REVIEW OF GOVERNMENT SUPPORTED RESEARCH ON AGING

Prepared by
The National Institute of Child Health
and Human Development
National Institutes of Health
in cooperation with
other Government Agencies

VOLUME I

BODY OF REVIEW

APPENDIX A

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

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INTRODUCTION

On September 26, 1966 the Committee on Government Operations issued House Report #2080 recommending that NIH, in cooperation with other Government agencies, review medical research in aging especially long-term studies with regard to gaps, duplications, and balance; prepare an action program to correct any deficiencies; and report the action taken to the Committee. This report represents the recommended activity conducted by the staff of the National Institute of Child Health and Human Development (NICHD) in cooperation with other Government agencies.

In order to identify Government-supported medical research on aging, the staff of NICHD in the summer of 1967 met individually with Government agencies that might support medical research on aging. Those agencies are listed in Appendix A.

In those meetings it became apparent that the review could best be considered in two parts; one consisting of Government-supported programs of medical research on aging -- each program containing many individual projects; the other consisting of longitudinal studies of aging in humans.

The agencies with programs of medical research on aging gave NICHD abstracts of relevant individual projects. The agencies with longitudinal studies of human aging supplied NICHD with descriptions of those studies. A conference on longitudinal studies on aging, supported by NICHD contract at Duke University, produced much information and opinion of value for the review.

The text of the review was prepared by NICHD in cooperation with the other involved agencies and circulated twice in draft among those agencies before being placed in final form.

SUMMARY OF FINDINGS

1. Research on aging processes is important to the health and welfare of the population of this country.

2. Research on all medical aspects of aging is underdeveloped and undersupported.

3. There is no unwarranted duplication in research on aging.

4. The populations investigated in longitudinal studies are different, but the functions studied are in many cases similar or identical. This study of similar or identical functions in different populations is desirable. However, the methods used are not identical. This is unfortunate since it makes the comparison of the same functions in different populations difficult.

5. There are a number of major problems connected with longitudinal studies that have not been satisfactorily solved. These problems involve population sampling, standardization of methodology, data reduction and storage, and methods of statistical analysis.

ACTION PROGRAM

1. The responsible Government agencies will continue programmatic activities to correct the existing gaps and imbalances and to prevent the development of unwarranted duplication in their programs of medical research on aging.

2. Every Government agency with a program of medical research on aging will store abstracts of the medical aging research it supports in the Adult Development and Aging Information Center of NICHD. Those abstracts will be periodically collated and analyzed by NICHD and other involved agencies as they were in this review. The results of these reviews will be distributed to the involved agencies and to interested investigators.

3. NICHD will hold periodic conferences for the interchange of ideas among agencies and investigators involved in longitudinal studies on medical aspects of aging with regard to the many common problems they face. NICHD will periodically review existing longitudinal medical studies of aging with regard to duplication, gaps, and imbalances.

4. The agencies involved in this action program will evaluate the action program at intervals to determine whether it should be modified.

AGING PROCESSES AND THEIR RELATIONS TO DISEASE PROCESSES

With increasing age humans lose functional capacity and eventually develop impairments from environmental damage or genetic defects that lead to death. These, medical science calls diseases. However, even in the absence of what can be identified as disease, all men who live long enough suffer great loss of functional capacity. This loss begins early in adult life and continues throughout the lifespan. For the purpose of this report, this universal, gradual loss of function through unknown mechanisms is defined as aging. When the word "aging" is used in this review to refer to a biological process, it will denote this universal process just indicated rather than cumulative damage due to identifiable disease processes.

Several types of biological processes occur with chronological aging:

1. There is the progressive loss of functional capacity of unknown origin that has just been described.

2. As a result of progressive loss of functional capacity, reduction in resistance to disease occurs. Resistance becomes so low that the elderly die of stresses that would not have killed them when they were younger.

3. Aging processes may themselves produce changes that are classified as diseases. For example, many cases of cataract formation may represent the end result of normal aging.

4. Cumulative damage due to prolonged exposure to environmental stress may produce disease. For example, prolonged exposure to sunlight may produce skin changes that were once considered part of normal aging.

5. Certain genetic defects may become manifest late in life. The process of evolution tends to shift the expression of some genetic defects from early to later life.

Psychological changes with aging are important in health and disease. There are changes in sensory, motor, and cognitive function with increasing age the mechanisms of which are unknown. In addition, psychological changes occur in the process of adjusting to biological, psychological, and social changes. Both types of psychological change are important determinants of normal function and mental health.

SCOPE OF THE REVIEW

This review covers two general areas. One is Government-supported programs of medical research on aging consisting of many individual projects. The other is Government-supported, longitudinal, medical studies of human aging. Only research supported in fiscal year 1967 is included in the review. A fiscal statement on research on aging for that year is given in Appendix D.

Government programs of research on medical aspects of aging are defined as programs in which the research is intentionally limited to aging processes as such rather than disease processes. Research on disease processes is included in those programs only when the emphasis is on the fact that the subjects are aging or aged rather than on the disease processes themselves. Most of the research on disease processes currently being conducted will be of value to the elderly. Obviously this review should not include that research. Individual research projects that are supported by the Government but which are not part of a research program on aging are not included in this review. Since their relevance to aging is usually secondary, their inclusion would make this review too diffuse.

An attempt was made to identify and include in the review all Government-supported, longitudinal, medical studies of humans

in which the emphasis is on aging processes as defined in the previous section of this review. All such studies are included whether or not the supporting agency has any interest in aging as such.

Longitudinal studies in which the emphasis is primarily on disease processes are in general not included in the review. The inclusion of such studies would swamp the longitudinal studies on aging as such and would destroy the focus of this review on aging processes. Several studies with a strong emphasis on disease appear to be collecting information relevant to an understanding of aging processes and are therefore included in the review.

Most longitudinal studies on aging do include medical examinations to identify disease processes in their subjects. This is necessary since without a knowledge of concurrent disease, interpretation of changes in physiological and psychological function may be impossible. Other reasons for including thorough medical examinations in longitudinal studies of aging are the possibility of uncovering interrelationships between aging and disease, and the fact that in some instances it is impossible to distinguish between the effect of aging and the effect of disease.

INTERRELATIONS OF RESEARCH ON AGING WITH RESEARCH ON DISEASE AND OTHER RESEARCH

The research efforts important to an understanding of aging processes fall into several categories. Not all of these categories should be defined as aging research, but to omit them from this discussion would give an incomplete view of research in relation to aging.

Research on Disease

There are obvious relationships between aging and disease, making it possible for a scientist interested in aging to become involved in the study of disease and vice versa. The biochemical, physiological, and psychological changes that occur with increasing age increase susceptibility to disease. Some of these aging changes in their extreme forms are probably considered diseases of unknown origin. Conversely, some processes considered aging changes are probably due to unidentified environmental factors and may eventually be recognized as diseases.

Other Research

Research not intentionally oriented toward aging processes but nevertheless producing information of vital importance to an understanding of aging is extremely important for a clarification of aging processes. If understanding of aging processes develops

in a manner similar to that by which understanding of disease processes has developed, such work will be of major importance. Most of what is known about biological and psychological aging is rooted in knowledge derived from such research.

Conversely, research directed toward an understanding of aging may uncover processes that require further investigation to elucidate the mechanism involved. Thus investigation of some aspects of aging will produce results having broader implications than those related to aging as such.

THE VALUE OF RESEARCH ON AGING AND LONGITUDINAL STUDIES

Aging processes are of great importance both to the individual and to society: to the individual because of their effects upon his health; to society because of the effect of the population's age structure on the function of society.

Aging processes are as important to health as disease processes because aging processes eventually produce changes as detrimental to the health of the individual as disease processes. As preventive measures and methods of treatment for various diseases have been discovered, aging processes have become progressively more important relative to disease processes. This trend will undoubtedly continue. Changes in physiological and psychological function occur throughout the entire lifespan, and the changes that occur once adulthood is attained are in large part detrimental. There is need for research on aging over the entire span of the adult years and not simply on the events of the terminal years of life.

Studies to determine age-related changes in humans have to be made on a number of different persons of different ages (the cross-sectional procedure) or by repeated examinations of a group of persons over a period of years (the longitudinal method). Cross-sectional studies provide information descriptive of living persons of specific ages and provide it quickly. Purely longitudinal studies of persons born at the same time provide information which describes the changes in individual subjects through the years. Most longitudinal studies start with subjects of different ages and provide data which can be analyzed cross-sectionally initially, and longitudinally later.

The type of knowledge which permits present characteristics to be used to predict the future probability of developing disease or other characteristics can best be obtained from longitudinal studies. Inferences concerning the ultimate effects of environmental factors on humans can also best be made from longitudinal studies. Cross-sectional information is particularly important when decisions must be based on what persons are currently like.

Both types of studies contribute information for informed decisions regarding individual and societal welfare. For example, the policy of the Government and industry with regard to the employment and retirement of airplane pilots needs to rest on both cross-section and longitudinal information.

THE PROBLEM OF DUPLICATION

The possibility of duplications always exists in scientific research. In general, however, duplication is not to the advantage of the investigators involved since a scientist gets little credit for a "discovery" that has already been made. Thus investigators are motivated by their own self-interest to avoid unnecessary duplication.

Scientific research proceeds by individual investigators asking questions that are raised by current knowledge and can be answered with existing techniques. It is natural that when some outstanding, answerable question is seen, more than one qualified scientist may try to answer it. This accounts for the occasional appearance in the scientific literature of papers reaching the identical answer to some specific question. This sort of duplication could hardly be prevented without stifling research.

In addition, it is not really desirable to prevent it. Individual scientists are not infallible. Because of this, a given discovery is much more widely accepted as true if it has been confirmed by someone other than the original discoverer. Such confirmation is usually obtained by investigators in the course of following up implications of an original discovery.

This is not to say that it is impossible to have unnecessary duplication. If an ill-informed investigator sets out to determine something that is already known and well-confirmed in the literature, then unnecessary duplication results. Duplication of this type tends to be prevented by the review mechanisms of funding agencies since these review mechanisms involve scientists who are well-grounded in the areas under consideration.

For the purpose of this review, duplication was said to exist if two studies had essentially the same approach to essentially the same subject and would yield results that reinforced each other only by increasing the quantity (rather than the kind) of data bearing on that subject. As indicated in the section on the collation of research projects, essentially no duplication was found in the programs of medical research on aging supported by Government agencies.

In the analysis given in the section describing longitudinal studies, it was found that similar measurements were made in different populations in some of those studies. This is not duplication since different information will be obtained by the

various studies because of the differences in populations. This topic of similarity of measurements in different populations is discussed in the section on longitudinal studies.

COORDINATION OF RESEARCH

Government agencies supporting research on aging need to coordinate their programs and individual investigators conducting research on aging need to coordinate their efforts. Both types of coordination must be based on an adequate exchange of information.

Methods of coordination between Government agencies include frequent exchanges regarding the assignment of research grants and liaison attendance of review meetings of one agency by members of other agencies. Periodic review similar to the present one would be useful.

Coordination of the research of individual investigators is based on the exchange of information informally, in the scientific literature, and at scientific meetings. NICHD is augmenting the methods of information dissemination concerning aging by the creation of the Adult Development and Aging Information Center which will identify individual papers on aging research in the world's literature, abstract those papers, store the abstracts in a computerized system, and publish an abstract journal containing the collected information.

Since the publication of results from longitudinal studies is usually delayed for many years, special efforts need to be made to facilitate exchange of information between the involved agencies and investigators. One useful mechanism for this would be the establishment of periodic conferences. Periodic reviews similar to the present one would be useful in this connection also.

