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BULLETIN *of the*

MEDICAL DEPARTMENT
BROOKHAVEN NATIONAL LABORATORY



July 1, 1961

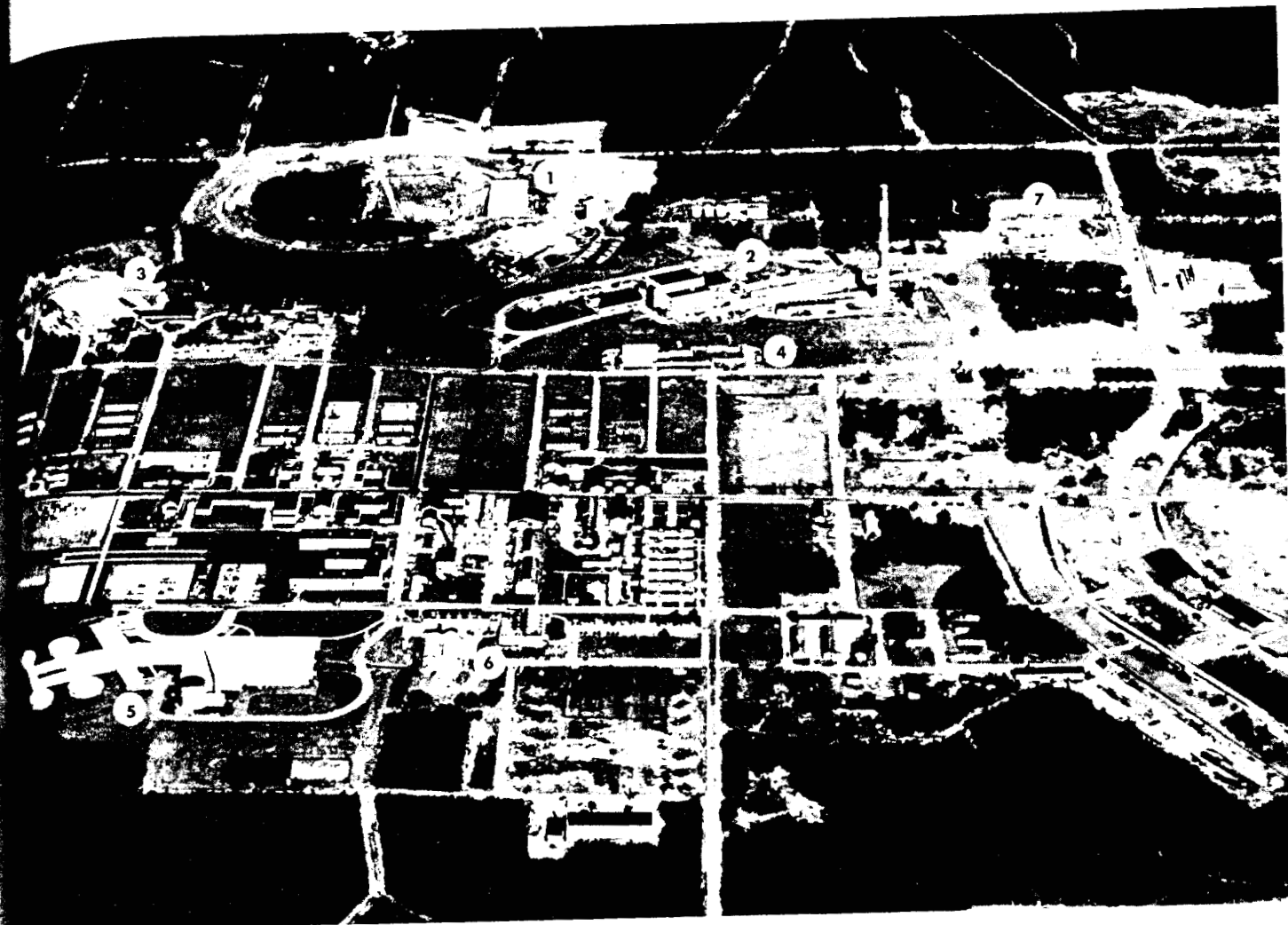
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AERIAL VIEW OF THE LABORATORY SITE

1. Alternating Gradient Synchrotron
2. Research Reactor and Hot Laboratory
3. Cosmotron
4. Cyclotron and Van de Graaff Building
5. Medical Research Center and Medical Reactor
6. Biology laboratories
7. Nuclear Engineering Building (under construction)

