PRIVACY ACT MATERIAL REMOVED

718828

S.H. Cohn

Form Approved
Budget Bureau No. 68-R0249

SECTION I

DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE

GRANT APPLICATION

LEAVE BLANK		
TYPE	PROGRAM	NUMBER
REVIEW GROUP		FORMERLY
COUNCIL *(Month, Year)*		DATE RECEIVED

TO BE COMPLETED BY PRINCIPAL INVESTIGATOR *(Items 1 through 7 and 15A)*

1. TITLE OF PROPOSAL *(Do not exceed 53 typewriter spaces)*

Epidemiology of Osteoporosis: Prevention and Therapy (deleted version)

2. PRINCIPAL INVESTIGATOR

2A. NAME *(Last, First, Initial)*

Cohn, Stanton H.

2B. TITLE OF POSITION

Senior Scientist

2C. MAILING ADDRESS *(Street, City, State, Zip Code)*

Medical Research Center
Brookhaven National Laboratory
Upton, New York 11973

2D. DEGREE: Ph.D.

2E. SOCIAL SECURITY NO.:

2F. TELEPHONE DATA: Area Code 516 TELEPHONE NUMBER AND EXTENSION 345-3591

2G. DEPARTMENT, SERVICE, LABORATORY OR EQUIVALENT *(See Instructions)*

Medical Dept., Brookhaven National Lab.

2H. MAJOR SUBDIVISION *(See Instructions)*

N/A

3. DATES OF ENTIRE PROPOSED PROJECT PERIOD *(This application)*

FROM: May 1, 1976 THROUGH: April 30, 1979

4. TOTAL DIRECT COSTS REQUESTED FOR PERIOD IN ITEM 3: $199,310

5. DIRECT COSTS REQUESTED FOR FIRST 12-MONTH PERIOD: $61,300

6. PERFORMANCE SITE(S) *(See Instructions)*

Medical Research Center
Brookhaven National Laboratory
Upton, New York 11973
Congressional District No. 1

REPOSITORY DOE RECORDS CENTER
COLLECTION 7723 ASEV CENTRAL FILES - 1975
BOX No 6075
FOLDER MH#5-21 BNL - JUL.-DEC. - 1975

7. Research Involving Human Subjects *(See Instructions)*

A. ☐ NO B. ☒ YES Approved: 11/21/74 (Date)
C. ☐ YES — Pending Review

8. Inventions *(Renewal Applicants Only - See Instructions)*

A. ☐ NO B. ☐ YES — Not previously reported
C. ☐ YES — Previously reported

TO BE COMPLETED BY RESPONSIBLE ADMINISTRATIVE AUTHORITY *(Items 8 through 13 and 15B)*

9. APPLICANT ORGANIZATION(S) *(See Instructions)*

Associated Universities, Inc.
Brookhaven National Laboratory
Upton, New York 11973

11. TYPE OF ORGANIZATION *(Check applicable item)*

☐ FEDERAL ☐ STATE ☐ LOCAL ☒ OTHER *(Specify)*
Private, non-profit

12. NAME, TITLE, ADDRESS, AND TELEPHONE NUMBER OF OFFICIAL IN BUSINESS OFFICE WHO SHOULD ALSO BE NOTIFIED IF AN AWARD IS MADE

James L. Desmond
Executive Assistant
Brookhaven National Laboratory
Upton, New York 11973

Telephone Number 516-345-3330

10. NAME, TITLE, AND TELEPHONE NUMBER OF OFFICIAL(S) SIGNING FOR APPLICANT ORGANIZATION(S)

N. Peter Rathvon, Jr., Secretary
Associated Universities, Inc.
Brookhaven National Laboratory
Upton, New York 11973

Telephone Number (s) 516-345-3328

13. IDENTIFY ORGANIZATIONAL COMPONENT TO RECEIVE CREDIT FOR INSTITUTIONAL GRANT PURPOSES *(See Instructions)*

Brookhaven National Laboratory

14. PHS ACCOUNT NUMBER *(Enter if known)* Entity No. 11-1630900

15. CERTIFICATION AND ACCEPTANCE. We, the undersigned, certify that the statements herein are true and complete to the best of our knowledge and accept, as to any grant awarded, the obligation to comply with Public Health Service terms and conditions in effect at the time of the award.

SIGNATURES (Signatures required on original copy only. *Use ink, "Per" signatures not acceptable)*	A. SIGNATURE OF PERSON NAMED IN ITEM 2A	DATE
	B. SIGNATURE(S) OF PERSON(S) NAMED IN ITEM 10	DATE

PHS-398
Rev. 3-70

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PRIVACY ACT MATERIAL REMOVED

S.H. Cohn

SECTION 1

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE

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PROJECT NUMBER

RESEARCH OBJECTIVES

NAME AND ADDRESS OF APPLICANT ORGANIZATION

Associated Universities, Inc.
Medical Research Center, Brookhaven National Laboratory, Upton, New York 11973

NAME, SOCIAL SECURITY NUMBER, OFFICIAL TITLE, AND DEPARTMENT OF ALL PROFESSIONAL PERSONNEL ENGAGED ON PROJECT, BEGINNING WITH PRINCIPAL INVESTIGATOR

S.H.Cohn, Ph.D. -	- Senior Scientist	- Medical Dept., Brookhaven Natl. Lab.
K.J.Ellis, Ph.D. -	- Asst. Scientist	- Medical Dept., Brookhaven Natl. Lab.
I.Zanzi, M.D.	- Associate Scientist	- Medical Dept., Brookhaven Natl. Lab.
H.Pate	- Scientist	- Medical Dept., Brookhaven Natl. Lab.
J.Aloia, M.D.	- Asst. Chief Endocrin.	- Nassau County Medical Center
S.Wallach, M.D. -	- Prof. Med.	- Downstate University of N.Y.
M.Roginsky, M.D.-	- Chief Endocrin Serv.	- Nassau County Medical Center
H.L.Atkins, M.D.-	- Senior Scientist	- Medical Dept., Brookhaven Natl. Lab.
J.Jowsey, Ph.D. -	- Director, Orthoped. Res.	- Mayo Clinic, Minn.

TITLE OF PROJECT

Epidemiology of Osteoporosis: Prevention and Therapy

USE THIS SPACE TO ABSTRACT YOUR PROPOSED RESEARCH. OUTLINE OBJECTIVES AND METHODS. UNDERSCORE THE KEY WORDS (NOT TO EXCEED 10) IN YOUR ABSTRACT.

The identification of the disease osteoporosis and the evaluation of programs of treatment have long been hampered by the lack of a sensitive quantitative measure of the condition. The following proposal offers such a quantitative measure, and further, d evelops both prophylactic and therapeutic programs which may be evaluated quantitatively and hence meaningfully compared.

The quantification rest primarily on the newly developed technique of total-body neutron activation analysis. A measure is made of the total-body calcium which reflects the skeletal mass. The normal skeletal mass can be predicted for an individual on the basis of sex, age, height and lean body mass. Thus the degree of difference between the measured and the predicted value can be calculated for each individual.