GOVERNMENT PROGRAMS OF RESEARCH IN AGING

There are five Government agencies that feel a responsibility for medical research on aging and that support programs in that area.

The National Institutes of Health with its broad mandate for medical research naturally conducts and supports through its Institutes much research on the body's organ systems and diseases relevant to health of persons in all age groups. A large fraction of the research supported by these Institutes is directly relevant to the health of young, middle-aged, and elderly adults. This research is considered disease-oriented research rather than research on aging.

At NIH research specifically oriented towards aging processes is conducted and supported by the National Institute of Child Health and Human Development. That Institute has an extramural program on aging administered by the Adult Development and Aging Branch and an intramural program on aging at the Gerontology Research Center. The latter is located on the grounds of the Baltimore City Hospitals. Both programs support research on biological, medical, and behavioral aspects of aging relevant to the health and well-being of the American people. The intramural research is done by NICHD scientists; the extramural is done under grants and contracts to scientists at research institutions, universities, and medical schools across the country.

The National Institute of Mental Health (NIMH) in line with its overall goal of improving the mental health of the people of the United States, has taken a particular interest in the aging in view of the fact that persons of advanced years are especially vulnerable to disabling mental impairment. The Section on Mental Health of the Aging, Division of Special Mental Health Programs, serves as coordinator and advocate for research on the mental health of the aging both outside the Institute and within the Institute's several Divisions. The Section has a specific program responsibility to develop knowledge and innovative services for the mentally impaired and to improve and sustain the mental health of the aging person through the NIMH extramural research, training, and service programs. In line with these two concerns, NIMH also supports research in psychopharmacology, the behavioral and social sciences, and clinical and biological sciences to generate greater knowledge of the mental health aspects of aging.

Because of the large number of elderly patients in Veterans Administration hospitals, that Administration has an interest in aging processes. Under its program a number of biomedical and behavioral aspects of aging are being studied.

The Atomic Energy Commission (AEC) is interested in the relationship between the effects of radiation and aging processes. It supports research by contracts in the National Laboratories and also by contracts with research investigators in universities and other settings. Radiation shortens the lifespan of animals. The research program of the AEC is concerned with whether this shortening is due to an acceleration of the natural aging process or to something fundamentally different.

The Health Services and Mental Health Administration (which now has the program supported by the Bureau of Health Services in fiscal year 1967) supports research grants to evaluate the quality of medical care to the elderly.

Brief descriptions of the individual research projects that in fiscal year 1967 made up the aging research programs of each of the above five agencies are listed by the agency in Appendix B.

The remainder of this section contains a collation of those projects according to content. The projects are organized into an outline which, although not exhaustive, covers many of the areas in which research might be undertaken. It therefore contains categories for which no research projects

are supported by Government aging programs. Each subdivision of the collation is headed by a brief statement concerning the area being investigated to place the listed research projects in perspective.

The preparation of this collation provided an opportunity to examine each individual research project at the same time as related projects were examined. These examinations made clear the fact that there was essentially no duplication of research. What is apparent from the collation is the inadequacy of the research effort on aging. In some areas there is no research being conducted and in no area is research being conducted by adequate numbers of investigators. There is some imbalance in that some areas are being investigated less than others of equal importance. However, at the current low level of activity, the important thing is not that there is imbalance but that there is too little research on all aspects of aging.

The structure of the collation is given in outline form below.

System for Collation of Research on Aging

Biology

- Organism
- Organ and Tissue Systems
  - Cutaneous System
  - Nervous System
  - Special Sensory Systems
  - Cardiovascular System
  - Respiratory System
  - Muscular System
  - Skeletal and Joint System
  - Connective Tissue System
  - Endocrine System
  - Alimentary System
  - Urinary System
  - Reproductive System
  - Blood, Lymphatic, and Immunologic Systems
- Cellular Systems
  - Cell
    - Cytoplasm
      - Cell Membrane
      - Ground Substance
      - Endoplasmic Reticulum
      - Ribosomes
      - Golgi Complex
      - Mitochondria
      - Lysosomes and Age Pigment

- Nucleus
  - Nuclear Membrane
  - Chromosomes
  - Nucleolus
- Tissue Culture
- Tissue and Cell Transplantation

Molecular Systems
- Proteins
- Enzymatic Proteins
- Lipids
- Nucleic Acids
- Free Radicals

Metabolism
- Nutrition
  - Calories
  - Proteins
  - Carbohydrate
  - Fat
  - Minerals
  - Vitamins
- Intermediary Metabolism
  - Total Energy Metabolism
  - Protein
  - Carbohydrate
  - Fat
  - Other
- Mineral Metabolism
  - Water
  - Sodium, Potassium, Magnesium, Chloride
  - Calcium, Phosphorus
  - Other

Pharmacology

Irradiation

Psychology and Social Science

Biological Bases of Behavior

Speed of Behavior

Sensation and Perception

Learning and Memory

Intellectual Performance

Psychological Adjustment

Psychopharmacology

Attitudes

Psychology of Retirement

Psychological Aspects of Housing

Disease

Health Services to the Elderly

Collation of Research on Aging

Biology

Organism

An important part of our knowledge of how man functions deals with his function as a whole individual. This organismic function involves the actions of the various organs of the body, the control of those actions, and the interactions between the various organs. The functional abilities of many organs of the body are known to decline with age. There is evidence that the overall function of the body declines at a much faster rate than the functions of its individual components. Little work is presently being conducted from the foregoing point of view. Several studies are listed here because they cover many organ systems.

W-7405-ENG-48 Durbin: Growth and Senescence of the Soft Tissue and Skeleton in the Normally Aging Female Rat

NICHD HD 00041 Getty: Gerontological Studies in the Dog and Hog

NICHD HD 00672 Lesser: Body Composition in Man - Aging and Obesity

VA Naumann: Chemical Changes of Aging

NICHD HD 01833 Glass: Lens Weight as an Age Determinant in Free-Tailed Bats

NICHD HD-AG 13 Meadow: Aging in the Rotifer

NICHD HD-AG 5 Norris: Age Differences in Body Size and Composition

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Organ and Tissue Systems

Cutaneous System

With increasing age there are striking changes in the skin and its derivatives: hair, sebaceous glands, and sweat glands. Some of the changes in exposed skin that were attributed to biological aging in the past are now known to be the result of exposure to sunlight. However, all of the changes that occur in aging skin cannot be so explained. Government programs of aging research support no research that is best classified here. However, there are several studies relevant to skin changes that are placed elsewhere in this collation.

Nervous System

Underlying many of the changes in mental functions with age are structural, physiological and biochemical changes in the brain. That organ decreases in overall size and microscopically this can be seen to be due in part at least to a loss of nerve cells. Changes occur in the microscopic structure of the cells. No doubt changes occur in the chemical composition and function of the cells, but little is known of such changes. Six studies of changes in nervous tissue are supported by Government programs on aging.

NICHD HD 00669 Edwards: Cell Death in the Insect Nervous System

NICHD HD 01491 Miras: Aging and Alpha-Hydroxy-Acid Decarboxylase of Brain

NICHD HD 02191 Kabara: Drugs and Brain Cholesterol during Development and Aging

AEC AT (04-1)-GEN-12 Mead: Effect of Aging and Irradiation of Brain Lipids

VA Simon: Performance on a Motor Steadiness Battery as a Function of Chronological Age with Older Normal Domiciliary Members

NIMH MH 01981 Kluver: Biological Mechanisms in Behavior

Special Sensory Systems

The special sensory systems serving vision, hearing, taste, and smell decline greatly in acuity with increasing age. Studies in this area are described in the collation under physiological psychology.

Cardiovascular System

With increasing age, the functional capabilities of the heart and blood vessels decrease. The ability of the heart to increase the rate at which it pumps blood and the ability of the cardiovascular system to supply blood to various areas of the body diminishes with increasing age. The analysis of the decrease in function due to aging processes is complicated by the high incidence of the diseases, atherosclerosis and hypertension. However, it appears probable that in addition to disease processes that affect the cardiovascular system of older persons there are aging processes that in themselves reduce functional capacity. Outside of long-term studies there are only four studies of cardiovascular function supported by Government aging programs.

NICHD HD 00672 Perl: Biophysical Studies of Kinetics of Circulation of Materials in Body

NICHD HD 02261 Strebel: Mechanism of Tissue Calcification in Aging

NICHD HD-AG 24 Shreiner: Work Performance of Rat Heart-Lung and Isolated Heart Preparation: Influence of Sex and Age

VA Pipberger and Freis: Demonstration of Aging Processes of the Cardiovascular System by Non-Traumatic Recording Methods

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Respiratory System

The respiratory system consists of the nasal passages, larynx, trachea, bronchi, and lungs. Its function is to move air into and out of the lungs so that oxygen can be absorbed into the body and the carbon dioxide produced within the body can be eliminated. With increasing age the rate at which this organ system can carry out its function is decreased. Several of the long-term studies include measurements of respiratory function. One study of respiratory function is supported by a Government aging program.

NICHD HD 00674 Williams: Degenerative Pulmonary Disease in Man

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Muscular System

The human muscular system transforms the chemical energy of food into mechanical work. With increasing age the muscular system atrophies, there are changes in its structure at a cellular level, and the ability of the muscles to transform chemical energy

into work diminishes. Some studies of the muscular capability of the body are conducted in long-term studies. Government aging programs support several studies of muscular function.

VA Murray: Studies of Normal and Abnormal Motion

NICHD HD 00669 Kohn: Aging Studies

NICHD HD 02586 Simonson: Physiology and Pathology of Fatigue

NICHD HD AG-4 Norris: Age Changes in Human Performance

Skeletal and Articular Systems

The skeletal system in addition to providing for body support and mobility through its component bones and joints, plays an important role in the calcium and phosphorus metabolism of the body and provides a tremendous reservoir for those elements. With increasing age, loss of the mineral elements and the organic components of bone occurs and fragility becomes a problem. Also, major changes occur in the joint structures and surfaces causing clinical problems. Government aging programs support studies on the chemical, structural, and functional changes that occur in the skeletal system with increasing age.

NICHD HD 00407 Jones: Radiographic and Pathologic Studies of Aging in the Primate Spine

NICHD HD 00510 Wickstrom: Responses of Bone to Changes in Age and Function

NICHD HD 00669 Klein: Study of Skeletal Collagen Metabolism

NICHD HD 00672 Schubert: Changes in Chemical Constitution of Cartilage with Age

NICHD HD 00674 Barland: Studies of Articular Tissues

NICHD HD 00674 Henneman: Osteoporosis and the Measurement of Growth Hormone in the Plasma

NICHD HD 01502 Tsaltas: Effect of Aging and Hormones on the Cartilage Matrix

NICHD HD 02033 Tappen: Structure and Function of Bone in Growth and Aging

NICHD HD 02119 Felts: Characteristics of Dental-Skeletal Aging

NICHD HD 02919 Lindsay: Age and Atrophy of Disuse

VA Abt: The Influence of Nutrition on Bone Healing

VA Rich: Versine Infusion Test in Osteoporosis

VA Schwartz: Clinical Physiology of Bone: Effect of Hormone and Vitamin D.

VA Thornton: Bone Tissue Metabolism as Influenced by Aging Factors

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Connective Tissue System

The materials between the cells form the connective tissue system -- the framework within which the cells live. Major components of this system are proteins and complex mucopolysaccharides. The protein found in greatest amount is collagen. Indeed, about 1/3 of the total protein of the body is collagen. In addition to forming a diffuse network of fibers throughout the body, collagen is a major component of the bones, tendons, and ligaments of the body. Another important connective tissue protein is elastin, a component of the elastic fibers of the body. The mucopolysaccharides are high molecular weight carbohydrates which contribute to the physical properties of many tissues and which, where they are found in high concentration, can be seen to be jelly-like in consistency.