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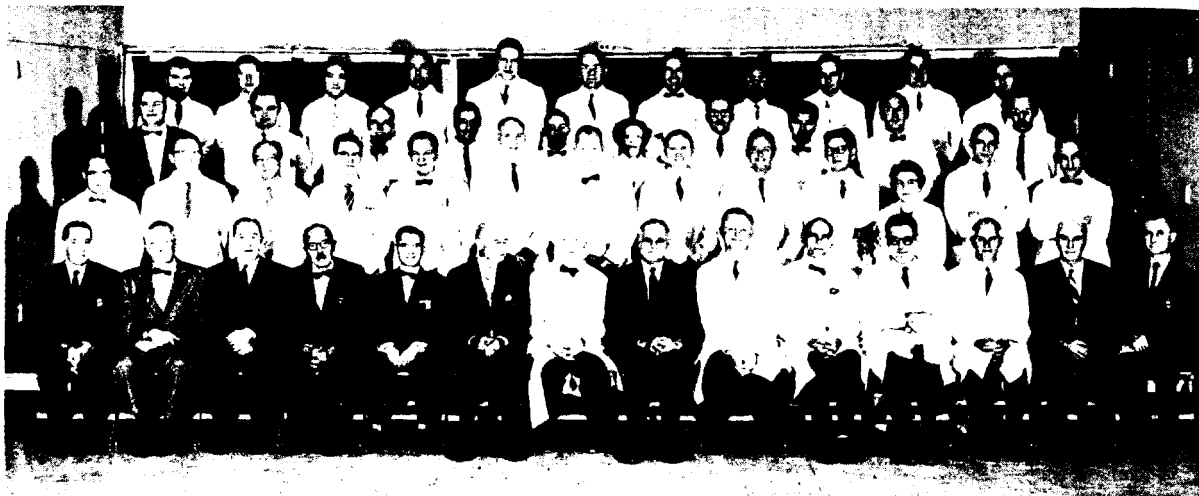
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*Resignation became effective June 12, 1969, upon appointment to Atomic Energy Commission.

RESEARCH COLLABORATORS

JULY 1, 1960 - JUNE 30, 1961

- AGNEW, COLVIN H., M.D.
Radiologist
University of Kansas Medical Center
Kansas City 12, Kans.
- ALBERT, ROY E., M.D.
Associate Professor of Industrial Medicine
New York University-Bellevue Medical Center
New York, N.Y.
- AMATO, CHARLES G., B.S.
Physicist
Industrial Reactor Laboratories, Plainboro, N. J.
- ANTOPOL, WILLIAM, M.D.
Clinical Professor of Pathology
New York University College of Medicine, and
Pathologist and Director of Laboratories and Research
Beth Israel Hospital, New York, N.Y.
- APONTE, GONZALO E., M.D.
Assistant Professor of Pathology
Jefferson Medical College
Philadelphia, Pa.
- ARIEL, IRVING M., M.D.
Pack Medical Group
139 East 36th Street, New York 16, N.Y.
- BLAS, MEYER, PH.D.
Professor of Biology
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- BRAGHELL, HAROLD C., PH.D.
Professor of Chemistry
University of Delaware, Newark, Del.
- BRASSIS, MARCEL C., M.D.
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The French International Blood Transfusion Center
Paris, France
- BRUMBERG, BARUCH, M.D., PH.D.
Chief, Geographic Medical and Genetics Section
National Institutes of Health, Bethesda 14, Md.
- BRUCHER, GEORGE, M.D.
Chief, Hematology Service
Clinical Pathology Department
National Institutes of Health, Bethesda 14, Md.
- BRUDSKY, ISADORE, M.D.
Assistant Professor of Medicine
Hospital of the University of Pennsylvania
Philadelphia, Pa.
- BROWN, RAYMOND R., PH.D.
Associate Professor of Surgery
University Hospitals, University of Wisconsin
Madison, Wis.
- BRUNLINGTON, HAROLD, PH.D.
Assistant Professor of Physiology
University of Cincinnati College of Medicine
Cincinnati, Ohio
- CARSON, PAUL E., JR., M.D.
Assistant Professor of Medicine
University of Chicago, Chicago, Ill.
- COHEN, CARL, PH.D.
Battelle Memorial Institute, Columbus 1, Ohio
- COMMERFORD, SPENCER L., PH.D.
(In Residence)
- CONN, HADLEY L., JR., M.D.
Hospital of the University of Pennsylvania
Philadelphia, Pa.
- CRANNY, ROBERT L., M.D.
Associate Professor of Pediatrics
Albany Medical College, Albany, N.Y.
- DELIHAS, NICHOLAS, PH.D.
Walker Laboratory
Sloan-Kettering Institute for Cancer Research
Rye, N.Y.
- DODGE, WARREN F., M.D.
Assistant Professor of Pediatrics
University of Texas Medical Branch
Galveston, Tex.
- DOOLAN, PAUL D., M.D.
Assistant Clinical Professor of Medicine
University of California School of Medicine, and
Director, Clinical Investigation Center
U.S. Naval Hospital, Oakland 14, Calif.
- DREILING, DAVID A., M.D.
Assistant Attending Physician
Mt. Sinai Hospital, New York, N.Y.
- EDER, HOWARD J., M.D.
Associate Professor of Medicine
Albert Einstein College of Medicine
New York 61, N.Y.
- EICHER, MAYNARD W., B.A.
Electronic Scientist
Naval Medical Research Institute, Bethesda 14, Md.
- FEINENDEGEN, LUDWIG E., M.D.†
(In Residence)
- FELDSTEIN, ARTHUR M., M.D.
Research Fellow, Metabolic Unit
Montefiore Hospital, New York, N.Y.
- FISHMAN, MARVIN, PH.D.
Associate in Research
Public Health Research Institute of the City of New York
New York, N.Y.
- FLIEDNER, THEODOR M., M.D.
Fellow in Medicine
University of Washington School of Medicine
St. Louis, Mo.
- FONG, CONRAD T.O., PH.D.
Department of Medicine
New York University College of Medicine
New York, N.Y. (In Residence)
- FRIEDKIN, MORRIS E., PH.D.
Chairman, Department of Pharmacology
Tufts University School of Medicine, Boston, Mass.

