions, and virtually all responses from females were affected by the age of the respondent. The cognitive recall data are far more complicated in the types of nonresponse due to higher overall percentages of incomplete response as well as a variety of types of nonresponse ("unable to participate," "don't know" responses, and refusals). Eight analyses were performed on these data, providing a variety of informative results on nonresponses and how to deal with them. In summary, the WLS analyses conducted here provide the simultaneous treatment of the different types of nonresponse, with each type retaining its own identity, so that biases are not recognizably pooled, and the technique allows for the identification of separate cross-classifications for imputation classes, creating more stable estimation procedures for each type of item nonresponse. It is concluded that imputation for missing values is a viable technique for remedying the incomplete data due to item nonresponse in the Iowa study. We believe similar results may apply to the other studies as well.

- The final data tapes for the NHANES I Epidemiologic Followup Survey arrived in EDB in the middle of FY 1985. A number of analyses involving Biometry Office staff have begun, with writing committees established for collaboration among several NIH Institutes and the National Center for Health Statistics. Draft papers have been completed on two studies involving hearing ability, one related to bone density and the other comparing three methods of obtaining data on hearing loss. Analyses are under way in the areas of weight and weight history, functional ability, mortality as related to a variety of predictors, and the circumstances of death.

- A professional services contract (No. 263-MD-504816) was awarded to study eating patterns in the elderly based on food frequency data from the NHANES I and the Followup Study. The investigator has established rules for comparing food groupings from the two surveys. Although they were not based on the same questions at baseline and followup, they can be used for comparison of dietary behavior over time. Principal components analyses were used to establish seven patterns of food groups which explain a majority of the variance in food groupings. These analyses will be used to compare eating patterns for the NHANES I versus the Followup, men with women, age groups 55 to 64 with 65 to 74 (at baseline), married versus non-married (i.e., all other marital status categories) elderly, and black versus white elderly.

- A professional services contract (No. 263-MD-523425) awarded to analyze NHANES I Epidemiologic Followup Survey data relating self-assessment of fatigue and of health to dietary patterns will be matched to the original NHANES I data. Changes in self-assessment of fatigue and of health will be related to each other and to dietary changes. Specifically, the hypothesis that constant fatigue indicates potential health problems and that self-assessment of health is a good indicator of health-status is related to dietary intake.

- An interagency agreement (AG-5-0057) was signed with the National Center for Health Statistics to support the National Mortality Followback Survey (NMFS). This is a study of characteristics of a national probability sample of 20,000 decedents whose next of kin will be surveyed via mail questionnaires to collect data on health care use in the last year of life, lifestyle and risk factors for "premature" death, socioeconomic differentials in mortality, and the reliability of certain non-cause-of-death items on the death certificate. This study bears a strong relationship to the Survey of the Last Days of Life and will permit investigation of associations between risk factors and lifetime prevalence of diagnosed dementia, as well as the lifetime history of nursing home admissions. The survey is being pretested at the present time, with the main study scheduled to begin in January 1986.

- An interagency agreement (AG-5-0062) was signed with the National Center for Health Statistics to support a study of nursing home admissions in the National Nursing Home Survey (NNHS). The original proposal to establish an

admissions cohort to be followed for a period of time as a part of the NNHS was evaluated in a pretest conducted in 1984. The results of that study indicated that it was not practically feasible to embed in the NNHS such an admissions cohort to be followed over time. Instead, the NCHS will identify, for a sample of nursing home residents, a next of kin for the sample resident who will be interviewed concerning the resident's history of nursing home admissions up to the time of the NNHS. In this way, it will be possible to establish, retrospectively, patterns of admission, discharge, and length of stay for a representative sample of persons admitted to nursing homes.

CONTRACT

Name and Number: DMH ASSOCIATES, INC. (NO1-AG-2-2137)

Title: Survey of the Last Days of Life

Date Contract Initiated: September 30, 1982

Total Cost of Contract: $475,550.