With increasing age there is a progressive change in collagen due to a gradual increase in cross-links between adjacent molecules of collagen. These cross-links affect the physicochemical properties of collagen, but the physiological effect of the alteration in physiocochemical properties is not known. Elastic tissue fibers and mucopolysaccharides also undergo progressive changes with age.

Government aging programs support studies on various aspects of changes in connective tissue elements.

NICHD HD 01179 Andrew: Age Changes in Cell Population of Connective Tissue

NICHD HD 02612 Selye: Studies on Tissue Development and Aging

NICHD HD 02646 Meyer: Mucopolysaccharides of Connective Tissue

NICHD HD-AG 39 Elden: Elasticity of Aging Connective Tissue: Cohesion of Collagen Fibers

VA Yu: Connective Tissues and Aging

VA McGavack: Aging in Connective Tissue II: Ground Substance: Urinary Carbohydrate-Protein Complexes

VA McGavack: Aging in Connective Tissue II: Ground Substance: Changes in the Composition of Ground Substance during Aging

VA Sobel: Age-Associated Changes in the Skin and their Systemic Metabolic Equivalents

VA Stidworthy: Biosynthesis of Glycosaminoglycans and Aging in vitro and in vivo

VA White: Arylsulfatase in Normal and Disease States

Endocrine System

The endocrine glands -- the pituitary, thyroid, parathyroids, adrenals, ovaries, testes, and islet cells of the pancreas secrete hormones which are transported by the circulatory system to all parts of the body. These hormones are of major importance in regulating the activities of the various organs and tissues. The function of many of the endocrine glands is known to diminish with age. For example, the production of thyroid hormone diminishes with age, the ability of the islet cells to secrete insulin declines, ovarian function declines dramatically at the menopause, and testicular function gradually declines during the later half of life. Government aging programs support five studies on various aspects of thyroid function, one study of parathyroid function, one study of adrenal function, one study of islet cell function, and two studies of ovarian function.

NICHD HD 00643 Randall: Oophorectomy with Hysterectomy

NICHD HD 00669 Levy: Relation of Age-Related Changes in Thyroid Hormone Metabolism to Gonadal Function

NICHD HD 00669 Schneiderman: Biological Action of Juvenile Hormone: Maturation and Aging in Insects

NICHD HD 00672 Gershberg: Growth Hormone and Parathyroid Relationships in Man as Measured by the Response to Acute Hypocalcemia

NICHD HD 02513 Hausknecht: Estrogen Precursors in the Post-Menopausal Female

NICHD HD-AG 9 Andres: Age Differences in the Control of Plasma Insulin Concentrations in Man and Insulin Production in Experimental Animals

NICHD HD-AG 21 Gregerman: The Renin-Angiotensin System: Chemical-Radioisotope Derivative Assay of Renin and Angiotensin

NICHD HD-AG 22 Gregerman: Relationship of Age to Thyroid Function and Thyroid Metabolism: Qualitative and Quantitative Appraisal

NICHD HD-AG 43 Elden: Endocrine Regulation of Connective Tissue Systems

VA Hoch: Iodine in Serum: Changes with Age and Thyroid Status

VA McGavack: Effect of Thyroid Hormone on the Production and Peripheral Transformation of Steroids in the Aged Individual

VA McGavack: Formation of Ketosteroids by Adrenals of Young and Old Guinea Pigs

VA Capers: Cooperative Studies in Pathology: Cooperative Study of Aging in Men: A Morphologic Study. I. Endocrinologic Aspects

AEC AT (30-1)1243 Dobyns: A Study of the Physiological Function and Histological Changes of Thyroids Irradiated with Radioactive Iodine

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Alimentary System

The alimentary or digestive system consists of the mouth, esophagus, stomach, and small and large intestines. Attached to it and usually classified with it are glandular structures -- the salivary glands, the pancreas, and the liver. The digestive system is essentially a tubular structure, the walls of which are formed mainly by muscular tissue and lined by epithelial cells which secrete various substances important in digestion and absorb the nutritive elements of food into the body.

Changes occur in the digestive system with increasing age. The epithelial cells that line the digestive tube atrophy and perform secretory and absorptive functions at a slower rate.

The muscular walls of the tube also become atrophic. There is a concomitant decrease in the size and activity of the glandular structures associated with the digestive tube. A few studies of changes in the digestive system are supported by Government aging programs.

NICHD HD 00674 Arias: Hepatic Excretory Function: Its Development and Senescence

NICHD HD 02207 Snook: Diet and Pancreatic Enzymes in Development and Aging

VA Schlenker: Biochemistry of Intestinal Tissue

VA Hogan: Gastric Secretory Capacity in the Normal Aging Population

VA Albacete: Aging Research

Urinary System

The urinary system includes the kidneys, ureters, bladder, and urethra and has as its function the excretion of some end products of metabolic activity and the regulation of the amount and composition of the body fluids. A reduction in the ability of the kidneys to excrete the waste products resulting from metabolic activity and a decrease in their ability to correct for maladjustments in the quantity and composition of the body fluids occur with increasing age. Some studies of kidney function are conducted in the long-term studies. Government aging programs support two studies of kidney function.

NICHD HD 00674 Royce: Control of Organ Growth; Hypertrophy and Hyperplasia of Kidney

NICHD HD 00674 Liebowitz: Degenerative Renal Disease

Reproductive System

The functions of the male and female reproductive systems are to produce spermatozoa and eggs respectively. In addition the female reproductive system has the function of supporting the developing fertilized egg until it is a viable infant. These

systems undergo major changes with age. In the male these changes occur gradually over the adult years while in the female there is a fairly abrupt cessation of ovarian activity at a relatively young age. Thus infertility occurs well before old age in the female. Government aging programs support several studies on reproduction and age.

NICHD HD 00636 Ewing: Effect of Aging and Stress on Testicular Metabolism

NICHD HD 00674 Geller: Pharmacologic and Endocrine Control of Growth of the Prostate

NICHD HD 02217 Jenkins: Relationships in Aging and Reproduction in Planarians

AEC W-7401-ENG-49 Casarett: Effects of X-Irradiation on Spermatogenesis in Dogs

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Blood, Lymphatic, and Immunological Systems

The red and several types of white blood cells are formed within the bone marrow. Other types of white blood cells are formed within the lymph nodes of the body. No striking changes in blood cell formation have been found with increasing age.

The immunological system of the body consisting of cells within the lymph nodes, bone marrow, and spleen forms proteins called antibodies which react with proteins foreign to the body in such a way that they damage the structure containing those proteins. Thus antibodies are extremely important in the defensive reaction of the body to various kinds of infection. Antibodies are probably also of importance in the defensive mechanisms that the body has against its own cells that become cancerous. The capability of the immunological system declines with increasing age of the individual. In addition aging individuals frequently form antibodies against the proteins of their own tissues. These antibodies, called autoantibodies, may damage the tissues against which they are formed.

Government aging programs support no studies of blood cell formation as such but do support several studies of changes in immune mechanisms with age.

NICHD HD 00534 Walford: The Role of Immune Phenomena of Aging

NICHD HD 00669 Svec: The Occurrence of Nuclear Reactive Factors in Sera of Non-Rheumatic Aged Persons

VA Huemer: Developmental Biology of Aging

AEC W-7405-ENG-26 Makinodan: Growth and Senescence of the Immune Mechanism

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Cellular Systems

The adult human body is composed of about 60 trillion cells set in the matrix of extracellular fluid and compounds. Although these cells are specialized into a great variety of types, there are certain general characteristics that the cells share. Research concerned with those general characteristics is described in this part of the collation. Research related to the specific characteristics of any cell type is placed in that part of the collation related to the organ and tissue systems.

Cells are so minute that their study only became possible with the invention of the light microscope. Many of the details of cell structure could not be seen until after the introduction of the electron microscope. In the past two decades that instrument has revolutionized knowledge of the structure of the cell revealing a number of complex structures within the cell itself.

Each cell is enclosed by a cell membrane and contains a relatively large structure called the nucleus. The nucleus is bounded by the nuclear membrane and contains chromosomes and a nucleolus. The non-nuclear portion of the cell is called the cytoplasm and contains a variety of organelles. These include the endoplasmic reticulum, the ribosomes, the mitochondria, the Golgi complex, the lysosomes, the centrioles, and secretory granules. These structures form the machinery that carries out the numerous biochemical processes that make life possible. Since there is reason to believe that aging is fundamentally a cellular process, it is reasonable to look for aging changes in the structural components that make up the cells. Government aging programs support several general studies on cellular aging.

VA Coleman:
(1) Changes in Aging Populations of Bacteria
(2) Possible Role of the Mycoplasma Group of Bacteria in Degenerative Disease and Aging
(3) The Formation of L-Type Growth in Senescent Cultures as well as the Relation of L-Forms and Protoplasts of Bacteria to Chronic Diseases

NICHD HD 00669 Burnett: Growth, Cell Differentiation and Aging in Hydra

NICHD HD 01186 Scott: Electron Microscope Studies of Aging

NICHD HD-AG 37 Brock: Studies of the Comparative Physiology of Aging

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Cytoplasm
Cell Membrane
Ground Substance
Endoplasmic Reticulum
Ribosomes
Golgi Complex
Mitochondria

The cell membrane is an actively functioning structure which, by retaining some chemical compounds within the cell and by permitting or forcing others to leave, contributes to the maintenance of the chemical composition of the cell. Changes in the permeability of the cell membrane have been suggested as being of importance in aging. The cytoplasm contains as a major component the ground substance, a viscous fluid rich in large and small molecules of biological importance and making up the liquid portion of the cytoplasm. Extending throughout the cytoplasm is the endoplasmic reticulum, a complex series of membranes which guide the flow of various compounds throughout the cell. On the endoplasmic reticulum and in the adjacent fluid are found the ribosomes, minute bodies important in protein systhesis. Also important in synthetic activities within the cell is the Golgi complex. Scattered throughout the cytoplasm are the mitochondria, the small structures which provide the mechanisms for energy transformations within the cells. A little research on these structures which are responsible for cellular activities is supported by Government aging programs.

NICHD HD 00672 Deutsch: Electrophysiologic Studies of Properties of Cell Membranes

NICHD HD-AG 32 Pharo: Studies on Mitochondrial Energy Metabolism

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Lysosomes and Age Pigment

The major structural change that has been found in cells with increasing age is the accumulation of a brown pigment called "age pigment." Age pigment begins to form in certain cells,

particularly heart cells and nerve cells, relatively early in life and collects in progressively increasing amounts throughout the lifespan. Eventually as much as 10% of the volume of some cells is occupied by this pigment. What effect this quantity of pigment has on cellular function is not known although it appears quite possible that it may have a serious detrimental effect. The chemical constitution of the pigment is now relatively well understood, and in recent years something has been learned of its mode of formation which seems related to lysosomal activity within cells.

Lysosomes are small bodies within the cytoplasm which contain digestive enzymes. When these bodies break down they release enzymes which digest foreign materials such as bacteria. They may also digest portions of the cellular cytoplasm. This digestion is thought to be incomplete sometimes and to leave behind components which the cell is unable to excrete and which form age pigment.

The chemical characterization of age pigment and the partial clarification of its mode of origin provide promising leads for the investigation of this, the major structural change that has been found at the cellular level in aging animals. Government aging programs support three studies on lysosomes and age pigment.