Effective July 1, 1961.

- FURCHGOTT, ROBERT F., M.D.
Professor and Chairman
Department of Pharmacology
Downstate Medical Center
State University of New York, Brooklyn, N.Y.
- FURTH, JACOB, M.D.
Roswell Park Memorial Institute
Buffalo, N.Y.
- GARVOCK, WILLIAM B., M.D., C.M.
University of Toronto, Toronto, Ontario, Canada
- GIDEZ, LEWIS I., PH.D.
Assistant Professor of Biochemistry
Albert Einstein College of Medicine
New York 61, N.Y.
- GITLIN, DAVID, M.D.
Associate in Pediatrics
Harvard Medical School, Boston, Mass.
- GLASER, ROBERT J., M.D.
Dean of the Medical School, and
Associate Dean of the Graduate School
University of Colorado, Denver, Colo.
- GORBMAN, AUBREY, PH.D.
Professor of Zoology
Columbia University, New York, N.Y.
- HALE, WILLIAM A., PH.D.
Professor of Bacteriology
University of Tennessee, Memphis 3, Tenn.
- HANNA, CALVIN, PH.D.
Associate Professor of Pharmacology
University of Vermont School of Medicine
Burlington, Vt.
- HARDING, CLIFFORD V., JR., PH.D.
Department of Ophthalmology Research
College of Physicians and Surgeons
Columbia University, New York, N.Y.
- HAYMAKER, WEBB, M.D.
Chief, Division of Neuropathology
Armed Forces Institute of Pathology
Washington 25, D.C.
- HAYMOND, HERMAN R., PH.D.
Associate Professor of Radiology
University of Southern California School of Medicine
Los Angeles, Calif.
- HELD, BARRY T., M.D.
Instructor in Radiology
Yale University School of Medicine
New Haven, Conn.
- HENSCHKE, ULRICH K., M.D., PH.D.
Associate Professor of Clinical Radiology
Memorial Center for Cancer and Allied Diseases
New York 21, N.Y.
- HOLLIDAY, MALCOLM A., M.D.
Associate Professor of Pediatrics
University of Pittsburgh, Pittsburgh, Pa.
- HOLLINGSWORTH, JAMES W., M.D.
Chief, Medical Service
Atomic Bomb Casualty Commission
A.P.O. 354, San Francisco, Calif.
- HUANG, YUN PENG, M.B.
Research Assistant in Neurosurgery
Mt. Sinai Hospital, New York, N.Y.
- JACOBSON, JERRY H., M.D.
Clinical Professor of Ophthalmology
New York Polyclinic Medical School, and
Director, Department of Electrophysiology
New York Eye and Ear Infirmary, New York, N.Y.
- JANOVSKI, NIKOLAS A., M.D.
Department of Obstetrics and Gynecology
Columbia Presbyterian Medical Center
New York, N.Y.
- JANSEN, CORNELIUS R., M.B., CHB.
Volks Hospital, Pretoria, South Africa
(In Residence)
- JOHNSON, HORTON A., M.D.
Assistant Attending Pathologist
Salt Lake General Hospital
University of Utah School of Medicine
Salt Lake City 15, Utah
- JOHNSON, JOHN E., JR., M.D.
Assistant Professor of Medicine
University of Texas Medical Branch
Galveston, Tex.
- KARA, GERALD B., M.D.
Director of Ophthalmic Research
New York Eye and Ear Infirmary, New York, N.Y.
- KARNOFSKY, DAVID A., M.D.
Associate Professor of Medicine
Cornell University Medical College
New York, N.Y.
- KELLY, LOLA S., PH.D.
Lecturer in Biophysics and Physiology
Donner Laboratory, University of California
Berkeley, Calif.
- KIEBEL, GERALDINE, PH.D.
Research Associate in Electrophysiology
New York Eye and Ear Infirmary, New York, N.Y.
- KILLMANN, SVEN-AAGE, M.D.
University of Copenhagen
Copenhagen, Denmark
- KLIGERMAN, MORTON M., M.D.
Professor and Chairman
Department of Radiology
Yale University School of Medicine
New Haven, Conn.
- KORMAN, SAMUEL, M.D., PH.D.
Assistant Attending Physician
Montefiore Hospital, New York, N.Y.
- KROHN, DAVID L., M.D.
New York University-Bellevue Medical Center
New York, N.Y.
- KRUEGER, ROBERT C., PH.D.
Associate Professor of Biological Chemistry
University of Cincinnati College of Medicine
Cincinnati 9, Ohio
- LALEZARI, PARVIZ, M.D.
Medical and Hematology Service
Montefiore Hospital, New York, N.Y.
- LAURER, GERARD R., BSEE, M.S.
Instructor, Department of Industrial Medicine
New York University-Bellevue Medical Center
New York, N.Y.
- LEFEVRE, PAUL C.
Department of
University of Louisville, Ky
- LEVINE, HARRY, M.D.
Associate Professor
University of Texas
Galveston, Tex
- LEWIS, WILLIAM
135 East 64th St
New York, N.Y.
- LORING, MARVIN
Assistant Professor
Cornell University
New York, N.Y.
- LOWREY, AUSTIN
Chief, Ophthalmology
Walter Reed Army Hospital
Washington, D.C.
- MALIS, LEONARD
Senior Attending
Department of
Mt. Sinai Hospital
New York, N.Y.
- MARC-AURELE, J.
(In Residence)
- MASON, RICHARD
Associate Professor
Seton Hall College
Newark, N.J.
- MAUTNER, HENRI
Assistant Professor
Yale University
New Haven, Conn.
- MAXFIELD, MYRL
Chief, Physical
U.S. Army Biochemical Research
Fort Detrick, Md.
- MAYNARD, LAURENCE
Department of
Downstate Medical Center
State University of New York
Brooklyn, N.Y.
- MEYER, JAMES V.
Department of
University of Texas
Galveston, Tex
- MEYER, LEO, M.D.
Director of Laboratory
South Nassau
Oceanside, N.Y.
- MILLER, C. PHILIP
Professor of Medicine
University of Chicago
Chicago 37, Ill.
- MILLMAN, IRVING
Public Health
New York, N.Y.
- MOLONEY, WILLIAM
Tufts University
Director of Clinical
Boston City Hospital