A prospective study will attempt to define a sub-group in a population of post-menopausal women who are considered to be at high risk for developing osteoporosis (on the basis of low skeletal mass). The effect of prophylactic estrogen supplementation to this above sub-group will be evaluated in terms of bone mass as well as the reduction in the incidence and severity of osteoporosis. Evaluation will also be made of the effectiveness of various regimens of treatment for osteoporosis; estrogen, androgen, fluoride and calcitonin, both singly and in combination. Human growth hormone will also be evaluated as a therapeutic agent. It acts to increase skeletal mass by increasing the bone accretion rate, unlike the above agents which act to decrease the bone resorption rate. Finally, the effects of physical activity on body composition and skeletal mass will be studied in a geriatric population.

An essential requirement in all these studies is the establishment of normal changes in body composition with age. The total body levels of calcium (skeletal mass) and potassium (lean body mass), as well as sodium, chlorine and phosphorus, will be measured in a population of normal subjects.

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NIH 398 (FORMERLY PHS 398)
Rev. 1/73

SECTION II – PRIVILEGED COMMUNICATION

DETAILED BUDGET FOR FIRST 12-MONTH PERIOD

FROM: May 1, 1976 THROUGH: April 30, 1977

DESCRIPTION (Itemize)		TIME OR EFFORT %/HRS.	AMOUNT REQUESTED (Omit cents)		
PERSONNEL			SALARY	FRINGE BENEFITS	TOTAL
NAME	TITLE OF POSITION				
S. H. Cohn, Ph. D.	PRINCIPAL INVESTIGATOR	25%	--	--	--
I. Zanzi, M.D.	Associate Scientist	50%	15,500	3,410	18,910
K. J. Ellis, Ph. D.	Assistant Scientist	25%	--	--	--
S. Yasumura, Ph. D.	Research Collaborator	5%	--	--	--
Technician	--	100%	12,000	2,640	14,640
Research Associate	--	100%	12,500	2,750	15,250
J. Aloia, M.D.	Research Collaborator	10%	--	--	--
S. Wallach, M.D.	Research Collaborator	5%	--	--	--
M. Roginsky, M.D.	Research Collaborator	10%	--	--	--
H. L. Atkins, M.D.	Senior Scientist	5%	--	--	--
C. Abesamis, M.D.	Research Collaborator	60%	--	--	--
J. Jowsey, Ph. D.	Research Collaborator	5%	--	--	--

CONSULTANT COSTS		
EQUIPMENT	--	
SUPPLIES	General laboratory supplies including calcium supplements	2,000
TRAVEL	DOMESTIC 3 trips to scientific meetings	1,000
	FOREIGN	--
PATIENT COSTS (See instructions)		--
ALTERATIONS AND RENOVATIONS		--
OTHER EXPENSES (Itemize)	Instrument maintenance & repair	2,000
	Machine shop time	1,000
	Computer usage and maintenance	1,500
	X-ray & Pathology Lab. service	5,000
TOTAL DIRECT COST (Enter on Page 1, Item 5)		$61,300

INDIRECT COST (See Instructions)

DATE OF DHEW AGREEMENT: 10/25/74 (Excl. Equip.)

____ % S&W*

38 % TDC*

☐ WAIVED

☐ UNDER NEGOTIATION WITH: _____

*IF THIS IS A SPECIAL RATE (e.g. off-site), SO INDICATE.

4004622

BUDGET ESTIMATES FOR ALL YEARS OF SUPPORT REQUESTED FROM PUBLIC HEALTH SERVICE
DIRECT COSTS ONLY (Omit Cents)

DESCRIPTION		1ST PERIOD (SAME AS DETAILED BUDGET)	ADDITIONAL YEARS SUPPORT REQUESTED *(This application only)*					
			2ND YEAR	3RD YEAR	4TH YEAR	5TH YEAR	6TH YEAR	7TH YEAR
PERSONNEL COSTS		48,800	53,845	59,165				
CONSULTANT COSTS *(Include fees, travel, etc.)*		-	-	-				
EQUIPMENT		-	-	-				
SUPPLIES		2,000	2,000	2,000				
TRAVEL	DOMESTIC	1,000	1,000	1,000				
	FOREIGN	-	-	-				
PATIENT COSTS		-	-	-				
ALTERATIONS AND RENOVATIONS		-	-	-				
OTHER EXPENSES		9,500	9,500	9,500				
TOTAL DIRECT COSTS		61,300	66,345	71,665				

TOTAL FOR ENTIRE PROPOSED PROJECT PERIOD *(Enter on Page 1, Item 4)* → $ 199,310

REMARKS: *Justify all costs for the first year for which the need may not be obvious. For future years, justify equipment costs, as well as any significant increases in any other category. If a recurring annual increase in personnel costs is requested, give percentage. (Use continuation page if needed.)*

Personnel salaries are increased at an annual rate of 9% for the 02 and 03 years.

SECTION II – PRIVILEGED COMMUNICATION

BIOGRAPHICAL SKETCH

(Give the following information for all professional personnel listed on page 3, beginning with the Principal Investigator. Use continuation pages and follow the same general format for each person.)

NAME	TITLE	BIRTHDATE *(Mo., Day, Yr.)*
Stanton H. Cohn	Senior Scientist	
PLACE OF BIRTH *(City, State, Country)*	**PRESENT NATIONALITY** *(If non-U.S. citizen, indicate kind of visa and expiration date)*	**SEX**
	U.S.A.	☒ Male ☐ Female

EDUCATION *(Begin with baccalaureate training and include postdoctoral)*

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	SCIENTIFIC FIELD
University of Chicago	S.B.	1946	Biochemistry
University of Chicago	SM	1949	Physiology
University of California (Berkeley)	Ph.D.	1952	Radiobiology

HONORS

Sigma XI

MAJOR RESEARCH INTEREST	ROLE IN PROPOSED PROJECT
Mineral Metabolism	Coordinator

RESEARCH SUPPORT *(See instructions)*

Associated Universities, Inc., Contract No. E (30-1)-16 with the U.S. Energy Research and Development Administration

Armour Pharmaceutical Co.; Effect of Calcimar (Calcitonin) in Patients with Primary Osteoporosis, August 1975-July 1977, $62,565.