NICHD HD 00042 Brandes: Study of Senescence at the Cell Level

VA Koenig:
1. Effect of Analog Substituted RNA's on Protein Synthesis
2. Studies of Neural Lysosomes

VA Sekhon: The Process of Aging in the Central Nervous System of the Mouse

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Nucleus
- Nuclear Membrane
- Chromosomes
- Nucleolus

The nucleus contains the chromosomes which not only transmit the characteristics of the species from parent to child, and the characteristics of the cell from mother cell to daughter cells during cell division, but which also control the daily chemical synthetic processes of the cell. The central importance of the latter two of these functions in the maintenance of the individual has led to the theory that mutations (changes) in the chromosomes

of the somatic (body) cells might be responsible for aging. This is known as the somatic mutation theory of aging. It has been linked to the fact that high energy irradiation produces somatic mutations and also produces body changes that resemble aging. In addition, it has been found that the number of somatic mutations per cell increases with increasing age. Government aging programs support several studies of changes in chromosomes with age. In addition, related material is described under the section of this review dealing with irradiation and the section dealing with nucleic acids which are important constituents of chromosomes. No studies are supported on the nuclear membrane, bounding the nucleus, or the nucleolus, a small structure lying within the nucleus and possibly related to ribosomal function.

VA Anday: Chromosomes in Old Age

AEC AT (30-1) 3314 Yuhas: Genetic Control of Aging and Radiation-Induced Life-Shortening in Mice

AEC AT (30-1)GEN-16 Curtis: Biological Research Effects of Radiation on Aging in Mice

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Tissue Culture

The term "tissue culture" is used to describe the culture of cells outside of the body in glass or other containers. Tissue culture is a powerful technique for the analysis of problems of cellular function since strict environmental control can be maintained and experimental manipulations not feasible in the intact animal are possible.

It has been believed since the first decade of this century that normal cells can continue to divide and exist indefinitely in tissue culture. Recent work has shown that this may not be the case although many abnormal cells, those with definite chromosomal abnormalities, can be cultured indefinitely. Normal human fetal cells can only divide about 50 times in tissue culture before dying. This number of divisions occurs in about 6 months in tissue culture.

This observation on tissue culture is very interesting when taken in conjunction with the fact that in the organism there is progressive death and failure of replacement of some types of cells with increasing age. This latter observation has suggested that the fundamental changes that occur in aging occur at a cellular level and produce the complex alterations that are seen in the

aging organism. If the fundamental changes in aging do occur at a cellular level then it would be highly advantageous if a simple system could be produced in which a homogeneous group of cells could be observed to age and could be studied free of the complexities produced by the interactions that occur within the intact organism. Such a system might make possible a major simplification of the analysis of the complex processes of aging and might greatly accelerate the clarification of the underlying nature of aging. Government programs of aging research support three studies of processes in tissue culture which appear to resemble aging.

NICHD HD 00703 Chang: Human Cells in vitro

NICHD HD 02721 Cristofalo: Carbohydrate Metabolism and Aging in vitro

NICHD HD-AG 36 Strehler: Studies in the Relationship between Proliferation, Regeneration, Differentiation, and Death of Cells in vitro and in vivo

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Cell Transplantation

Cell or tissue transplantation from one animal to another offers interesting experimental opportunities in the study of aging. It is not yet established whether biological aging is a result of processes that are inherent in the cell or whether aging results from interactions between cells or between cells and the extracellular environment in the multicellular organism. If aging does not occur at a cellular level, but rather is a result of complex interactions between cells within the total organism, then it should be possible to keep cells from a donor alive indefinitely by transplanting them from young host to young host. There are several different techniques by which this type of study can be carried out. Tissue may be transplanted. Skin has been utilized in studies of this type. Cells from one animal may be transplanted into diffusion chambers placed in another animal and so constructed as to prevent the admixture of host and donor cells. Cells may be injected intravenously under conditions which permit their subsequent identification. Although some work has been done on the maintenance of cells and tissues by successive transplantation through young hosts, a well-systemized field of knowledge has not yet been developed. A Government program of medical research on aging supports one study of transplantation of skin through successive generations of young hosts.

Molecular Systems

This section is not concerned with chemical transformations within the body but rather with the alterations that may occur in the structure of certain molecules with increasing age.

No list will be given of the many large molecules (lipids, porphyrins, etc.) in which such changes might occur. Instead, only those which have been investigated for structural change will be mentioned.

Proteins

Proteins are centrally important within the human body. They to a large extent form the structures of which the body is composed, and they are essential components of the metabolic mechanisms that transform chemical components within the individual. Proteins are large, complex molecules, and some of them are known to be very slowly renewed in the body. It seems probable that there may be important structural changes in slowly renewed proteins with increasing age.

Collagen, the most abundant protein in the human body, makes up one third of the total body protein. Collagen is the major component of the fibers which form the soft, supportive framework of the body and is also an important component of bone. The occurrence of increased cross-linking of collagen with increasing age was discussed earlier in this section. Another important constituent of the supportive framework of the body is the protein elastin, a component of elastic fibers. Scientists suspect that cross-linking may occur in this protein also. Although increased cross-linking of collagen with increasing age is definitely established, the functional significance of this for the aging individual is yet to be determined. Such a striking structural change may have important functional implications.

Hemoglobin is constantly being produced and destroyed in the body. Thus at any given time the body contains hemoglobin molecules of different ages. Means are now available for separating young and old hemoglobin. The young and old molecules have been found to differ in several characteristics.

There are many other protein molecules with slow renewal rates. The investigation of possible changes in those molecules with age presents a large field for investigation.

Government aging programs support several studies of changes in protein molecules with age.

NICHD HD 00669 Bensusan: Aging of Collagen

NICHD HD 00674 Gallop: A systematic Analysis of the Structure and Biosynthesis of Collagen

NICHD HD 01066 Snyder: Molecular Interactions in Skin

NICHD HD 02377 Sinex: A Biophysical Study of Fluorescence in Aging Tissue

NICHD HD-AG 38 Elden: Fractionization of Aging Connective Tissue

NICHD HD-AG 40 Elden: Hydration of Aging Connective Tissue

VA Buchanan: Metabolic Origin of Beta-Aspartyl Peptides

VA Needleman: Amino Acid Analogs and the Etiology of Collagen Disease

VA Walter: Differentiation of Young and Old Protein Molecules and Separation of Cells and Particles by Counter-Current Distribution

AEC AT(45-1) 581 Kolder: Studies of Genetic Alterations in Human Cells and Molecules and Factors Influencing Them

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Enzymes

Enzymes are organic catalysts that produce chemical reactions that would not otherwise occur. Almost all the chemical transformations that maintain life are made possible by the enzymes of the body. When enzymatic action becomes defective, the individual functions inadequately or dies. Enzymes are protein molecules. There are probably at least 1,000 different enzymes in the body. Because of the central importance of enzymatic activity to bodily function, it is important that enzymatic changes with age be investigated. Past studies have revealed some changes in enzymatic activity with age, but no general pattern has emerged. Government aging programs support several studies of changes in enzymatic activity with age.

NICHD HD 00261 Rockstein: Some Physiological Aspects of Aging

NICHD HD 00571 Rockstein: Aging in Musca Domestica L

NICHD HD 00988 Gottlieb: Enzyme Activities in the Development of Fungi

NICHD HD 02741 Lansing: Experimental Cytology of Aging Cells and Tissues

NICHD HD-AG 12 Barrows: Age Changes in Cellular and Tissue Biochemistry

NICHD HD-AG 30 Eichhorn: The Function of Metal Ions in Enzymatic Reactions

NICHD HD-AG 35 Gold: Changes in Molecular Population during Development, Maturation, Aging and Cellular Death

VA Haining: The Regulation of Intracellular Protein Metabolism during Development

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Nucleic Acids

The keystone of the modern revolution in biology has been the discovery that in the chemical structure of the deoxyribonucleic acids of the chromosomes is coded the information which guides the construction and subsequent function of living organisms. By a series of complex steps the information in chromosomal deoxyribonucleic acid is transferred to ribonucleic acid which is transported to the ribosomes. Here the coded information is used to guide the formation of proteins. These proteins -- structural and enzymatic -- create and maintain the living creature.

Deoxyribonucleic acid is unusual in that it is not continually being renewed as so many other components of the body are. Indeed, once a cell is formed, there is no further creation of deoxyribonucleic acid until that cell divides creating two daughter cells. Since many cells of the body never divide after the birth of the individual containing them, their deoxyribonucleic acid is as old as that individual is. It seems likely that in the course of a lifetime alterations might occur in the structure of deoxyribonucleic acid changing the information coded in it and thus making the function of the individual inadequate. Indeed, this possibility has been proposed as the underlying cause of aging.

There is now some evidence that there may be physical or chemical changes in deoxyribonucleic acid and ribonucleic acid

with age, but a great deal remains to be done to determine the nature and significance of these changes. Government aging programs support several studies on nucleic acids.

NICHD HD 00670 Sallman: Cellular Metabolic Changes in the Rat Heart with Aging

NICHD HD 00670 Schaiberger: Age-Associated Changes in Nucleic Acids and Proteins in E. coli

NICHD HD 00670 van Wagtendonk: Aging in Paramecium

NICHD HD 00672 Post: Effects of Age upon DNA Replication

NICHD HD 01971 Sallman: Studies in the Aging of Cellular Components

NICHD HD-AG 28 Eichhorn: Structure of Nucleic Acids

VA Lindsay: Effects of Aging and Hormones on Pyrimidine Utilization for Nucleic Acid Synthesis

VA Piko: Properties and Function of Mitochondrial DNA in Relation to Development and Aging

VA Sinex: Age-Related Differences in DNA and Deoxyribonucleo-Protein

VA Wang: Relation of Age to Protein Synthesis and Enzymatic Activities

NIMH MH 13682 Herrman: Tissue-Specific DNA-Histone Interaction

AT(30-1)3518 Wulff: A Study of the Effects of Aging and Ionizing Radiation on Nucleic Acid Metabolism and Protein Synthesis in Visceral and Central Nervous System Tissues

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Free Radicals

Free radicals are a particular type of chemical structure that can be formed within the body in a variety of ways including irradiation. Free radicals are highly reactive entities which may disrupt portions of the complex metabolic machinery of the cells by damaging the molecules involved in that machinery. It has been suggested that the formation of free radicals is important in the normal aging process. If free radicals could be

prevented from forming or if their periods of existence could be shortened, then aging might be retarded. A Government aging program supports one study that attempts to extend the lifespan of mice by the administration of compounds which might be expected to reduce the number of free radicals present in the body.

NICHD HD 00977 Harman: Effect of Antioxidants on the Lifespan of LAF_1 Mice

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Metabolism

"Metabolism" is a general term covering all chemical changes in the living individual.

Nutrition

- Calories
- Protein
- Carbohydrate
- Fat
- Minerals
- Vitamins

The chemical changes within the body have the food taken in by the individual as their base of operation. The science of nutrition is thus closely linked to metabolism.

It appears probable that the diet that the individual eats over his lifetime might be a major determinant of his health and longevity. This has been shown to be the case with regard to total caloric intake. Reduction of caloric intake early in life will greatly expand the lifespan of mice and rats and delay the onset of many of the chronic diseases of later life. Doubling of the lifespan of rodents may be achieved by such dietary restriction. The mechanisms of this prolongation of health and life have not yet been determined. Their study should be given high priority.

Similar lifespan studies need to be done on the effects of all nutrients on health and longevity. Not only total caloric intake, but also its distribution among proteins, carbohydrates, and fat may be of major importance. The particular proteins, carbohydrates, and fats involved may well be found to make a difference.

In addition, more needs to be known about the effects of the intake of the various minerals and vitamins over the lifespan.

Government aging programs support several studies of nutrition and aging.