†Effective July

0019970

Ph.D.
Pharmacology
Louisville School of Medicine

D., Ph.D.
School of Medicine
Texas Medical Branch

, Jr., M.D.
New York, N.Y.
M.D.
School of Radiology
University Medical College

M.D., COL. (MC, USA)
ology Service
Military Medical Center

M.D.
Physician
Neurosurgery
New York, N.Y.
M.D.

, Ph.D.
School of Physiology
School of Medicine and Dentistry

, Ph.D.
School of Pharmacology
New Haven, Conn.
M.D., Ph.D.
Science Division
Biological Warfare Laboratories
Derick, Md.

SE S., M.D.
Psychiatry
Hospital Center
New York, Brooklyn, N.Y.
R., M.D.
Surgery
Texas Medical Branch

atories
Communities Hospital

M.D.
icine
Chicago School of Medicine

Ph.D.†
Research Institute of the City of New York

C., M.D.
Medical School, and
Laboratories
Hospital, Boston, Mass.

NAJAC, HAROLD W., M.D.
Resident Fellow
New York Eye and Ear Infirmary, New York, N.Y.

NASH, JOE B., Ph.D.
Associate Professor of Pharmacology
University of Texas Medical Branch
Galveston, Tex.

NIELSEN, NIELS O., D.V.M.†
College of Veterinary Medicine
University of Minnesota, St. Paul 1, Minn.

PAGE, ARTHUR R., M.D.
Department of Pediatrics, University of Minnesota
Minneapolis, Minn.

PAINTER, ROBERT B., Ph.D.
Battelle Memorial Institute, Columbus, Ohio

PARNIANPOUR, HASSAN
Tehran University, Tehran, Iran (In Residence)

PATTERSON, MARCEL, M.D.
Associate Professor of Internal Medicine
University of Texas Medical Branch
Galveston, Tex.

PERMAN, VICTOR, D.V.M.
Instructor, College of Veterinary Medicine
University of Minnesota, St. Paul 1, Minn.

PRUSOFF, WILLIAM H., Ph.D.
Associate Professor of Pharmacology
Yale University School of Medicine
New Haven, Conn.

RALL, JOSEPH EDWARD, M.D.
Chief, Clinical Endocrinology Branch
National Institute of Arthritis and Metabolic Diseases
Bethesda 14, Md.

RASMUSSEN, HOWARD, M.D., Ph.D.
The Rockefeller Institute, New York, N.Y.

RAY, BRONSON S., M.D.
New York Hospital, New York, N.Y.

REIZENSTEIN, PETER G., M.D.
Karolinska Institute, Stockholm, Sweden

ROSE, JERZY E., M.D.
Professor of Physiology and Psychiatry
Department of Neurosurgery
University of Wisconsin, Madison, Wis.