RESEARCH AND/OR PROFESSIONAL EXPERIENCE *(Starting with present position, list training and experience relevant to area of project. List all or most representative publications. Do not exceed 3 pages for each individual.)*

See attached Curriculum Vitae

CURRICULUM VITAE

Stanton H. Cohn

Born: Chicago, Illinois

I. EXPERIENCE

1958 - to present	Senior Scientist, Medical Physics Division Medical Research Center Brookhaven National Laboratory Upton, L.I., New York 11973
1950 - 1958	Head, Internal Toxicity Branch Bio-Medical Division U. S. Naval Radiological Defense Laboratory San Francisco, California
1949 - 1950	Research Assistant Crocker Radiation Laboratory University of California Berkeley, California
1946 - 1949	Biochemist, Bio-Medical Division Argonne National Laboratory University of Chicago Chicago, Illinois
1943 - 1946	Biochemist, Laboratory of the 203 rd Gen. Hosp. U. S. Army Paris, France
1942 - 1943	Chemist, Explosive Kankakee Ordnance Works Joliet, Illinois

II. EDUCATION

1952	University of California Berkeley, California	Ph.D., Physiology (Dr. Hardin Jones)
1949	University of Chicago Chicago, Illinois	S. M.,Physiology (Dr. Franklin McLean)
1946	University of Chicago Chicago, Illinois	S. B.,Biochemistry
1945	Sorbonne University Paris, France	French Literature
1941	Illinois Inst. of Technology Chicago, Illinois	Engineering Science Defense Training

[redacted]

Stanton H. Cohn CURRICULUM VITAE (continued)

III. OTHER ACTIVITIES, MEMBER OF

A. National Council on Radiation Protection, Scientific Committee 34. 1970-

B. Editorial Board, Radiation Research Journal. 1965-196

C. National Committee on Radiation Protection, Subcommittee 2. 1961-196

D. Subcommittee on Inhalation Hazards of the Pathological Effects of Atomic Radiation Committee, National Academy of Sciences. 1956-196

E. U. S. Medical Team which provided emergency medical treatment for the Marshall Islanders accidentally exposed to fallout in 1954. Studied the internal radioactive contamination of the exposed Marshallese.

F. AEC Medical Team which carried out medical surveys of the Marshallese in 1959 and 1961. Measured the body burdens of 200 Marshallese, using a "portable" whole-body counter.

G. Consultant to Armed Forces Radiobiology Research Institute, National Naval Medical Center. 1962-196

H. Lecturer for Medical Education for National Defense, American Institute of Biological Sciences 1962-196

IV. SCIENTIFIC SOCIETIES, MEMBER OF

A. American Physiological Society

B. Radiation Research Society

C. Sigma Xi

D. Health Physics Society

[redacted]

93. Effect of porcine Calcitonin on calcium metabolism in osteoporosis.

S. H. Cohn, C. S. Dombrowski, W. Hauser, J. Klopper and H. L. Atkins. J. Clin. Endocrin. & Metab. 33; 719, 1971.

94. Determination of body composition by neutron activation in patients with renal failure.

S. H. Cohn, T. J. Cinque, C. S. Dombrowski and J. M. Letteri J. Lab. Clin. Med. 79: 978, 1972.

95. Design and calibration of a broad-beam ^{238}Pu.Be source for total body neutron activation analysis.

S. H. Cohn, K. K. Shukla and R. G. Fairchild J. Nucl. Med. 13: 487, 1972.

96. Calcitonin Treatment of Osteoporosis.

S. Wallach and S. H. Cohn Seminar in Drug Treatment, Vol 2, No. 1 (June) 1972.

97. Effects of chronic calcitonin administration in the bone disease of Thalassemia.

F. Shai, S. Wallach, S. H. Cohn and R. K. Baker In Clin. Aspects of Metabolic Bone Disease, Ford Hospital, Detroit, Michigan (Excerpta Medica) 1972.

98. Calcium homeostasis - The hard facts about soft bones.

S. H. Cohn, Brookhaven National Laboratory Lecture, No. 109, March 1972.

99. Skeletal calcium metabolism and body composition in acromegaly.

J. Aloia, M. Roginsky, C. S. Dombrowski and S. H. Cohn J. Clin. Endoc. & Metab. 35: 543, 1972.

100. Determination of whole-body magnesium by in-vivo neutron activation in the rat.

C. S. Dombrowski, S. Wallach, K. K. Shukla and S. H. Cohn Int. J. Nucl. Med. and Biol. 1: 15, 1973.

101. Physiological variations of total-body potassium in man. K. K. Shukla, K. Ellis, C. S. Dombrowski and S. H. Cohn J. Appl. Physiol. 224: 271, 1973.

102. Body composition changes in children receiving human growth hormaone.

P. J. Collipp, V. Curti, J. Thomas, R. K. Sharma, J. T. Maddiah and S. H. Cohn Metab. 22: 589, 1973.

[redacted]

103. Fallout ^{137}Cs levels in man over a twelve year period.

K.K. Shukla, C. S. Dombrowski and S. H. Cohn
Health Phys. 24: 555, 1973.

104. Alterations in elemental body composition in thyroid disorders.

S. H. Cohn, M. S. Roginsky, J. F. Aloia, K. J. Ellis and K. K. Shukla
J. Clin. Endocrinol. Metab. 36: 742, 1973.

105. Alterations in skeletal calcium and phosphorus in dysfunctions of the parathyroid.

S. H. Cohn, M. S. Roginsky, J. F. Aloia, K. J. Ellis and K. K. Shukla
J. Clin. Endocrinol. Metab. 36: 750, 1973.

106. Alterations in skeletal mass in endocrine dysfunction as determined by total-body neutron activation analysis.

S. H. Cohn, M. S. Roginsky, J. F. Aloia, K. J. Ellis and K. K. Shukla
Proc. Ninth European Symposium on Calcified Tissue, Baden, Austria 1972, 1973.

107. Theoretical considerations in the selection of neutron sources for total-body neutron activation analysis.

S. H. Cohn, R. G. Fairchild and K. K. Shukla
Phys. Med. Biol. 18: 643, 1973.

108. Formulation of a stochastic model of long-term strontium data using the likelihood function.

J. R. Sheer and S. H. Cohn
J. Theoret. Biol. BNL 13167-1973

109. Effect of calcitonin on calcium metabolism in the rat. Ph.D. Thesis St. John's University.

C. S. Dombrowski, K. K. Shukla and S. H. Cohn BNL 17784 (1973).

110. Measurement of calcium in rats by total body neutron activation analysis.

K. K. Shukla and S. H. Cohn
Intern. J. Nucl. Med. Biol. 1: 73, 1973.

111. A multivariate predictor of total-body calcium

S. H. Cohn, K. K. Shukla and K. J. Ellis
Int. J. Nucl. Med. Biol. 1: 131, 1974

[redacted]

112. Recent advances in whole-body counting.

S. H. Cohn and H. E. Palmer
Int. J. Nucl. Med. Biol. 1: 155, 1974.

113. Neutron sources, energy, flux density and moderation in total-body neutron activation analysis.

S. H. Cohn, R. G. Fairchild and K K. Shukla
IAEA Panel on In-vivo Activation Analysis, IAEA Pl-493/2, Vienna, 1973.

114. Comparsion of techniques for the total-body neutron activation analysis of calcium in man.

S. H. Cohn, R. G. Fairchild and K. K. Shukla
IAEA Panel on In-vivo Activation Analysis, IAEA Pl-493/3, Vienna, 1973.

115. A total-body neutron activation facility employing portable (cn) sources developed for medicine research.

S. H. Cohn, K. K. Shukla, C. S. Dombrowski and R. G. Fairchild
Neutron Activation Techniques in Life Sciences-Bled Yugoslavia IAEA-1972.

116. Experimental particle radiation therapy in animal neoplasia. 1. Electron vs x-irradiation.

S. W. Lippincott, J. L. Montour, J. D. Wilson, S. H. Cohn and R. E. Flora
Acta Radiol. Ther. Physics & Biol. 12: 541, 1973.

117. A predictor for total-body potassium in man based on height, weight, sex and age: Application in metabolic disorders.