NICHD HD 00086 Ross: Effects of Changes in Enzyme Levels on Lifespan

NICHD HD 00490 Ross: Aging of Cells and Tissues -- Enzymatic Correlations

NICHD HD 00642 Weil: Early Nutrition, Body Composition and Aging

NICHD HD 02566 Wachsman: Unbalanced Growth: A Molecular Basis of Death

NICHD HD 02888 Swendseid: Single Amino Acid Deficiencies in Aging

NICHD HD-AG 15 Barrows: The Relationship of Nutrition to Biological Aging

NICHD HD-AG 42 Weglicki: Distribution and Metabolic Function of Vitamin E in Young and Aged Rat Hearts

VA Davis: (1) Effect of Maternal Dietary Deprivation on the Aging of Progeny; (2) Vitamin B-12 Metabolism in Aging Populations; (3) Study of Effects of Nutrition and Aging on Bacterial Cell Surface Sites Reactive to Nucleic Acids, Vitamin B-12, Antibiotics, and Other Compounds; (4) Serum Enzyme Studies of Different Aging Populations

VA Frenkel: Aspects of the Radioisotope-Hematology Research Program as It Relates to Aging

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Intermediary Metabolism
Total Energy Metabolism
Protein
Carbohydrate
Fat
Other

"Intermediary metabolism" covers the transformations that organic foodstuffs undergo in the body. These transformations make up a complex series of integrated biochemical pathways that are enzymatically regulated. They provide for the formation of new constituents for the body to replace those that are periodically destroyed and for the release of energy in the various processes that the body carries out. There is evidence that some of these transformations are impaired with age. The total energy

production of the individual is known to decrease with increasing age, as is the ability to utilize carbohydrate and to maintain blood lipids at a low level. However, the age-dependence of most processes of intermediary metabolism has not been studied. Changes in these metabolic capacities may have a major impact on the health of individuals. Indeed, if the criteria established on young persons for the glucose tolerance test were applied to older persons, about half of the population over 50 years of age would be said to have diabetes mellitus.

Government aging programs support several studies of intermediary metabolism.

NICHD HD 00494 Zorzoli: Age and Cellular Metabolism

NICHD HD 00648 Weiss: Tissue Changes with Aging in Highly Inbred Rats

NICHD HD 00670 Dietrich: Coenzyme Metabolism in Aged and Stressed Animals

NICHD HD-AC 10 Andres: Age Changes in Carbohydrate Metabolism in Man

NICHD HD-AG 41 Avruch: Efflux of Free Fatty Acids from Isolated Adipose Tissue Cells

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Mineral Metabolism
Water
Sodium, Potassium, Magnesium, Chloride
Calcium, Phosphorus
Other

"Mineral metabolism" covers the metabolic processes in which the non-organic substances of the body are involved. One important bodily function is to maintain in the body water the appropriate concentrations of the ionized forms of certain elements such as sodium, potassium, magnesium, and chloride. The degree of acidity of the body fluids must also be kept within appropriate limits. What little is known about age changes and body fluids suggests that the ability of the body to maintain their composition under stress declines with age. Calcium and phosphorus metabolism affects the bones. The fragility of bone that occurs in old age is associated with the loss of calcium and phosphorus from the body. Some studies related to this are listed under the skeletal system. Little is known about age changes related to a number of

other non-organic substances such as iron, iodine, and manganese that are necessary for health. Government aging programs support two studies most appropriately listed with this section.

VA Lindeman: The Effect of Surgical Trauma on Renal Excretion of Calcium, Magnesium, and Zinc

VA Magid: Gastrointestinal Absorption of Calcium in the Male using Calcium 47 and Calcium 45

Pharmacology

Some differences in the tolerance of the young and the aged to drugs are known to exist. The intelligent use of therapeutic agents in the elderly would be facilitated by an understanding of the differences in responses of the young and the elderly to those agents. The number of pharmacologic agents used in the elderly is, of course, quite large. The effectiveness and toxicity of drugs in the elderly should ordinarily be established by the same investigators that make such determinations for the rest of the population. Most of this type of research is supported by disease-oriented programs. A Government aging program supports one study of the effect of aging on tolerance to alcohol.

VA Barboriak: Effect of Aging on Alcohol Tolerance

Irradiation

The effect of various types of high-energy irradiation such as that from X-rays and radioactive elements has been the subject of a good deal of investigation because of the belief that irradiation may accelerate natural aging. Whether or not this is the case has not been definitely established, but it is clear that in many ways the effects of irradiation mimic natural aging. Government aging programs support a number of studies on the relation of irradiation damage to natural aging.

NICHD HD 02194 Anderson: The Pathology of Accelerated Aging in Germ-Free Mice

VA Soldo: Effect of Radiation on Aging, Protein, and Nucleic Acid Synthesis

AEC W-7405-ENG-26 Upton: Long-Term Effects of Irradiation

AEC W-7401-ENG-49 Casarett: Pathologic Mechanisms of Permanent and Delayed Radiation Effects

AEC AT(30-1) 2071 Brent: The Effect of Embryonic Irradiation on Adult Life Expectancy and Adult Pathology in Mice and Rats

AEC AT(11-1)1474 Brizzee: Long-Term Effects of Prenatal X-Irradiation on Cerebral Cortex

AEC AT(30-1)3394 Mancuso: Study of Mortality Patterns of AEC Contractor Installations in Terms of Different Environmental Exposures

AEC W-7401-ENG-49 Baxter: Radiobiological Studies with Drosophilia

AEC W-31-109-ENG-38 Sacher: External Radiation Toxicity Effects on Cells and Physiological Mechanisms

AEC W-31-109-ENG-38 Sacher: Theoretical Biology

AEC AT(04-1)-GEN-12 Bennett: Late Effects, Radiobiology

AEC AT(11-1)34 Wood: Study of the Kidney in Aging and X-Irradiated Animals with Particular Reference to the Role of Immunity in the Pathogenesis of Late Effects of X-Ray

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Psychology and Social Science

With increasing age there are major changes in psychological function which affect the health and welfare of the individual and determine what he can contribute to society and must ask of it.

Biological Bases of Behavior

Currently there is great general interest in the structural, biochemical, and physiological processes which form the bases of mental activity. The study of these processes forms a link between psychology and the other biological sciences.

Development of this area in a general way is providing a base for studies directed specifically toward the biological changes that underlie some of the psychological changes that occur with increasing age. Thus an attack on the physical bases of the deterioration of a great variety of physiological processes with age may become possible. A number of studies seeking relations between psychological functioning and underlying physiological events are supported by Government aging programs.

NICHD HD 00668 Cohen and Schmavonian: Central and Autonomic Nervous System Mechanisms in Psychophysiological Responses in Young and Aged Persons

NICHD HD 00668 Obrist: Aging and Cerebral Evoked Responses

NICHD HD 00668 Thompson: Hyperbaric Oxygenation, Behavior and EEG in the Aged

NICHD HD 01325 Botwinick: Psychophysiological Aspects of Aging

NICHD HD 01615 Jarvik: Behavior and Chromosomal Changes of Aging

VA Apfeldorf: EEG Rhythm and Auditory Reaction Time as Functions of Aging

VA Canestrari: Cerebral Circulation and Behavioral Deficit

NIMH MH 06022 Schmavonian: Factors in Autonomic Conditionability

NIMH MH 10927 Feinberg: Sleep Patterns in Mental Illness

Speed of Behavior

A change that occurs in almost every psychological process with age is progressive slowing of the rate at which the process occurs. Slowing occurs in perception, reaction time, information processing, learning, and problem solving. This slowing is of a sufficient degree to be important in certain demanding activities in the middle years and in everyday activities in the later years of life. In addition, it is so general a phenomenon that an insight into its origin may increase understanding of many aspects of psychological aging. Government aging programs support two studies related to the problem of psychological slowing.

NICHD HD 01989 Brinley: Sets in the Speeded Performances of the Elderly

NICHD HD-AG 27 Goodrick: An Experimental Analysis of Rodent Exploratory Behavior as a Function of Age

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Sensation and Perception

In general, it appears to be true that the senses involved in vision, hearing, taste, smell, and touch diminish in acuity with increasing age. In addition, rapidity of perception, the interpretation of complex stimuli, declines. Accurate quantification of these losses is important in determining what age groups are liable to have impairment of significant degree to justify frequent testing in connection with potentially hazardous activities such as driving. In addition, studies are needed to determine whether modifiable environmental factors are concerned. Excessive exposure to noise over a lifetime, for example

may account for much hearing loss attributed to age per se. Government aging programs support a number of studies on sensation and perception.

NICHD HD 00340 Talland: Aging and the Selection of Information

NICHD HD 02558 Bergman: Hearing and Aging: Description and Implications

NICHD HD-AG 8 Arenberg: The Relations Between Age and Time Estimation Measures of Accuracy, Variability, and Context Effects

NICHD HD-AG 26 Goodrick: Fluid Preferences of Rodents as a Function of Age

VA Pishkin: Auditory Concept Identification as a Function of Age and Sex

VA Sklar: Psychoacoustic Parameters of Presbycusis

VA Smith: The Effect of Varying Signal-to-Noise Ratios on Speech Discrimination Ability as a Function of Age

NIMH MH 08061 Liebowitz: Analytic Studies of Visual Perception

NIMH MH 13434 Eriksen: Temporal Factors in Visual Perception Related to Aging

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Learning and Memory

The study of learning and memory has shown that there are important changes with age in these functions. Memory is now thought to be a multiple process, with registration, then a brief period of short-term memory possibly electrical in nature, and finally a period of a permanent brain registration process possibly chemical in nature. Recent evidence suggests that there are several distinct neural processes from stimulation to permanent memory, and that some processes deteriorate faster than others with advancing age. Age-related deficits in memory and learning could be due to defects in sensation, perception, initial registration of stimuli, short-term retention, permanent consolidation of memory, or retrieval of memory. Alertness, emotion, or motivation may be of importance. Government aging programs support a small number of studies on learning and memory.

NICHD HD 00668 Eisdorfer: Verbal Learning in the Aged: Psychological and Psychophysiological Approaches

NICHD HD 01691 Griew: Aging and the Development of Anticipatory Responses

NICHD HD 02250 Inglis: Age and Short-Term Memory

NICHD HD 02582: Effect of Aging on Short-Term Memory

NICHD HD-AG 7 Arenberg: Verbal Learning and Age

NICHD HD-AG 25 Goodrick: Operant Responding of Rats, Hamsters, and Mice as a Function of Age

VA Canestrari: Verbal Learning

VA Cherkin: Aging and Memory

VA Jakubczak: Gerontological Psychology Research

NIMH MH 08556 Buschke: Retention in and Retrieval from Immediate Memory

Intellectual Performance

Overall intelligence as measured by psychological tests declines with age. Analysis of the results of such tests have shown that all types of intellectual abilities do not decline at the same rate. Predominantly verbal abilities are very well maintained in many adults until late in life. The maintenance of such abilities appears correlated with the initial level of intelligence. Persons with high ability early in life tend to maintain it, perhaps because of continued practice. They naturally undertake the type of work that requires that they use their verbal abilities. Problem-solving abilities are not so well maintained. Instead, they deteriorate progressively during the later years of life. Government aging programs support some studies of changes in intellectual performance described under longitudinal studies and the two projects listed below.

NICHD HD-AG 6 Arenberg: Problem Solving and Age

VA Coppinger: A Collaborative Study of Automated Assessment of Psychological Deficits

Psychological Adjustment

The problems of psychological adjustment to aging are major ones. As a person passes through the various stages of the lifespan, he has to adjust to his changing capabilities, responsibilities, and opportunities. The later years of life are frequently characterized by poor health, inadequate economic resources, loss of loved ones and friends, and lack of an interesting and rewarding role in life. Adjustment to these deprivations must be made at the same time that the individual's psychological abilities themselves are declining. Proper structuring of the environment has been shown to be of great importance in permitting a successful adjustment to the problems of the later years. Government aging programs support the studies listed below.