ROSEN, VICTOR J., Jr., M.D.
Massachusetts General Hospital, Boston, Mass.

ROSSI, HAROLD H., Ph.D.
Associate Professor of Radiology
Radiological Research Laboratories
Columbia University, New York 32, N.Y.

RUBINI, JOSEPH R., M.D.
Chief, Radioisotope Service
Veterans Administration Hospital, and
Southwestern Medical School, Dallas, Tex.

SANDERS, BENJAMIN E., Ph.D.
Merck Institute for Therapeutic Research
West Point, Pa.

SCANU, ANGELO M., M.D.
Research Associate
Cleveland Clinic, Cleveland, Ohio

SCATLIFF, JAMES H., M.D.
Yale University School of Medicine
New Haven, Conn.

- SCHEINBERG, ISRAEL H., M.D.
Professor of Medicine
Yeshiva University, New York, N.Y.
- SCHLOERB, PAUL R., M.D.
Assistant Professor of Surgery
University of Kansas Medical Center
Kansas City 12, Kans.
- SCHNEIDER, MARTIN, M.D.
Professor of Radiology
University of Texas Medical Branch
Galveston, Tex.
- SCHWARTZ, ROBERT, M.D.
Associate Professor of Pediatrics
Western Reserve School of Medicine
Cleveland, Ohio
- SHAY, HARRY, M.D.
Professor of Clinical Medicine
Temple University School of Medicine
Philadelphia, Pa.
- SHELLABARGER, CLAIRE J., PH.D.
Professor of Zoology, and
Coordinator, Kresge Laboratories
University of Michigan, Ann Arbor, Mich.
- SHEMIN, DAVID, M.D.
College of Physicians and Surgeons
Columbia University, New York, N.Y.
- SINEX, F. MARROTT, PH.D.
Professor and Head, Department of Biochemistry
Boston University School of Medicine
Boston, Mass.
- SOBEL, ALBERT E., PH.D.
Head, Department of Biochemistry
The Jewish Hospital of Brooklyn, Brooklyn, N.Y.
- SONDHAUS, CHARLES A., PH.D.
Biophysicist
Donner Laboratory, University of California,
Berkeley, Calif.
- SORENSEN, DALE K., D.V.M., PH.D.
Associate Professor
Division of Veterinary Medicine and Clinics
College of Veterinary Medicine
University of Minnesota, St. Paul 1, Minn.
- SPENCER, HERTA, M.D.
Physician-in-Chief
Metabolic Research Unit
Montefiore Hospital, New York, N.Y.
- STEINFELD, JESSE L., M.D.
Assistant Professor of Medicine
University of Southern California
School of Medicine, Los Angeles 33, Calif.
- STOHLMAN, FREDERICK, JR., M.D.
National Institutes of Health
Bethesda 14, Md.
- STRICKLER, JAMES C., M.D.
Instructor in Medicine
Cornell University Medical College
New York 21, N.Y.
- SUTOW, WATARU M., M.D.
Associate Pediatrician
M.D. Anderson Hospital and Tumor Institute
Houston, Tex.
- SZENT-GYORGYI, ALBERT, M.D., PH.D.
Chief Investigator
Institute of Muscle Research
Marine Biological Laboratory, Woods Hole, Mass.
- TAPLIN, GEORGE V., PH.D.
Chief, Nuclear Radiology Division, Department of
Nuclear Medicine and Radiation Biology
University of California at Los Angeles
West Los Angeles, Calif.
- TERRES, GERONIMO, PH.D.
Assistant Scientist and Assistant Professor
Department of Physiology
Stanford University, Stanford, Calif.
- THOMAS, JOHN, M.D.
Associate Professor of Medicine
McHarr Medical College, Nashville, Tenn.
- THORP, W.T.S., D.V.M.
Dean, College of Veterinary Medicine
University of Minnesota, St. Paul 1, Minn.
- TRAUTMAN, RODES, PH.D.
Biophysicist
Plum Island Animal Disease Laboratory
Greenport, N.Y.
- TRUAX, WAYNE E., M.D.
Department of Medicine
University of Texas Medical Branch
Galveston, Tex.
- TSUYA, AKIRA, M.D.
Professor of Radiology
Yokohama Municipal University
Yokohama, Japan
- USENIK, EDWARD A., M.D., PH.D.
College of Veterinary Medicine
University of Minnesota, St. Paul 1, Minn.
- VICUNA, XIMENA C., M.D.
New York Eye and Ear Infirmary, New York, N.Y.
- VON FOERSTER, HEINZ, PH.D.
Department of Electrical Engineering
University of Illinois College of Engineering
Urbana, Ill.
- WASSERMAN, LOUIS R., M.D.
Director, Department of Hematology
Mt. Sinai Hospital, New York, N.Y.
- WELCH, ARNOLD D., M.D., PH.D.
Chairman, Department of Pharmacology
Yale University School of Medicine
New Haven, Conn.
- WILLIGAN, DONALD A., D.V.M.
Instructor, College of Veterinary Medicine
Michigan State University
East Lansing, Mich.
- WRIGHT, THOMAS L., M.D.
Instructor in Medicine
University of Cincinnati College of Medicine
Cincinnati, Ohio
- YAKOVLEV, DAVID L., M.D.
Curator, Warren Anatomical Museum, and
Department of Neuropathology
Harvard Medical School, Boston, Mass.