K. J. Ellis, K. K. Shukla and S. H. Cohn
J. Lab. Clin. Med. 83: 716, 1974.

118. Absolute and relative deficit in total skeletal calcium and radial bone mineral content in osteoporosis.

S. H. Cohn, K. J. Ellis, S. Wallach, I. Zanzi, H. L. Atkins and J. F. Aloia
J. Nucl. Med. 15: 428, 1974.

119. Altered Calcium metabolism in chronic renal failure.

J. M. Letteri, D. Orfino, S. Ruggieri, K. J. Ellia and S. H. Cohn
Kidney Intern. 6: 45, 1974.

[redacted]

120. Application of coincidence counting techniques in a fixed geometry whole-body counter.

N. S. Chen, K. J. Ellis, H. R. Pate and S. H. Cohn
Int. J. Nucl. Med. & Biol. 1: 175, 1974.

121. Correlation of radial bone mineral content with total-body calcium in various metabolic disorders.

S. H. Cohn, K. J. Ellis, I. Zanzi, J. Letteri and J. Aloia
Int. Conf. on Bone Mineral Measurements, Chicago, 1973. DHEW (NIH) 75-683.

122. In vivo neutron activation analysis: Clinical potential in body composition studies.

S. H. Cohn, K. J. Ellis and S. Wallach
Amer. J. Med. 57: 683, 1974.

123. Skeletal metabolism and body composition in Cushing's disease.

J. F. Aloia, M.S. Roginsky, K. J. Ellis, K. K. Shukla and S. H. Cohn
J. Clin. Endo. & Metab. 39: 981, 1974.

124. An improved radionuclide distribution profile from a fixed array whole-body counter using a mathematical analysis technique.

N. S. Chen and S. H. Cohn
Int. J. Nucl. Med. & Biol. 1: 169, 1974.

125. Calcitonin in treatment of ostoeporosis.

S. Wallach, S. H. Cohn, H. L. Atkins, K. J. Ellis and J. F. Aloia
Int. Symp. on Calcitonin, Carlo Erba, Milan, 1974.

126. The correlation between skeletal mass and muscle mass in man.

K. J. Ellis and S. H. Cohn
J. Appl. Physiol. 38: 455, 1975

127. Treatment of osteoporosis with growth Hormone.

J. F. Aloia, I. Zanzi, K. J. Ellis, M. Roginsky, S. Wallach and S. H. Cohn.
In Advances in Hormone Research (899-916) Ed. S. Raite, HEW-NIH-74, 612, 1974.

128. Skeletal turnover and total body elemental composition during extended calcitonin treatment of Paget's disease.

S. Wallach, A. Avramides, A. Flores, J. Bellavia and S. H. Cohn
Metabolism. 24: 745, 1975.

PRIVACY ACT MATERIAL REMOVED

S.H. Cohn

SECTION II – PRIVILEGED COMMUNICATION

BIOGRAPHICAL SKETCH

(Give the following information for all professional personnel listed on page 3, beginning with the Principal Investigator. Use continuation pages and follow the same general format for each person.)

NAME	TITLE	BIRTHDATE (Mo., Day, Yr.)
Italo Zanzi, M.D.	Associate Attending Physician MRC, BNL. Visiting Assoc. Scientist, BNL.	
PLACE OF BIRTH (City, State, Country)	PRESENT NATIONALITY (If non-U.S. citizen, indicate kind of visa and expiration date)	SEX
	Chile, H-1 (3 yr more)	☒ Male ☐ Female

EDUCATION *(Begin with baccalaureate training and include postdoctoral)*

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	SCIENTIFIC FIELD
School Sacred Hearts. Santiago, Chile	Bacc.	1949	
Univ. Chile Medical Sc., Santiago, Chile	M.D.	1/9/1957	Medicine
Royal Postgraduate Med. School, London	——	1964	Endocrinology
Cornell Univ. Med. Center (HSS), N.Y.	——	1968-69	Metabolic Bone Diseas

HONORS Awards: "Prof. R. Vicuna Foundation" for thesis, 1957
"Ayerst-Chile" 1963, for paper in collaboration
"Ayerst-Chile" 1967, for paper in collaboration
Member NIH Site Visit (1974 and 1975)

MAJOR RESEARCH INTEREST	ROLE IN PROPOSED PROJECT
Endocrinology (Metabolic Bone Diseases) Nuclear Medicine	Clinician

RESEARCH SUPPORT *(See instructions)*

Associated Universities, Inc., Contract No. E(30-1)-16 with the U.S. Energy Research and Development Administration.

Armour Pharmaceutical Co.; Effect of Calcimar (Calcitonin) in Patients with Primary Osteoporosis, August 1975-July 1977, $62,565.

RESEARCH AND/OR PROFESSIONAL EXPERIENCE *(Starting with present position, list training and experience relevant to area of project. List all or most representative publications. Do not exceed 3 pages for each individual.)*

EXPERIENCE:

-Associate Attending Physician, Hospital of the Medical Research Center, Brookhaven National Laboratory, Upton, New York, 1973 to present date.
-Research Collaborator, Medical Research Center, Brookhaven National Laboratory, Upton, New York, 1973.
-Visiting Associate Scientist, Medical Research Center, Brookhaven National Laboratory, Upton, New York 11973 1974 to present date.
-Research Collaborator, Nassau County Medical Center, East Meadow, New York, 1973.
-Consultant, Department of Medicine, Division of Endocrinology, Nassau County Medical Center, East Meadow, New York, 1974 to present date. Incharge of the Metabolic Bone Clinic.
-Assistant Professor of Medicine, State University of New York at Stony Brook, 1973 to present date.
-1957 to 1975: Attending Physician, Endocrinology Center or Section of Endocrinology, Chair or Department of Medicine, Hospital Clinico Jose J. Aguirre. Since 1960 on the Staff of the Radioisotope Laboratory; 1969-1972, in charge of it. Instructor in Medicine (1957-1964); Assistant Professor of Medicine, 1965-1975, University of Chile Faculty of Medicine.
-Visiting Scientist and Research Fellow, Hospital for Special Surgery and Cornell Medical Center, New York, 1968-1969.

NIH 398 (FORMERLY PHS 398)
Rev. 1/73

4004631

U. S. GOVERNMENT PRINTING OFFICE : 1971 O - 451-736

TRAINING:

-Courses on several aspects of Internal Medicine, Organized by the University of Chile Post Graduate Medical School, Chilean Society of Endocrinology and Medical Society of Santiago. (1957-1958).
-Puerto Rico Nuclear Center, 1960, courses on Radioisotopes. - Northwestern University, 1960, clinical and research training. - Royal Postgraduate Medical School, and Guy's Hospital, London, 1964-1965, clinical and research training.
-Course on Bone Pathology, New York, 1968.
-Courseson Endocrinology: Glasgow, 1964, London 1972 (Royal Postgraduate Medical School).
-Courses on Nuclear Medicine: New York 1975, Maine 1975.

PERTINENT PUBLICATIONS:

"Raquitismo y Osteomalacia de Origen Tubular Renal" (Rickets and Osteomalacia), in colaboration; Rev. Med Chile 90:158, 1962. Presented at the 2nd. Panamerican Congress of Endocrinology. Ayerst (Chile) Award.