NICHD HD-AG 1 Martin: Marital and Sexual Aspects of Aging

VA Apfeldorf: MMPI Responses, Antisocial Behavior in Aged Maladjusted Subjects

VA Bortner: Laboratory Risk-Taking Behavior

VA Bortner: Stages of Adult Development

VA Cleveland: Psychological Aspects of Aging

VA Dolson: Gerontological Research in Social Work Service

VA Phillips: The Relation between Social Behavior Pattern and the Functional Aging of Humans

NIMH MH 04902 McKain: Older Persons in Connecticut

NIMH MH 12400 Antonovsky: Socio-Cultural Patterns and the Involutional Crisis

NIMH MH 12492 Anderson: The Adaptive Tasks of Aging: A Psychosocial Analysis

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Psychopharmacology

In recent years there has been great interest in the effects of various drugs on mental function. Pharmacological agents of considerable value in the treatment of neurotic and psychotic

diseases have been developed. Hope has arisen that drugs that will improve mentation in the elderly can be developed. Some experimental studies on animals have shown that certain drugs do exert a favorable effect on the registration of memories. However, nothing of practical use in humans has yet been developed. Government aging programs support several studies seeking drugs to favorably affect mental function in the elderly.

VA Connor (with HD 00668 Eisdorfer): Effect of Magnesium Pemoline on Cerebral Function and Physiological Responses in Human Subjects. Effect of Autonomic Nervous System Blocking Agents on Adaptation in the Elderly

VA Edwards: Prophylactic Psychopharmacology and Age-Correlated Intellectual Changes

NIMH MH 08060 Lehmann: Psychoactive Drugs in the Aged

Attitudes

The attitudes of the elderly toward themselves and the attitudes of others toward them play a significant role in the adjustment that the elderly make to their personal situations and to society. The following studies are supported by Government aging programs.

NICHD HD 02304 Taylor: Behavioral Components of Attitudes Toward the Aging

NIMH MH 14915 Thune: A Study of Racial Attitude Change in Older Adults

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Psychology of Retirement

Retirement frequently brings to the elderly the problems associated with low income, loss of status, loss of social contacts, and loss of a meaningful role in life. Research on factors affecting the response of individuals to these problems was described under the section on psychological adjustment. Additional studies supported by Government aging programs are given below.

NICHD HD 00668 Maddox: Studies on Social Aspects of Aging and Human Development

NICHD HD 01550 Goldstein: Changing Consumption Patterns of the Aging

NIMH MH 12132 Gordon: Personal Autonomy and the Social Processes of Aging

Psychological Aspects of Housing

The elderly who are well enough and do not require institutional, hospital, or nursing home care have, in general, three choices with regard to housing. They can live with their children, they can live in dwellings scattered throughout the total community, or they can live in group housing especially designed for the elderly. The type of housing they choose or have forced on them may have a major impact on their life and health. Government aging programs support the following studies on the impact of housing on the psychological and social welfare of the elderly.

NIMH MH 14881 Wilner: Psychosocial Factors in Housing for the Aged

NIMH MH 15020 Hamovitch: Housing Needs and Satisfactions of the Elderly

Disease

In general, research on disease as such is not included in the scope of this review. However Government aging programs do support some studies on disease in which the emphasis is on aging rather than disease as such. They are listed below.

NICHD HD 00599 Tobis: Study of Physical Performance of the Elderly Patient

NICHD HD 00669 Houser: Study of the Role of Inadequate Protein Intake on the Development and Course of Chronic Illness

NICHD HD 00669 Katz: Multidisciplinary Studies of Illness in Aged Persons

NICHD HD 00517 Jones: Disease in Animals Related to Aging

NICHD HD 00769 Homburger: Aging Studies in the Syrian Hamster

NICHD HD 01274 Donahue: Milieu Treatment of Older Mental Patients (Other half of study funded by NIMH)

NICHD HD 02416 Adams: Exploration of Illness Crisis in Family of the Aged

NICHD HD 00364 Lieberman: Adaptation and Survival Under Stress in the Aged

NICHD HD 00669 Liebman: Effect of Restricted Neonatal Growth on Atherosclerosis in the White Carneau Pigeon

VA Brochu: Response of Extracellular Fluid and Red Cell Volumes to Surgery

VA Fisher: Immunization to Influenza, Diptheria and Tetanus, Duration and Intensity of Protection

VA Tice: Follow-up of Aged Patients Who Undergo Surgery

NIMH MH 11668 Engel: Psychological Determinants of Organic Disease

NIMH MH 14894 Donahue: Milieu treatment of Older Mental Patients (Other half of study funded by NICHD)

NIMH MH 14889 Kastenbaum: A Training Program for Work with the Aged and Dying

NIMH MH 15047 Brody: Individualized Treatment of Mentally Impaired Aged

NIMH MH 14926 Nathanson: Workshop for the Mentally Impaired Institutionalized Aged

NIMH MH 14832 Stotsky: Study of Mental Patients in Nursing Homes

NIMH MH 13821 Kleban: The Institutional Milieu of the Senile Patient

NIMH MH 08534 Spitzer: Evaluation of Psychiatric Status and History

NIMH MH 04591 Robins: Brain Biochemistry in Manic-Depressive Disease

NIMH MH 10359 Samuels: Biochemical Studies of Senile Dementia

NIMH MH 10895 McHugh: Visceral Function in Affect and Brain Disorders

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Health Services to the Elderly

The provision of medical services to the elderly raises the same sorts of problems that the provision of medical services to the population at large raises. However, in addition there are some problems involving the elderly that need special consideration. Government programs of medical research on aging support a number of studies of the provision of medical services to the elderly. Most of these studies may be classified in five broad categories:

Organization
Staffing
Financing
Utilization
Understanding and Acceptance

A few are quite general, or multi-faceted.

Projects related to the organization of health services for the aging may be directed either to institutional health care or to home health services. The problems of integrating all community resources, from both the public and private sectors, in order to provide the type of care most appropriate for the individual needs of the aged population are receiving particular attention.

NIMH MH 14888 Wylie: Mobilization of Aging Resources for Community Service

NIMH MH 14893 Hall: Guardianship and Protective Services for Older People

NIMH MH 14917 Carey: Senior Advisory Service for Public Housing Tenants

NIMH MH 14923 Lawton: Social and Medical Services in Housing for the Aged

NIMH MH 14423 Gaitz: Comprehensive Care of Suspected Mentally Ill Aged

BHS CH 23-26 May: Converging Community Services on a Home-for-Aged Waiting List

BHS CH 27-23 Slattery: Non-Institutional Care of Aged and/or the Chronically Ill

BHS CH 00363 Parker: Study of Recreation on Institutionalized Aged

BHS CH 00384 Pihlblad: Health and Adjustment of Older People in Small Towns

BHS CH 29436 Manheimer: The Neighborhood Approach to Identifying and Meeting the Health and Related Needs of the Aged

BHS CH 34997 Woodside: Health Services for the Aged in Garfield Terrace Public Housing Project

BHS CH 59458 Laue: A Home-Delivered-Meals Service for the Chronically Ill and Aged in Selected Areas of a Metropolitan Community with Central Coordination and Supporting Services

BHS CH 89488 Pirri: Coordinated Day Care Adult Foster Home and Volunteer Services for the Aging

BHS CH 99006 Trager: A Demonstration of District-Based Health Department in-Home Service to the Chronically Ill and Aging in San Francisco

BHS PH 108-66-233 Barbaccia: Planning and Initial Establishment of a Model Health Maintenance Program in an Urban Community

BHS PH 108-66-281 Krumbiegel: Develop and Demonstrate a Model Adult Health Maintenance Program in an Urban Community

BHS PH 108-67-41 Gitman: Development of a Model Hospital-Based Health Maintenance Program for a High-Density Low-Income Urban Population

BHS PH 110-67-216 Letcher: Working Relationship between a State Health Agency and State Schools of Higher Education, Extended Care, Nursing Homes and Related Facilities, Hospitals, and other Related Health Agencies

Shortage of trained manpower for the delivery of health services continues to be a serious problem. Eight studies are directed to identifying the kinds of services that can be rendered by home health aides, and to the kind of training and supervision required by such auxiliary personnel. Other projects are concerned with the training needs for hospitals and nursing home staffs.

NIMH MH 14924 Blackburn: Social Work Team with Aging Family Service Clients

BHS CH 37-19 Little: Home Health Aide Care for the Chronically Ill and Feeble Aged in a Five-County, Two-State Metropolitan Area

BHS CH 00329 Babchuk: Personal Influence and Participation by Older Adults

BHS CH 00362 Fowler: Screening Elderly Nursing Home Patient Problems

BHS CH 00385 Blenkner: Home Aide Service and the Aged: A Controlled Study

BHS PH 108-67-39 Crooks: The Development of a Simulated Exercise to be Used in Conjunction with the Medicare Workshops for Nursing Home Administrators

BHS PH 110-67-21 Ward: Establishment of a Center for Gerontology Studies to Provide Continuing Education for Health-Related Professionals and Semi-Professionals

BHS PH 110-67-231 Wright: Demonstrating a Method of Collaborative Planning for Training Programs to Increase Effectiveness of Medicare

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Methods of financing health services for the elderly are being studied from the points-of-view of providers of care, insurance carriers, and beneficiaries.

BHS PH 108-67-66 Glasser: Assessment of Effects of a Nationwide Nursing Home Benefit and the Development of a Research Program

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Six projects are addressed to the factors affecting utilization of health services by the elderly. Particular emphasis has been given to studying Utilization Review Plans implemented under the Health Insurance for the Aged Program.

BHS CH 00386 Richardson: Medical Care of the Very Aged

BHS PH 108-66-189 Irish: Regional Utilization and Medical Review in New York State

BHS PH 108-67-96 Robben: Plan For, Establish and Support Initial Operation of a Community-Based Utilization Review Plan

BHS PH 110-67-83 White: Design, Implementation, and Evaluation of Regional Utilization Review Plan

BHS PH 110-67-148 Lewis: Utilization Review for Extended Care Facilities

BHS PH 110-67-185 Roney: A Study to Assess the Effects of Medicare on the Providers of Service under Part A, Title XVIII, P.L. 89-97, in Four Communities

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Knowledge, understanding, and attitudes of both providers and consumers of care are directly related to the utilization of health services. The aged have special problems in learning of existing health services and the conditions under which such services are available to them. Several demonstrations aimed at developing and strengthening information, referral, and counseling services for the chronically ill and the aged are being supported. Other studies are addressed to the attitudes of physicians toward different forms of providing and paying for care.

BHS CH 00249 Colombotos: Physicians and Medicare: A Study of Attitude Change

BHS CH 29434 Johnson: Information, Deferral and Counseling Services for the Chronically Ill and Aged

BHS PH 110-67-217 DeFries: A Pilot Project Designed to Develop and Test a Method of Health Counseling for Aging Persons, using a Randomly Selected Group of Social Security Applicants or Beneficiaries as Recipients of this Counseling

BHS PH 110-67-238 Mosher: Pilot Project Designed to Develop and Test a Method of Health Counseling for Aging Persons

BHS PH 110-67-239 DiJioia: Provide Assistance, Advice, and Services in Carrying Out a Pilot Project Designed to Develop and Test a Method of Health Counseling

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Five projects concerned with health services for the elderly are either multi-fold in purpose--combining several component elements: organization, financing, and utilization--or do not fall within any of the designated categories.