ALLEN, P.
New Y.
BREITFEL
New Y.
CARMEL,
Bellev
DUSHMAN
Colum
ELLIOTT,
Univer
FERRIS, J.
52 Nor
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HWANG, V.
(In Res
JONES, IRV
South N
KRITCHER
Hospital
KURTH, D
Depart
Univers
Salt Lak

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Coordinat

Participati
Faculty M
JOHNSON
Students¹ -
E. LOTV
WALTON

Participati

¹All from
Tex.; prese
Medical Ce
²All from
Tex., excep
Center, Kan
³Universit
⁴Cornell U
⁵Universi
Angeles, Cal
⁶Universi
Ohio.

TECHNICAL COLLABORATORS

JULY 1, 1960 - JUNE 30, 1961

M.
Eye and Ear Infirmary, New York, N.Y.
JULIANNA M.
Eye and Ear Infirmary, New York, N.Y.
ER W., B.A.
College of Medicine, New York, N.Y.
IRIAM B.
University, New York, N.Y.
N D.
of California at Berkeley, Berkeley, Calif.
ROLYN
Broadway, White Plains, N.Y.
JAMES J.
fass.
MAN H.
t of Public Health
ifornia, Berkeley, Calif.
SHUI S., B.D.S., M.S.
ice)
L.
u Communities Hospital, Oceanside, N.Y.
E M.
he University of Pennsylvania, Philadelphia, Pa.
M.
of Internal Medicine
f Utah School of Medicine
ity 15, Utah

LORENZ, ANN F.
Department of Medicine and Radiology
Albert Einstein College of Medicine, New York, N.Y.
MAISKY, STANLEY J., M.S.
Radiotherapy Physics Section, and
Head, Physics Laboratory
Veterans Administration Hospital, New York 55, N.Y.
MILLER, INEZ
South Nassau Communities Hospital, Oceanside, N.Y.
PERKINS, MYNELL A.
c/o Dr. L.I. Malis
Department of Neurosurgery
Mt. Sinai Hospital, New York, N.Y.
SALOMON, PATRICIA A.
Brandeis University, Waltham, Mass.
SCHNEIDER, MARTIN F.
Yale University School of Medicine, New Haven, Conn.
SCOTT, WALTER N.
New England Center Hospital, Boston, Mass.
SELLECK, BURNELL H.
Department of Physiology
University of Rochester School of Medicine
Rochester, N.Y.
SUDBOROUGH, H.S.
Department of Physiology
Johns Hopkins University School of Medicine
Baltimore, Md.

MEDICAL STUDENT RESEARCH PRECEPTORSHIP NUCLEAR MEDICINE METHODOLOGY AND PRACTICE

WALTON W. SHREEVE, M.D., Ph.D.

SUMMER SESSION 1959

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. M.D.; JOE B. NASH, Ph.D.
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HAFFER, CLAUDE B. TATE, FRANK WEBBER.

SUMMER SESSION 1960

chool - University of Texas Medical Branch.
ersity of Texas Medical Branch, Galveston,
dress of C.H. AGNEW, University of Kansas
Kansas City, Kans.
ersity of Texas Medical Branch, Galveston,
L. SCHLOERB, University of Kansas Medical
ity, Kans.
exas Medical Branch, Galveston, Tex.
ity Medical College, New York, N.Y.
outhern California School of Medicine, Los
incinnati College of Medicine, Cincinnati,

Faculty Members² - HARRY LEVINE, M.D., Ph.D.;
JAMES V. MEYER, JR., M.D.; JOE B. NASH, Ph.D.;
PAUL R. SCHLOERB, M.D.; MARTIN SCHNEIDER, M.D.;
WAYNE E. TRUAX, M.D.
Students³ - JAMES D. BLACKBURN; ANNE R. COOK;
JOSEPH D. NALL; HUGH F. STEGALL, JR.; WILLIAM
K. ZUNG.