"Enfermedades de las Glandular Endocrinas en Chile" (Diseases of the endocrine glands in Chile) Rev. Med. Chile 91:609, 1963. Presented at the 3rd. Chilean Endocrinological Meeting.

"Osteomalacia y Mionpatia Hipofosbemica No Familiar por Defectos Selectivo de la Absorcion Intestinal de Calcio". Litvak, J., Conteras, W., Zanzi, I., Riesco, J., Armendaris, R., Diaz, S. Presented at IIas Jornadas de Medicina Interna, Santiago, 1965.

"Determinacion Externa de las Curvas de Captacion Osea del Ca-47 en Enfermedades Metabolicas Oseas". Zanzi, I., Litvak, J., Bozzo, S.M., Alliende, I. Rev. Med. Chile 94:221, 1966. Presented at IIas Jornadas de Medicina Interna Santiago, 1965.

"Consideraciones sobre la Determinacion Externa de la "Captacion" Osea de Ca-47 y Sr-85". Zanzi, I., Bozzo, S., Litvak, J. y Alliende, I. Resumenes de las Communicaciones cortas. 1er Congreso Chileno de Endocrinologia y Metabolismo, pag. 75, Santiago, 1966.

"Enfermedades de las Paratiroides". Litvak, J., y Zanzi, I., en "Endocrinologia Clinica". Comision Central de Publicaciones de la Universeidad de Chile, Santiago, 1967.

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EPIDEMIOLOGY OF POST-MENOPAUSAL
OSTEOPOROSIS: PREVENTION AND THERAPY

I. Epidemiology of Post-Menopausal Osteoporosis and its Prevention by Estrogen Administration

A. Introduction

1. Objective: To study the epidemiology of post-menopausal osteoporosis and its possible prevention by administration of estrogens.

2. Background: Although the etiology of primary osteoporosis has not been clearly elucidated, a number of possible factors have been identified. Various investigators have indicated roles for the following factors: reduction of levels of sex hormones at menopause, inadequate dietary calcium intake, impaired calcium absorption, high phosphorus intake, hypersensitivity of bone to parathyroid hormone, physical inactivity, hereditary factors, unresponsiveness to growth hormone, and aging (1).

Initially it was believed that the onset of osteoporosis represented a decreased level of bone formation resulting from a decrease in the level of gonadal steroids (2). The present consensus, however, is that an increase in bone resorption rather than a decrease in bone formation is primarily responsible for the onset of osteoporosis (1,3,4). When resorption is extensive and of long duration, the density of the skeleton may decrease sufficiently to result in the spontaneous vertebral collapse characteristic of osteoporosis.

The extent of osteoporosis in the population, and the efficacy of therapeutic programs are both difficult to assess because, at the present time, there exist no generally accepted quantitative measurements for determination of the degree of severity of the condition. There is a need for a sensitive measure of skeletal mass to provide early detection of subtle changes in bone. Radiographic techniques are useless for detection of any but gross demineralization. Analysis by histological, chemical and microradiographic techniques of biopsy samples of bone have yielded much useful information. These techniques, however, provide information on small localized areas only; extrapolation is required for estimation of changes in total skeletal mass. Densitometric techniques based on photon transmission are more precise but again yield essentially localized information on changes in the degree of demineralization.

The most sensitive and direct measure of total skeletal mass is obtained with the recently developed technique of total-body neutron activation analysis (TBNAA). With this technique the absolute amount of Ca is measured with a precision of 1% (S.D.) and the total skeletal mass can consequently be determined.

3. Rationale: In the present study the unique Brookhaven neutron irradiation facility and the whole-body counter is employed for TBNAA to quantitate the levels of total-body Ca and P in post-menopausal women. TBNAA is the principal technique used to quantitate the alteration in skeletal composition with age or following institution of appropriate therapy for the condition, over long periods of time.

Even though estrogens have not proved efficacious in reversing the accumulated effects of an osteoporotic condition that has been extant for a period of time, it is possible that administration of estrogen at menopause may slow or inhibit the development of osteoporosis (3,5-8). Thus, estrogens may be useful in a prophylactic program.

It is proposed first to identify a group of women who are considered to be at

high risk for developing osteoporosis, and then to treat a portion of the group with estrogens administered prophylactically from the onset of the menopause. The women will be selected on the basis of a high probability that osteoporosis will develop, in accordance with current theory. The hypothesis is that those women who, before menopause, have a smaller than average skeletal mass for their age and habitus are at greatest risk for early development of osteoporosis. Under the hypothesis, it is assumed that the rate of loss of calcium due to senescence is fairly standard for all women (9, 10). In that case, the degree of osteoporosis would be a direct function of the size of the skeletal mass at menopause.

B. Specific Aims

The present program was thus designed to facilitate the diagnosis of osteoporosis by the development of a set of quantitative measurements for clinical use (in particular, skeletal mass), and further, to develop and assess specific prophylactic effects of estrogens. The specific aims of this study are:

1. to identify, by means of the measurement of skeletal mass, a group of women close to menopause who appear to be at high risk for osteoporosis;

2. to determine, over an extended period of time, whether administration of estrogens starting at the onset of menopause will result in a significant reduction in the number of cases of osteoporosis and further, of the degree of severity of osteoporosis, as compared to the incidence and degree in a control group.

3. To determine the average rate of loss of calcium for all three groups of post-menopausal women in the ten year period of study.

C. Methods of Procedure

The skeletal mass will be measured in 100 women who have recently terminated their menses. Measurement of the skeletal mass will be made by the technique of total-body neutron activation analysis (11-13). The density of the radius will also be measured by photon densitometry (15-16).

The normal level of body calcium will be calculated for each patient. For this purpose, a multivariate predictor by means of which normal calcium mass can be estimated using height and total body potassium (measured by whole body counting) was developed in a study of a normal population (14). With this technique, the normal total body calcium in any subject can be predicted to within 5% (1 S.D.). Comparison of the direct measurement of skeletal mass with the predicted total body calcium for each subject will determine the percent deviation from the normal for each subject.

The original group of women will be separated into two groups on the basis of their measured calcium mass in relation to their predicted normal calcium. The group with the lowest values of skeletal mass (i.e., lowest total-body Ca) will be further subdivided into two groups. One group will receive estrogens (2.5 mg conjugated estrogens per day) and calcium supplements; (0.5 g Ca per day); the other group will receive only calcium supplements (which have been shown to be of some benefit, 17). A third group will receive no treatment, and will serve as the contrast population.

It is planned to measure the total-body calcium in this group of post-menopausal women on a yearly basis for a period of ten years. With the high precision of the TBNAA technique, differences in total-body calcium can be measured over a period of years at the 2% level with 95% confidence (2 S.D.).