VA Linn: (1) Nursing Home Studies
(2) Aging and Socio-Environmental Stress
(3) Physical Resistance in the Aged

BHS CH 34-48 Torrons: Morningside Gardens Retirement Health Services Research and Demonstration Project

BHS CH 00392 Friedmann: Changing Community Patterns: Health Services for Aging

BHS PH 110-67-65 Gravel: Study to Determine Impact of Federal Health Legislation on the Operation and Utilization of Louisiana's State Hospitals and Related Health Institutions

BHS PH 110-67-100 Howell: Development of a Systematic Approach to Functional Appraisal of Aging Individuals

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GOVERNMENT SUPPORTED LONGITUDINAL STUDIES - THE SPECIAL PROBLEMS OF LONGITUDINAL STUDIES

Fifteen Government-supported, longitudinal studies have been identified as appropriate for this review. They can be divided into three groups.

The first group is concerned with developmental and aging processes, as distinguished from disease processes. In the second group the major concern is with disease processes that develop over a long period of time, but a good deal of important information about aging processes is gathered. In the third group the major goal is the surveillance of the fitness of a group of persons, but information on aging processes is obtained.

In the first group--the one concerned with developmental and aging processes as distinguished from disease processes--the following studies are placed (short titles follow the official titles):

Longitudinal Program of the Gerontology Research Center
(The Baltimore Study)
Baltimore City Hospitals
Baltimore, Maryland

Study of Physiologic and Psychologic Aging in Pilots
(The Lovelace Study)
Lovelace Foundation for Medical Research and Education
Albuquerque, New Mexico

Normative Aging Study (Veterans Administration Study)
Veterans Administration
Boston, Massachusetts

Longitudinal Study of Aging (The Duke Study)
Duke University
Durham, North Carolina

Human Aging Project (Human Aging Study)
Philadelphia Geriatric Center
Philadelphia, Pennsylvania

Intellectual Functioning in Later Life
(Age Center of New England Study)
Age Center of New England
Boston, Massachusetts

Institute of Human Development Studies
(California Studies)
University of California
Berkeley, California

Brown University Longitudinal Study of Aging
(Brown University Study)
Brown University
Providence, Rhode Island

Consistency of Personality and Adjustment in Old Age
(Pennsylvania State University Study)
Pennsylvania State University
University Park, Pennsylvania

The Gerontology Research Center Study, the Lovelace Foundation Study, and the Veterans Administration Study are concerned with physiological and psychological changes with age over the entire span of adult life. Although they are not primarily concerned with disease processes, they include thorough medical examinations since their subjects will inevitably develop diseases, and the effects of these diseases must be understood if the other findings are to be interpreted satisfactorily. The Duke University Study and the Human Aging Study are also concerned with physiological and psychological processes primarily but their populations are composed of subjects over 65 years old rather than of adults of all ages.

In the second group--the group consisting of studies which are concerned primarily with diseases but which also yield information on aging processes--the following studies are placed:

Pensacola Study of Naval Aviators
(Pensacola Study)
Naval Aerospace Medical Institute
Pensacola, Florida

Studies in Geriatric Mental Illness
(San Francisco Study)
Langley Porter Neuropsychiatric Institute
San Francisco, California

The Atomic Bomb Casualty Commission Study
(Atomic Bomb Casualty Study)
Hiroshima, Japan

The Tecumseh Community Health Study
(The Tecumseh Study)
University of Michigan
Ann Arbor, Michigan

In the third group--the one concerned with the surveillance of the fitness of groups of persons--the following studies are placed:

The USAF Aerospace Medical Fitness Program
(Air Force Fitness Program)
USAF School of Aerospace Medicine
Brooks Air Force Base, Texas

FAA Air Traffic Controller Health Program
(Air Controller Study)
Federal Aviation Administration
Washington, District of Columbia

Content of Longitudinal Studies

The longitudinal studies are described in detail in Appendix C. An overall description of the subjects studied and of the research done is given below. This description indicates the similarities and differences between the studies.

Subjects

The subjects in the various studies differ from each other greatly in occupation, socioeconomic background, geographical location, health status, and other characteristics. Some studies such as the Baltimore one follow volunteers from a rather limited area, others such as the Air Force Fitness Program have at their disposal the entire membership in a specific population, and still others attempt to follow the members of an entire community such as Tecumseh. In no case is any one population equivalent to any other. Women are well represented in some studies, but overall, considerably more men than women are subjects of the longitudinal studies.

The description in the following paragraphs indicates the measurements made in the various studies. It will be apparent that frequently similar measurements are made in different studies. Unfortunately these measurements are not standardized so that a given measurement in one study is known to be accurately comparable to a similar one in another study. This does not interfere with the conclusions drawn in any one study but does make it difficult to take advantage of the diversity of subjects by cross-comparison between the different studies.

Anthropometric Measurements

A number of measurements of body dimensions are made in five of the studies. There is a general similarity in the measurements made. These measurements or combinations of them characterize body build and may prove to have predictive value with regard to length of life and diseases patterns.

Skinfold thickness is used as a measure of body fat in four of the studies. An increase in skinfold thickness is a better measure of obesity than weight relative to height since there is a striking variation between individuals in other factors that affect the weight-height relationship, such as bone structure and muscle mass. The degree of obesity may be related to length of life and to the development of certain diseases.

Other measurements of body composition, such as determination of bone density by X-ray and body water by appropriate measurements, are each made in only one study.

Cardiovascular System

All nine of the studies that include measures of cardiovascular function include a medical history and physical examination in the periodic examinations. They all include a standard electrocardiographic examination. The Lovelace, Tecumseh, and Pensacola Studies include vectorcardiographic examination; the Baltimore, Lovelace, Tecumseh, and Pensacola Study include a startle electrocardiogram. The Lovelace and Pensacola Studies are exploring the processing of electrocardiograms by computer techniques. All nine of the studies that include measures of cardiovascular function include an X-ray of the chest. Four of the studies include measurements of cardiovascular response to exercise. A number of cardiovascular measurements being made in only one study are listed in Appendix C.

Pulmonary Function

All nine of the studies that include measures on pulmonary function include a medical history and physical examination in the periodic examinations. All include a chest X-ray. The ability of gas to diffuse from the lungs into the blood passing through them is determined in two of the studies. Certain other determinations, such as maximum breathing capacity, maximum expiratory flow indices, and pulmonary function during exercise are determined in single studies only.

Biochemical Measurements

The state of carbohydrate tolerance is determined by an oral glucose tolerance test in three studies. In addition, special studies concerned with carbohydrate tolerance are carried out in two of the studies. The studies are designed to test for the type of defect found in diabetes mellitus. The

following chemical constituents of the blood serum are measured in from two to five studies: albumin, globulin, triglycerides, cholesterol, creatinine, and uric acid. Some other biochemical measurements are made in single studies.

Visual Function

Eight studies include tests of visual acuity. The Veterans Administration Study and the Duke Study measure depth perception and width of visual field. The Duke Study measures the ability to see in the presence of glare. The ability to determine that a rapidly flickering light is not shining continuously is measured in the Lovelace Study and more elaborately in the Veterans Administration Study. The ability to see in dim light is measured by the Lovelace and the Veterans Administration Studies. Three studies make photographs of the interior of the eye. One study measures visual recognition time, the time which just allows recognition of a visual display.

Hearing

Eight studies measure hearing acuity for pure tones in the range of frequencies important to hearing. Three studies measure speech perception.

Neurological Function

Eight studies assess neurological function by physical examination. Two record electroencephalograms and analyze them qualitatively and quantitatively. Two studies measure the speed of reaction to stimuli. One study measures the ability to smell and taste low concentrations of certain substances.

Psychological Function

Seven studies include intelligence tests. Ten studies assess personality factors by means of questionnaires. Two studies test learning and memory, including verbal associative learning and retention. One study also measures visual retention or short-term memory for geometrical displays and test problem-solving ability.

Two studies measure rates of information handling by giving the subjects tasks in which sequential, multiple-choice responses must be made as rapidly as possible in response to a visual display. An additional study measures reaction times of a less complicated nature.

Two studies measure physiological correlates of psychological performance. The Baltimore Study takes electroencephalograms and measures galvanic skin responses, as indices of central and autonomic nervous system functioning, during reaction time and learning tasks.

Social Factors

All the studies record some personal information which relates to social factors, such as educational level, ethnic background, birthplace, income bracket, occupation, etc. The Brown University and San Francisco Studies obtain the most elaborate demographic information.

The Brown and Tecumseh Studies focus on patterns of contact among subjects in the larger community and thus obtain information on neighborhood and community features bearing on social activities and opportunities. The Tecumseh Study also catalogs neighborhood and community features which may bear on health. Four studies--Duke, Brown, California, and San Francisco give considerable attention to the subjects' occupations, social achievements, and family relationships.

Four of the studies--Baltimore, Veterans Administration, Duke, and Pennsylvania State University--give questionnaires on social attitudes and opinions. The Baltimore Study also measures attitudes toward old people in young and old persons.

The Brown University and San Francisco Studies gather data on familial and other social activities and participation in groups. The Pennsylvania State University Study is interested in relating activities, especially social activities, to survivorship. The Veterans Administration and Duke Studies are interested in general activity level and some special activities as an index of vitality and general functioning.

Observations of actual social behavior have been made extensively only by the California Study. The Pennsylvania State University Study gets at actual social behavior less directly by utilizing observations elicited from the subjects' peers about extent of social activity and participation.

Family relations measures form a central part of the California Study. The Brown University Study is also interested in relations between its older couples and their relatives, especially grown children. The Duke Study gets at family relations by interview and questionnaire.

The Duke and Brown University Studies investigate the reasons for retirement and post-retirement activities and adjustment. The Brown University Study chose its subjects so that most of the men would be employed at the start of the study and retired by the last round of interviews.

Health Attitudes

The Brown University and Tecumseh Studies collect information on health attitudes and medical utilization from their subjects.

Special Problems of Longitudinal Studies

Subjects of Studies

The selection of subjects for longitudinal studies is a major problem. One goal that might be conceived is the selection of a group of subjects so that they constituted a statistically valid sample of the entire population of this country. Based on results from such a sample, one could make statements that were valid for the entire population of the country. However, that population is so diverse that the selection of such a sample is not practical. The sample would have to be tremendously large and the logistics of the study would not be workable. What should be attempted is the selection of smaller populations suited to the particular needs of each individual study. This is the procedure that the directors of existing longitudinal studies have tried to follow.

A major goal of some studies has been to study physiological and psychological aging uncomplicated by what are clearly recognized to be disease processes. This has led to the selection of healthy persons in the initial phases of these studies. Such studies bear particularly on aging processes, and since everyone is affected by such processes, those studies are of interest with regard to the population at large. However, the population at large is not free of disease, and thus the results of the study of persons selected on the basis of freedom from obvious disease cannot be applied in detail to less healthy subjects.

Other studies are conducted for the surveillance of the health of particular occupational groups of persons. The yield of scientific information on aging is a by-product of those studies conducted either for the welfare of the subjects or to assure that the subjects are fit to carry out their occupational duties. Despite the fact that the findings cannot be generalized in detail to the population as a whole, the findings do provide clues to what may be going on in the total population.

It is very difficult to recruit and keep subjects for detailed studies that will be repeated periodically over many years. Self-recruitment techniques are thus frequently used to obtain highly motivated subjects. Even when no explicit effort is made toward self-recruitment, the subjects that are finally obtained tend to be volunteers. It is generally recognized that volunteers may differ physically and psychologically from non-volunteers. Nevertheless, their use is frequently justified in that it makes the studies possible.