SUMMER SESSION 1961

Participating Schools - University of Texas Medical
Branch, University of Southern California, University
of Cincinnati, and Cornell University.
Faculty Members - HAROLD BURLINGTON, Ph.D.;⁶
HERMAN R. HAYMOND, Ph.D.;⁵ MARVIN F. LORING,
M.D.;⁴ MARCEL PATTERSON, M.D.;³ MARTIN SCHNEIDER,
M.D.;³ JESSE L. STEINFELD, M.D.;⁵ JAMES C. STRICKLER,
M.D.;⁴ THOMAS L. WRIGHT, M.D.⁶
Students - JAMES A. ALLUMS;³ ED F. BAYOUTH;³ JOHN
PAUL BOARD, JR.;³ JOHN T. CELENTANO;⁵ WILLIAM R.
HAZZARD;⁴ ALVA EUGENE JACKSON;³ JAMES LU-MENG;⁵
DONALD R. McMEEKEN;⁵ DENNIS O'KEEFE;⁴ RICHARD
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Ph.D.
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General Safety Coordinator for Medical Department -
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Civil Defense Plans Liaison Officer - ROBERT A. CONARD, M.D.

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MARY COYLE, R.N.

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COHN, STANTON H.
Kinetics of skele
sorbed fallout.

CONARD, ROBERT A.
Marshall Island
skin, gastrointest

COTZIAS, GEORGE C.
Mn⁵⁴ in studies o
diseases; radiatic

CRONKITE, EUGENE
Effects of radiati
cell production;

DAHL, LEWIS K., M
Sodium metabo.

DREW, RUTH M., J
Radioisotopic st

EASTERDAY, OTHO
Pharmacology &

FARR, LEE E., M.I
Neutron capturi
operational crite

HANKES, LAWREN
Tritium and C
niacin metaboli

HUGHES, WALTER
Metabolism of
preparation of s

LIPPINCOTT, STUA
Pathology of p
neoplasia.

LOVE, ROBERT A.
Treatment of a
nation and radi

ROBERTSON, JAME
Kinetics of trac
radiation detec

SHREEVE, WALTO
Use of C¹⁴ and
and lipid meta

STICKLEY, ELMER
Medical reacto

STONER, RICHARD
Effects of radi
lism of parasite

VAN SLYKE, DON
Chemistry an
balance; renal
C¹⁴ method ar

ALAGHEMAND, A
Radiation in

RESEARCH INTERESTS OF THE SCIENTIFIC STAFF OF THE MEDICAL DEPARTMENT

RESEARCHING STAFF

Ph.D.
mammals; kinetics of cell pro-

D.
metabolism; significance of ab-

D.
Medical Study; radiation effects on
tact, and bone growth.

D.
degenerative central nervous system
ects; activation analysis.

M.D.
hematopoiesis; kinetics of blood
ation carcinogenesis.

and hypertension.

of cultured mammalian cells.

Ph.D.
toxicology of boron compounds.

rapy; nuclear reactor design and
or medical uses.

Ph.D.
elated amino acids and tryptophan-
neoplasia; parasitologic metabolism.

Ph.D.
proteins and nucleic acids and the
ic labeled precursors.

, M.D.
radiation; protein metabolism in

D.
ental radioactive isotopic contami-
n exposure.

M.D., Ph.D.
behavior; neutron capture therapy;
instrumentation.

, M.D., Ph.D.
um labels in study of carbohydrate
n in man.

Ph.D.
rational criteria; radiation dosimetry.
Ph.D.

on immune mechanisms; metabo-

D., Ph.D.
siology of amino acids; acid-base
ology; blood gases and electrolytes;
lications; collagen.

TERM STAFF

M.D.

therapy.

ARONSON, ROBERT B., Ph.D.

Chemistry and metabolism of collagen.

BATEMAN, JOHN L., M.D.

Particle radiation effects in mammals; diagnosis and
treatment of blood dyscrasia.

BORG, DONALD C., M.D.

Trace metal metabolism; activation analysis; radiation
effects.

CALVO, WENCESLAO, M.D., Ph.D.

Neuropathological studies on neutron capture therapy;
histochemistry of central nervous system after radiation
from heavy particles.

COMMERFORD, SPENCER L., Ph.D.

Iododeoxyuridine as a label for DNA.

COTTIER, HANS, M.D.

Morphogenesis and function of hemopoietic tissue;
radiation effects in mammals.

FINE, SAMUEL, M.D.

Medical instrumentation; neutron capture therapy.

FORSYTH, EDITH M., M.B., Ch.B.

Industrial Medicine Clinic.

HAMMERSTROM, RICHARD A., Ph.D.

Effects of irradiation on immune mechanisms.

LAX, LOUIS C., M.D.

Sodium turnover in hypertension.

ODARTCHENKO, NICOLAS, M.D.

Foreign tissue reactions.

PAPAVASILIOU, PAUL S., M.D.

Mn⁵⁶ in studies of degenerative central nervous system
diseases; radiation effects; activation analysis.

POPENOE, EDWIN A., Ph.D.

Structure and function of glycoproteins; C¹⁴ labels in
collagen biosynthesis.

PRICE, DAVID C., M.D.

Studies of iron metabolism in blood dyscrasias.

RAI, KANTI R., M.D.

Applications of radioactive isotopes to clinical problems.