Baseline Studies: All studies will be performed on an outpatient basis. In addition to routine history (including dietary history) and a general physical examination, vaginal cytology will be performed. Blood samples will be obtained for complete blood count (CBC), blood urea nitrogen (BUN), fasting blood sugar (FBS),

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serum glutamic oxalacetic transaminase (SGOT), Ca, P, bilirubin, alkaline phosphatase, and serum protein electrophoresis. In addition a urinalysis will be made. Twenty-

found an anabolic steroid to be as effective as estrogens in reduction of bone-resorbing surfaces (3).

c. Fluoride: Fluorosis has been observed in areas where there is excessive fluoride in the drinking water (21). This disorder is characterized by bony exostoses, calcification of ligaments and excessive bone density. However, many individuals are asymptomatic and exhibit only increased radiodensity. It was because of this finding that Rich (22,23) proposed the use of fluoride for treatment of osteoporosis. Study of bone biopsy specimens from animals and also from human subjects has clearly shown that the basic effect of fluoride is the stimulation of osteoblasts by inducing bone crystal growth (24-26). Moreover, the incorporation of F into the hydroxyapatite crystal of bone is thought to produce more stable bone which is resistant to resorption by parathyroid hormone. There are numerous papers concerning the efficacy of fluoride therapy, but few researchers have utilized objective techniques in their investigation. Two recent studies merit consideration (27).

Here, at Brookhaven, the short-term effects of daily administration of 20 mg of fluoride on ^{47}Ca tracer kinetics and total body calcium has been studied in an osteoporotic population (27). The lack of significant improvement was attributed to the short period of treatment (2 months) and the fact that calcium supplements were not administered.

A variety of morphologic techniques have demonstrated that the newly formed osteoid induced by F therapy may be poorly mineralized as evidenced by the osteoid seams (characteristic of osteomalacia) which develop. Jowsey found that administration of less than 45 mg of NaF daily (20.5 mg of fluoride) did not consistently increase bone formation, whereas the administration of 60 mg or more produced parathyroid hyperplasia and thereby increased bone resorption levels (25).

3. Rationale

It has been known for some time that bone formation and bone resorption are normally coupled. The objective in the treatment of osteoporosis is to effect uncoupling -- i.e., to increase bone formation to a level higher than that of bone resorption, or to reduce bone resorption to a level less than that of bone formation. It appears that sex hormones and calcitonin successfully reduce bone resorption. However, it is suggested that after several months, the formation and resorption levels become coupled again, thereby limiting the net increase in skeletal mass that can be attained. Riggs and Jowsey has provided confirmatory evidence for this hypothesis in her analysis by quantitative microradiography of bone biopsies of sex-steroid treated osteoporotics (5).

It would appear that a reasonable approach would be to treat patients with a combination of agents, i.e., to combine an agent that stimulates bone formation with an agent that inhibits bone resorption. Preliminary data from Jowsey's group suggests that this may be most efficacious for long-term therapy. Her group found improvement, as indicated by bone biopsy, with treatment by fluoride, calcium supplements and vitamin D (25).

B. Specific Aims

To evaluate the effectiveness of regimes of treatment for osteoporosis that employ agents both singly and in combination. Evaluations will made on the basis of serial measurements of skeletal mass by TBNAA and density measurements of the radius made by photon absorptiometry.

C. Methods of Procedure

1. Treatment Groups: Twelve patients with primary osteoporosis will be included in each of the six treatment groups: estrogens alone (2.5 mg conjugated), anabolic steroid alone, fluoride alone (20 mg/d), fluoride plus estrogen, fluoride

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plus anabolic steroid, fluoride plus calcitonin 50 MRC units, 3 times weekly. All patients will receive calcium supplements (1 gm/d).

2. Baseline Studies: In addition to routine chemistry, skeletal survey, and determination of parathyroid hormone levels and urinary hydroxyproline, the following will be performed:

a. total body neutron activation analysis;

b. bone biopsy for analysis by tetracycline labeling and quantitative microradiography;

c. bone density measurement by the photon absorption technique;

d. ^{47}Ca tracer kinetic studies in selected patients. (This study will be performed only for a few selected patients on a combination therapy regime).

3. Follow-up: Subjects will be evaluated on an outpatient basis at eight-week intervals. Laboratory data obtained at these times will include C.B.C., bilirubin, total protein, albumin/globulin (A/G) ratio. Blood will also be obtained for analysis for Ca, P, hydroxyproline and creatinine. TBNAA will be repeated every three months, along with measurement of bone density by densitometry.

4. Final Study Period: At twelve month intervals, subjects will be readmitted, and all baseline studies will be repeated.

D. Significance

The importance of achieving a successful treatment of osteoporosis, even one that may only slow the rate of loss of Ca from the skeleton, is obvious. With six million post-menopausal women suffering from the effects of osteoporosis, any effective therapy would be of great value. The evaluation of the effectiveness of existing treatments by such objective end-points as skeletal mass would in itself be important to settle the controversy that now exists in the efficacy of the current agents employed for the treatment of osteoporosis.

III. Effect of Growth Hormone on Skeletal Metabolism and Body Composition in Primary Osteoporosis

A. Introduction

1. Objective:

a. To determine the efficacy of growth hormone therapy in primary osteoporosis.

b. To quantitatively determine the effect of growth hormone administration on skeletal metabolism and body composition in an adult population.

2. Background: Several short-term studies of the effect of human growth hormone (GH) in adults have been reported. In one such study, Root (28) suggested that older subjects may be relatively resistant to growth hormone. Rudman and his colleagues (29), however, have recently shown that a dosage of 0.168 u/kg (BW) is effective in increasing the retention of Na, K, N and P.

There are several reports on the treatment of osteoporosis with growth hormone (30-33). The results of these studies are encouraging. In six subjects, aged 68-83 years, an increase in calcium absorption, positive calcium balance and reduction in urinary hydroxyproline was achieved by treatment with 2 mg of HGH daily for 50 days.

Recently, Harris and Heaney (34-35) studied the effect of 3 months administration of exogenous growth hormone in intact adult dogs. Morphometric studies revealed a marked increase in new bone formation, decreased endosteal resorption and increased endosteal new bone formation. In addition, periosteal new bone

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formation increased, resulting in a net increase in skeletal mass. Kinetic studies were also performed, on the same dogs, using ^{47}Ca and ^{45}Ca as tracers. An increase in dietary calcium absorption, positive calcium balance, and an increase in mineral accretion of 21-41% was noted. These dramatic increases in skeletal mass in adult animals suggest the use of growth hormone treatment of osteoporotic patients.

3. Rationale

The majority of treatments devised to counter osteoporosis have been directed at the reduction of bone resorption. It would at first seem to be a reasonable approach. Jowsey (36) has demonstrated, with the technique of quantitative microradiography, that bone resorption surfaces are increased in primary osteoporosis, whereas bone formation surfaces are in the normal range. However, Heaney (2) has argued that bone formation is at least relatively decreased in this disorder, since under normal circumstances, bone formation and resorption are coupled. Thus, since there is no increase in bone formation to compensate for the increase bone resorption in osteoporosis, a disorder of bone formation must be implicated as well.

Moreover, if any therapeutic measures were able to inhibit completely bone resorption, only modest increases in skeleton could be expected. This follows from the fact bone turnover (as measured by kinetic tracer techniques) is not high in primary osteoporosis. The marked reduction of skeletal mass seen in osteoporosis takes place over a long period of time. Therefore, reduction of bone resorption will increase skeletal mass by only modest increments over a prolonged period of time. It is to be noted that patients with roentgenographic evidence of osteoporosis have lost 25-40% of their skeletal mass. Thus, the limitations of therapy directed solely at inhibition of bone resorption can be appreciated.