Men have been studied more than women primarily because certain occupational groups have formed the source of subjects. Obviously efforts should be made to include women in long-term studies.

A good deal of thought needs to be given to the problem of the selection, recruitment, and maintenance of subjects for longitudinal studies. Opportunities should be provided for directors of such studies to meet together and consider the available alternative sampling procedures and the impact of those procedures on the results of longitudinal studies.

Standardization of Methodology

The description given earlier of what is included in the various longitudinal studies makes it clear that many of the same measures are being used in the individual studies of different populations. This is not duplication, since although the measures are similar they are not being applied to the same populations. The application of similar measures to different populations is useful in that it makes comparison of the populations possible. Such comparison may provide information on the effect of different environments and ways of life on health and longevity. In addition, when similar results are obtained in studies of different populations, it establishes those results much more strongly as generally true.

However, a serious problem connected with the application of similar measures to different populations is that the similar measures are not identical. Thus, it is difficult to compare the findings in different populations. The correction of this situation is much more difficult than might be thought. Even so apparently simple a problem as the standardization of the determination of blood cholesterol, so that the same result on a given sample could be obtained in different laboratories, has proved difficult to solve in the past. Conferences, workshops, and the opportunity for investigators to visit each other's laboratories should be provided to facilitate standardization of methodology.

Management of Data

Longitudinal studies generate large amounts of data which can only be handled satisfactorily by the use of digital computers and the appropriate programs for them.

Investigators must have procedures for the storage of data awaiting analysis. Usually the best procedure is to store the information on magnetic tape which can be used for computer analysis without further processing. This frequently involves digitizing graphic information to make it suitable for storage on tape.

The statistical analysis of longitudinal data involving many variables presents problems. There are a number of techniques that are useful and necessary for such analysis. However, optimal techniques for handling such data have not yet been devised.

Workshops and conferences to permit persons concerned with longitudinal studies to exchange information and ideas on the many aspects of data processing, storage, and analysis are needed.

Communication between Studies

Since longitudinal studies generate data slowly, results from them tend to be published slowly. This has in the past tended to make communication concerning such studies less rapid than communication on short-term research. Conferences to facilitate interchange between persons conducting longitudinal studies would be useful.

PLANNING FOR RESEARCH ON AGING -- DUPLICATION, GAPS, AND BALANCE

An estimate of the intensity of present programs of research on aging can be obtained by consideration of the amount of money spent on such research relative to research on health and disease as a whole.

In fiscal year 1967 NIH spent $4,979,942 on the support of research on aging. This represented about 0.5 percent of the total expenditure of NIH on research in that fiscal year. NIMH spent $2,040,820, 3.0 percent of its research funds, on aging; the BHS spent $2,890,466, 12.4 percent of its research funds, on aging; the VA spent $1,227,706, 2.9 percent of its research funds, on aging; and the AEC spent $2,991,724, 3.5 percent of its biomedical research funds, on aging. These agencies spent $14,130,658, 1.2 percent of their combined medical research funds on aging research.*

Thus aging research, viewed as a whole, is a greatly undersupported area--a gap area. Some aspects of aging are being studied less inadequately than others and thus some imbalance exists. However, with the entire area so poorly developed, it does not seem appropriate to put much emphasis on imbalance.

Research funds for medical research on both disease processes and aging processes are limited. Therefore, it is vitally important that unnecessary duplication be eliminated. However, as indicated in the collation of research projects in Government programs of research on aging, there is essentially no duplication in the research projects on aging. Similar or identical biological and psychological functions are investigated in different longitudinal studies, but since the populations studied are different, the study of many of the same functions is desirable. The longitudinal studies do have problems with the selection of subjects, the standardization of methodology, the management of data, and communication between studies. Those problems were discussed in the section on longitudinal studies.

If research on aging is to be most effectively conducted, then programs must be laid out and pursued vigorously. This section gives a brief overview of the areas that require study. Aging affects a great many of the organ systems, biochemical

*See footnote on page D1.

processes, and cellular and molecular functions of the body. In addition, there are psychological and societal aspects to aging which have significance for health. Thus, the field for descriptive studies of aging processes and for their experimental analysis is large. That field can be considered under the following subdivisions:

1. Molecular and Cellular Biology of Aging

2. Biochemical and Physiological Change with Age at the Organ and Organismic Level

3. Psychological and Societal Changes with Age

4. Aging and Disease

5. Research on Provision of Health Services to the Elderly.

Molecular and Cellular Biology of Aging

The molecular and cellular biology of aging is of central importance to an understanding of aging processes. As noted above, aging affects most of the components of the body. The effects of aging that are seen at the organ and organismic level are probably the complex results of processes that began at a molecular or cellular level. It is important that there be studies of these complex results since they affect the health of the individual and since it may prove possible to ameliorate them. However, the study of end-results may give little insight into the causal processes at a sub-cellular and cellular level. Therefore, part of the strategy of research on aging should consist of attempts to get at the relatively simple processes that underlie the complex end-results. Although it is probably not profitable to view aging as a disease, there is an analogy between the study of disease and the study of aging that appears useful. Many diseases have a great variety of manifestations that hardly seem related when first encountered. The chronic infectious disease, syphilis, is an excellent example. The identification of the many types of organ involvement that can occur in that disease was a very difficult task. The demonstration that all of its varied manifestations as it occurs in different patients can be attributed to one disease remained difficult and speculative until the discovery of the microscopic organism that causes the disease. The discovery of that agent made crystal clear what had been a very confusing process. Many other examples of diseases in which a simple process at a molecular or cellular level causes a very complex series of events at a clinical level could be cited. The discovery of the underlying simple events greatly advances the understanding of the whole processes involved. The foregoing discussion is not meant to imply that there is a single underlying molecular or cellular process responsible for aging. However, it does seem possible that there may be a relatively small number of underlying processes.

Thus, there is very little known about the molecular and cellular biology of aging, it represents an area of crucial importance to an understanding of aging, and very little work is currently being done on it. The absence of a large program on aging at a molecular and cellular level represents a major gap. The research leads that exist should be pursued vigorously and new approaches should be sought. High priority areas at this level are:

1. The Limited Lifespan of Normal Human Cells in Tissue Culture

2. Deoxyribonucleic Acid, Ribonucleic Acid, Synthesis of Enzymes, and Aging

3. Somatic Mutations and Aging

4. Lysosomes and Age Pigment

5. Connective Tissue and Aging--Collagen, Elastic Fibers, and Mucopolysaccharides.

There is a great need for the scientists in the biological fields that provide the knowledge on which medical science is based to work on the underlying mechanisms of aging processes. There is also a need for the development of facilities which will provide them with suitable experimental animals of the appropriate ages.

Biochemical and Physiological Changes with Age at the Organ and Organismic Level

Most of what is known about the biology of aging has been learned at this level. Although organ systems vary greatly in the degree of damage that they suffer in the course of aging, many such systems are known to be damaged. In addition, there are striking changes with age in the rates at which chemical compounds are transformed within the body into other compounds. Although a moderate amount of information has been collected in this area, a great deal still remains to be learned. Changes at the organ and organismic level whose study should receive high priority are those that seem to be related to prevalent disease processes. Outstanding examples are:

1. Metabolism of Carbohydrates and Lipid

2. Changes in Immunomechanisms with Age

3. Diet and Aging.

Changes in carbohydrate metabolism with age are very prevalent and resemble the changes that occur in diabetes mellitus, a common disease of the elderly. With increasing age there is an increase in blood lipids, a process that may be important in the development of atherosclerosis. These changes in biochemical function at an organismic level with increasing age have been studied very little. Their study may be of great practical importance since they may prove to be particularly sensitive to factors such as exercise and diet.

Reduction in the efficacy of the immune mechanisms with age may be important in the development of cancer in the elderly.

There is evidence that diet is of great importance in the development of disease and in length of life. The only experimental procedure that has been found which will greatly prolong mammalian life is undernutrition early in life. This was found for rodents. The significance of the finding for man is not known. However, obesity in the human is known to be associated with an increased incidence of certain diseases and with increased mortality.

In studies of changes at the level of the organ systems and the organism, it is particularly important to have well designed studies of human populations. Information obtained on experimental animals although suggestive cannot be transferred with complete confidence to the human species. In addition, quantitative details with regard to the time of onset and the degree of impairment of various systems will necessarily differ between man and experimental animals such as mice, rats, and dogs. This, then, is the area where appropriate longitudinal and cross-sectional studies of human subjects are vitally needed.

Very few longitudinal studies have been designed to cover the entire lifespan. There is a real need for this type of study because some of the determinants of function in middle and old age undoubtedly are operating very early in life. The quickest way to get results from such studies is to extend into the adult years the longitudinal studies of children that were started for other reasons. A reasonable approach toward the extension of such studies would be conferences involving investigators working on longitudinal studies in infants and children and investigators working on longitudinal studies of adults.

Psychological and Societal Changes with Age

Areas of high priority for study are:

1. Biologic Bases of Psychological Change with Age

2. Sensation, Perception, Psychomotor Skill, Information Processing, Learning, and Problem-Solving as a Function of Age

3. Psychological Adjustment in the Elderly--Retirement, Housing, Chronic Disease, and Bereavement.

Major and important changes occur in the function of the brain and in psychological behavior with age. Many of the psychological changes that occur with age no doubt have their origin in biochemical and physiological changes in the brain. Thus studies of those changes provide information which is useful in connection with more purely psychological studies. The statement that more remains to be learned of the function of the brain than of that of any other organ is probably a fair one. Thus the base of knowledge from which to investigate age changes in the brain leaves much to be desired. However, currently progress is being made in the study of the biochemical and physiological processes that underlie psychological behavior. As these processes become clarified, avenues for research on age changes in them open up. Promising leads are beginning to develop with regard to learning and memory for example and should be followed up. A study of underlying neurophysiological processes may also provide leads for the development of pharmacological agents that will aid the mental processes of the elderly.

In addition, a great deal of more purely psychological work on aging processes needs to be done. The areas of analysis of psychological change with age cover almost all of psychology. Particularly important are age changes in sensation, perception, learning, memory, concept formation, problem solving, creativity, emotional processes, and personality change.

Psychological adjustment in the elderly is an area which is also health related. The provisions that society makes relative to retirement and housing may affect the health of the elderly significantly. Appropriate studies need to be carried out in this area.

Aging and Disease

This review is not primarily concerned with disease. However, it is appropriate to point out that a knowledge of the general disease patterns of persons of various ages is important. There should be cross-sectional and longitudinal studies that will further develop knowledge in this area. Both studies

designed primarily to investigate aging and studies designed to study specific diseases may contribute to a general knowledge of disease patterns. Communication between investigators involved in both types of studies should be facilitated.

Research on Provision of Health Services to the Elderly

Another area of importance is that of the provision of health services to the elderly. A large fraction of health services go to the elderly simply because they are the most unhealthy fraction of the population. The mechanisms for getting health services to the elderly have improved greatly in recent years but continuing study of existing and possible mechanisms is needed.

APPENDIX A

Agencies that participated in or were contacted in the preparation of this review were:

Department of Health, Education and Welfare
- United States Public Health Service
  - The National Institutes of Health
  - The National Institute of Mental Health
  - The Bureau of Health Services
  - The Bureau of Disease Prevention and Environmental Control
- The Administration on Aging
- The Vocational Rehabilitation Administration
- The Food and Drug Administration
- The Social Security Administration

The Department of Defense
- United States Air Force
- United States Navy

The Department of Agriculture

The Department of Transportation
- Federal Aviation Administration

The Veterans Administration

The National Aeronautics and Space Administration

The Atomic Energy Commission

Some of the above agencies now have a different organizational position than they had in 1967. They are listed as they were in 1967.