Objectives: The purpose of this project is to collect descriptive data on the last days of life for a community sample of persons age 65 and older whose deaths occurred in a one-year period. In addition to providing specific data on basic events and circumstances surrounding death, the study will provide lifetime prevalence data for a set of conditions related to, but not necessarily causing death. The new knowledge gained from this study will be extremely valuable in relieving the burden of anxiety on family, friends of the dying person, and to providers of care.

Methods Employed: A sample of death certificates will be selected over a period of one year in Fairfield County, Connecticut. Retrospective information concerning the decedent's last days of life will be obtained in a face-to-face interview with an informant identified from the information contained on the death certificate. Followup information will be obtained from medical sources identified by the informant for those cases in which it is appropriate.

Current Status/Major Findings: The pretest was completed in June 1984 with an overall response rate of 85 percent and successful location of a knowledgeable informant for each responding case. Thus, the feasibility of our approach to the study has been established. The pretest data have been analyzed, appropriate modifications have been made in the questionnaire and procedures, and the main field work began in January 1985. Two papers have been presented to the American Statistical Association meetings describing the design and pretest results.

Significance to Biomedical Research: A considerable body of literature exists in the geriatric and psychological fields as well as in the lay press about dying. Yet specific data about basic events associated with dying are lacking --such as who dies peacefully in his/her sleep, who dies in great pain, what persons are present at the time of death, who dies after a long illness with full awareness of his impending demise, and who dies suddenly with no warning. Further, the proportion of the dying who need and actually receive pain medication is unknown. The study will provide an opportunity to obtain epidemiological data on the numbers of persons affected by the major health conditions that confront the dying elderly as well as the lifetime likelihood of certain events and conditions such as blindness, deafness, dementia, hip fracture, and others.

Proposed Course: After revisions to the originally tested questionnaire were made the study went into the field in January 1985. Excellent progress is reported being made in the data collection phase of the study. Close examination of the first 2 months' data showed that response rates are continuing at an 85 percent level and the data are showing the same kinds of patterns expected based on the pretest data. We anticipate that the fieldwork will continue until March 1986, and that data will be available for analysis in the fall of 1986.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 06060 01 EDBP

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

National Mortality Followback Survey

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

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:

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 survey will provide information on the characteristics of decedents and on the circumstances associated with their deaths that would supplement existing information on the death certificate. Specific areas to be studied include socioeconomic differentials in mortality, risk factors associated with what NCHS refers to as "premature" death, health care in the last year of life, and reliability of certain items reported on the death certificate. Through this interagency agreement NIA would be providing support to enrich the NCHS survey in those areas of importance to NIA research goals. Specifically, we are interested in obtaining national data concerning those characteristics of elderly decedents related to cognition, and the use of health care in the last year of life. A nationally representative sample of deaths could provide much needed data on the proportion of decedents showing signs of cognitive impairment, or decedents who were reported by their proxies to have been diagnosed by a physician to have had Alzheimer's disease or other dementing illness. This would provide better information than has been previously available on the relationship between dementing illness, cause of death and associated risk factors. In addition, these data will complement and enhance community-level data on similar topics being collected for NIA in the Survey of the Last Days of Life.

PHS 6040 (Rev. 1/84) GPO 914-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 06050 02 EDBP

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Pretesting of the 1984 National Nursing Home Survey

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

Daniel J. Foley, EDBP, NIA
W. Edward Bacon, Ph.D., Director, Division of Health Care Statistics, NCHS

COOPERATING UNITS *(if any)*

National Center for Health Statistics

LAB/BRANCH

Biometry Office

SECTION

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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 interagency agreement between NIA and NCHS covers the cost of work to be done by NCHS in developing and implementing survey instruments and procedures for the 1985 National Nursing Home Survey. This agreement is to reimburse the Center for costs related to the collection of information on the Next of Kin Component to be used to describe the nursing home utilization patterns of an admissions cohort. All necessary clearance and sampling procedures will be developed by NCHS; all data collection and followup will be performed by a contractor under the direction of NCHS. NCHS will provide NIA with an analysis of the survey data identifying the characteristics and utilization of an admission cohort.

PHS 6040 (Rev. 1/84)

GPO 914-918