The studies with calcitonin carried out at Brookhaven confirm the theoretical analysis. Although salmon calcitonin administration thus far appears to stabilize or increase total body calcium, the changes produced are modest (37-38). A previous study also indicates that only small increments in total body calcium result from treatments with porcine calcitonin (18).

It appears, then, that therapy for osteoporosis must also be directed at increasing bone formation. Growth hormone is an obvious agent to be utilized for this purpose.

A study was recently completed at Brookhaven National Laboratory on skeletal metabolism and body composition in patients with acromegaly. The disorder was characterized by markedly increased levels of HGH and total body Ca, N, P, Cl, Na and K. In addition, compartmental analysis, with ^{47}Ca used as the kinetic tracer, revealed markedly accelerated accretion rates (39).

B. Specific Aims

The aim of this study is to evaluate the effect of long-term administration of growth hormone to osteoporotic patients. The growth hormone acts to increase the skeletal uptake of calcium and therby increases bone density and skeletal mass. This increased skeletal mass should serve to diminish the rate of spontaneous fracture, bone pain and other concomitants of osteoporosis.

C. Methods of Procedure

1. Subjects: Ten patients over 50 years of age with primary osteoporosis will be selected for therapy. All subjects will have extensive osteoporosis, i.e., vertebral compression fractures.

2. Baseline Studies: Subjects will be hospitalized in the Medical Research Center for 17 days, and maintained under classic balance conditions. In addition to routine studies (including skeletal survey, oral glucose tolerance test, and urinary

hydroxyproline), the following will be performed:

a. calcium balance study with controlled diet;

b. compartmental analysis, using ^{47}Ca as the tracer over a ten-day period;

c. iliac crest biopsy for analysis by quantitative microradiography;

d. total body neutron activation analysis.

Dosage: Subjects will receive 2 units daily of HGH for a period of one year. Patients will be instructed in subcutaneous injection technique so that this can be performed on an outpatient basis.

Follow-up: Subjects will be evaluated on an out-patient basis at monthly intervals. Laboratory data taken at these times will include BUN, FBS, Serum Ca, P, Alkaline phosphatase, CBC, reticulocyte count, SGOT, bilirubin, total protein, and A/G ratio. In addition, 24-hour urine collections will be obtained for analysis of Ca, P, hydroxyproline and creatinine.

At six-week intervals following the initiation of HGH therapy, the subjects will undergo TBNAA for quantitative determination of total body Ca, P, N, Cl, and Na; ^{40}K will be determined as well.

Final Study Period: At the end of one year, subjects will be readmitted to the research center, and all baseline studies will be repeated (i.e., Ca balance, compartmental analysis, quantitative microradiography, and TBNAA).

At the end of the first year, depending on the progress, half of the patients will be continued on HGH and the other half will receive synthetic calcitonin in addition to HGH. The latter procedure is an effort to decrease the bone resorption rate while continuing to stimulate the skeletal accretion rate by HGH. These studies will be continued during the third year with the dose of HGH adjusted, depending on the results achieved to that time.

D. Significance

If the effects of HGH on skeletal metabolism are beneficial in an osteoporotic population, growth hormone will be a useful therapeutic agent in the therapy of osteoporosis when it becomes available in sufficient quantity.

IV. Effect of Physical Activity on Body Composition in Osteoporotic Patients

A. Introduction

1. Objective: To evaluate the effect of physical activity on skeletal mass and lean body mass in a geriatric population.

2. Background: The osteoporosis that results from immobilization of patients is a common clinical problem which serves to emphasize the importance of physical exercise in calcium homeostasis. The typical osteoporotic patient is a small, frail dowager, and it has been suggested that the diminished physical activity of this individual is one of the contributing factors leading to osteoporosis.

There are a number of observations which suggest that physical activity can prevent the osteoporosis that develops from immobilization or decreased physical activity. In the clinical situation Whedon (40) demonstrated that the negative calcium balance of disuse can be diminished by use of an oscillating bed. Issekutz (41) showed that simply rising to a standing position diminishes the negative balance of immobilization.

Donaldson (42,43) was able to demonstrate an increase in the weight of the humerus

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of rats exercised on drums. Mice exercised on a treadmill also developed bones with greater ash content that were more resistant to fracture than those of the controls (44).

In elderly patients, exercise was shown to increase the bone accretion when measured with radioactive tracers (45). Smith (46) observed an increase in bone density in elderly subjects following an exercise program. A 2.6% increase in bone mineral was determined by photon transmission spectrometry after eight months of an exercise program. The differences noted between members of the exercise group and those in the control group, which did not exercise, were not significant. It should be emphasized, however, that this technique measures the changes in density of the radius only, and does not necessarily reflect the entire skeleton. The only technique that is capable of measuring small changes in skeletal mass is TBNAA.

3. Rationale

It is reasonable hypothesis that a program of light exercise or physical therapy can increase bone mass and ameliorate some of the symptoms of osteoporosis such as spontaneous fractures.

B. Specific Aims

The aim of this study is to measure skeletal mass by total body neutron activation, and bone density by ^{125}I photon densitometry before and after a one-year period of physical exercise. By comparing the rate of change of skeletal mass (and lean body mass) along with a contrast non-exercising group, the effects of the exercise on skeletal mass may be quantitated.

C. Methods of Procedure

All studies will be performed on an outpatient basis. Patients will be evaluated in the clinic of Brookhaven National Laboratory at 3 month intervals. There will be two treatment groups: one receiving only calcium supplement, and the other also receiving calcium supplement and also exercising.

Patients: Twenty patients will be selected on the following basis:

1. absence of diseases or drugs known to affect bone metabolism;
2. ambulatory;
3. not greatly deviated from ideal weight;
4. osteoporosis diagnosed on the basis of x-ray and/or the Norland-Cameron densitometer;
5. absence of relative contra-indications to exercise.

Patients are to be matched in each group for age, sex and race.

Diet:

1. Regular diet: 1000 mg Ca will be prescribed.
2. Special diet: For 3 days every 3 months patients will be on a low hydroxyproline diet for urinary collections.

Medications:

Neocalglucon, 15 cc tid, with meals will be given to each group.

Physical Activity

All patients will be encouraged to remain active. The patients who are in the physical activity group, however, will participate in programmed physical activity.

Baseline Studies:

1. Routine: CBC, urinalysis, urine and S erum Ca and p, alkaline phosphatase,

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electrophoresis, thyroxine, BUN, FBS, EKG.

2. Skeletal survey and chest x-ray.

3. Bone density using ^{125}I photon densitometer.

4. Determination of ^{40}K (an index of lean body mass) by whole body counting.

5. Determination of total body Ca, Cl, Na, and P by TBNAA.

Follow-Up

All studies except x-rays and EKG will be repeated every three months for a period of one year. At the end of one year the x-rays and EKG will be repeated.

D. Significance

If limited physical activity can increase the skeletal mass in a geriatric population with mild osteoporosis, this should provide a means to decrease the incidence of osteoporotic symptoms such as spontaneous fracture. Such a program of simple therapeutic exercise may be of benefit to a large segment of our society. The procedures to be followed may be very simple.

V. Body Composition as a Function of Age in a Normal Population

A. Introduction

1. Objective: To characterize the changes in skeletal mass (total-body calcium) and lean body mass (total-body potassium) in both a white and a black population as a function of age.

2. Background: Several studies have attempted to relate serial changes in skeletal mass with age (55-57). Data for the assessment were derived from changes in stature as well as changes in bone density of the appendicular skeleton. Only since the advent of the technique of total-body neutron activation analysis has it been possible to measure directly the total-body calcium, and hence, the skeletal mass. Changes in lean body mass with age have also been measured, but not in conjunction with the body composition of other elements such as calcium, phosphorus, sodium and chlorine. Differences in skeletal mass and lean body mass have been observed between males and females. A study of a black and white population indicated a difference in lean body mass when potassium was expressed in g/Kg body weight (58).

3. Rationale: In order to determine absolute deficits in skeletal mass (TBCa) and lean body mass (TBK), it is first necessary to establish normal levels as a function of age, sex and race. The normal range of values for TBCa and TBK can be established from data taken on individuals covering the adult age span. It should then be possible to develop a mathematical model for both skeletal and muscle mass as a function of age. Once the baseline values and their variability are determined, it is possible to determine the deficit of TBCa and TBK in an individual. Hence there will be available diagnostic criteria for the evaluation of the degree of osteoporosis and muscle loss in individual patients.

The difference in body composition between males and females has already been established for TBK (50, 59, 60). It should be possible to establish the differences as well for Ca, P, Na and Cl, and additionally, their inter-relationship. In like manner, differences in body composition between black and white subjects can also be investigated, and further, can be related to age.

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B. Specific Aims

1. A large population or normal volunteers (male and female, black and white) will be analyzed by total-body neutron activation analysis. Their absolute levels of Ca, P, Na, Cl and K will be measured. Five male and five female subjects will be measured for each decade from age 30 through age 89, in order to cover the span over which normal subjects lose Ca and hence decrease in stature.

2. From the data, a mathematical model will be established to characterize loss of TBCa in terms of height, TBK and other significant parameters.

3. Data from an individual could then determine the degree of deviation from the normal with respect to TBCa, and hence provide a quantitative diagnosis of the degree of osteoporosis where it exists.

C. Methods of Procedure

1. Subjects

The skeletal mass and the lean body mass in 60 white and 60 black males and females will be measured by TBNAA. The average body levels of Ca, P, Na, Cl and K will be determined for these adults from age 30 to age 89. Hence the normal level of body calcium, phosphorus, sodium, chlorine and potassium will be establshed with sex, age and race as parameters.

2. Baseline Studies

A clinical examination will be conducted for each subject. Appropriate history yielding information pertinent to calcium metabolism will be recorded in a manner easily translated to computer input. An extensive computer analysis of the relationships of the pertinent parameters of Ca metabolism will be undertaken.

D. Significance

The total body composition of calcium, phosphorus, sodium, chlorine and potassium will be determined in a normal population for the first time. These measurements can be made with the use of the unique technique of total-body neutron activation (TBNAA). It will be possible to state the mean value and deviation of skeletal mass and lean body muscle mass of normals, as a function of age, sex and race. This information is of course of basic physiological interest. However, it is additionally very important in that it provides quantitative measures for the determination of the degree of osteoporosis, and can also yield quantitative information on efficacy of various therapies.

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E. Facilities Available

A 48-bed research hospital with metabolic wards is available for subjects in the kinetic studies, and also for the clinical work-up of all subjects. A complete chemical laboratory with all standard equipment is available. Further, the most advanced computer facilities are available for the collation and analysis of the data.

The two principal techniques employed in these studies on calcium metabolism of osteoporosis-^{47}Ca tracer kinetic studies and total-body neutron activation analysis (TBNAA) -- were developed and have been in use at Brookhaven National Laboratory.

1. Kinetic tracer studies with ^{47}Ca are carried out to provide data for compartmental analyses (47). These metabolic studies can only be performed on the metabolic ward of a hospital. The solution of the differential equations for the compartmental model are performed at high speed by the large BNL computers.

2. The in-vivo neutron activation, a newly developed quantitative technique, is used to measure the total body calcium and phosphorus. The whole-body neutron activation technique has made it possible, for the first time, to make an absolute measurement of total body Ca. This direct measurement of Ca (which is proportional to skeletal mass) provides a quantitative means for assessing the changes induced by various therapies in osteoporotic patients.

There are, at the present time, only two other total-body neutron activation facilities in the world. The other facilities (the University of Washington and the University of Birmingham) utilize a cyclotron for neutron activation. These instruments were designed for use in physics research, and are not primarily adapted to medical research (48).

The new BNL patient irradiation facility utilizes partially moderated 4.5 MeV neutrons. It is composed of 14 encapsulated 50 Ci ^{238}Pu,Be sources (13). It is the first neutron irradiation facility designed solely for medical research (13). It gives results considerably more precise (1%) than those obtained by previously used techniques. It also has a number of advantages. For example, the radiation dose to the patient in this procedure is 0.277 rem, which is approximately 1/10 of the dose received in the two other activation facilities.

The induced activities are measured with the 54-detector BNL whole-body counter

with its on-line computer (49). The counter represents the most significant advance in whole-body counting in recent years. In addition to having a high sensitivity, the counter is unique in having an invariant counting response to the geometry and the attenuation of the emitted gamma radiation. The whole-body counter also permits the most accurate measurement of total-body potassium (an index of lean body mass, 50). The total body K is used in the prediction of normal total-body calcium in each subject.

This whole body neutron activation technique has been applied in a number of clinical research projects which involve skeletal metabolic disorders other than osteoporosis (51-54).

F. Collaborative Arrangements

This project is a unique example of an inter-disciplinary approach to a medical problem that could only be undertaken in a large research center such as Brookhaven National Laboratory.

In approaching the problem of characterizing, preventing and treating the condition of osteoporosis, the unique facilities and expertise of the staff of Brookhaven National Laboratory are utilized. The essential techniques employed, total-body neutron activation analysis and compartmental analysis of kinetic data derived from radioactive tracer studies, were developed at BNL. The development and application of these techniques requires the combined talents of physicists, computer experts, medically oriented scientists, engineers and electronic specialists. In addition, all of the techniques employed utilize the high-speed computers available at BNL for the collection, storage and analysis of the data. Further, the medical aspects of the study require a metabolic ward and the facilities of a research hospital such as that at BNL with its specialized staff of dieticians, nurses and health physics specialists.

Collaborating medical personnel from other institutions in the area include endocrinologists, specialists in metabolic bone disorders from Downstate Medical Center, Nassau County Medical Center and the Mayo Clinic. All of these individuals (with the exception of Dr. Jowsey) hold collaborative staff appointments in the medical department of Brookhaven National Laboratory.

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Principal Investigator Assurance:

"The undersigned agrees to accept responsibility for the scientific and technical conduct of the research project and for provision of required progress reports if a grant is awarded as the result of this application."

9-26-75 — Date

Stanton H. Cohn — Principal Investigator

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