SCHACKOW, ECKART, M.D.

Trace metals in hypertension.

SCHWARTZ, IRVING L., M.D.

Mechanism of hormone action - membrane permea-
bility, active transport; fat metabolism.

SPRAGER, SANFORD C., M.D.

Local factors and atherosclerosis.

TONNA, EDGAR A., Ph.D.

Biochemistry and physiology of bone growth; effects of
radiation on skeletal system.

RESEARCH COLLABORATORS IN RESIDENCE

FEINENDEGEN, LUDWIG E., M.D.

Nucleic acid metabolism with tritium and C¹⁴ labels;
dynamics of cell proliferation.

JANSEN, CORNELIUS R., M.B., Ch.B.

Accelerator particle radiation effects; I¹³¹ protein
studies in man.

MARC-AURELE, JULIEN, M.D.

Renal physiology; mechanism of hormone action.

BIOGRAPHIES OF CONTINUING STAFF MEMBERS

VICTOR P(OTTER) BOND, M.D., PH.D.

Senior Scientist; Assistant Chairman, Medical Department;
Head, Division of Microbiology;
Assistant Attending Physician,
Hospital of the Medical Research Center.

A.B. University of California at Berkeley 1943; M.D. University of California at San Francisco 1945; Medical Officer, Active Duty, U.S. Navy 1943-45; Ph.D. University of California at Berkeley 1951; Head, Experimental Pathology Branch, U.S. Naval Radiological Defense Laboratory, San Francisco 1948-54; Scientist, Brookhaven National Laboratory 1954-58; Senior Scientist 1958—

STANTON H(ARRY) COHN, PH.D. Scientist

S.B. University of Chicago 1946; S.M. 1949; Ph.D. (physiol-radiobiol) University of California 1952; Chemist, Explosives, Kankakee Ordnance Works, Joliet 1940-42; Active Duty U.S. Army 1943-46; Biochemist, Argonne National Laboratory 1946-49; Assistant Radiobiologist, Crocker Radiation Laboratory 1949-50; Head, Internal Toxicity Branch, Biomed Division, U.S. Naval Radiological Defense Laboratory, San Francisco 1950-58; Scientist, Brookhaven National Laboratory 1958—

ROBERT A(LLEN) CONARD, M.D. Scientist; Chief, Marshall Islands Medical Study Project; Assistant Attending Physician, Hospital of the Medical Research Center.

B.S. University of South Carolina 1936; M.D. Medical College of South Carolina 1941; Medical Corps U.S. Navy 1941-56; Medical Research Project Officer, U.S. Naval Radiological Defense Laboratory, San Francisco 1948-49; Visiting Scientist, Argonne National Laboratory 1949-50; Head, Department Radiobiological Research, Naval Medical Research Institute 1950-55; Scientist, Brookhaven National Laboratory 1956—

GEORGE C(ONSTANTIN) COTZIAS, M.D. Senior Scientist; Head, Division of Physiology; Attending Physician, Hospital of the Medical Research Center.

National University, Athens, Greece 1935-40; M.D. (cum laude) Harvard Medical School 1943; Assistant in Neurology, Harvard Medical School and Massachusetts General Hospital 1945; Assistant Physician, Hospital of the Rockefeller Institute for Medical Research 1946-51; National Research Council Fellow at Rockefeller Institute for Medical Research 1951-52; Assistant to the Institute, Rockefeller Institute for Medical Research 1952-53; Scientist, Brookhaven National Laboratory 1953-55; Senior Scientist 1956—

EUGENE P(ITCHER) CRONKITE, M.D. Senior Scientist; Head, Division of Experimental Pathology; Attending Physician, Hospital of the Medical Research Center.

A.B. Stanford University 1936; M.D. Stanford University Medical School 1941; Assistant Resident in Medicine,

Stanford University Hospital 1941-42; Medical Corps U.S. Navy 1942-54; Head, Hematology Division, Naval Medical Research Institute 1946-54; Senior Scientist, Brookhaven National Laboratory 1954—

LEWIS K(ITCHENER) DAHL, M.D. Senior Scientist; Head, Division of Hospital; Chief of Medical Service, Hospital of the Medical Research Center.

B.Sc. University of Washington, Seattle 1935; M.D. University of Pennsylvania 1939; Assistant Resident in Medicine, Massachusetts General Hospital, Assistant in Medicine, Harvard Medical School 1941-42; Medical Officer, Active Duty U.S. Army 1942-45; Resident and Chief Resident in Medicine, Massachusetts General Hospital, Assistant in Medicine, Harvard Medical School 1946-48; Assistant in Medicine, Rockefeller Institute for Medical Research and Assistant Physician, Hospital of the Rockefeller Institute 1948-52; Senior Scientist, Brookhaven National Laboratory 1952—

RUTH M(IRIAM) DREW, PH.D. Scientist; Bacteriologist, Hospital of the Medical Research Center.

A.B. (biol) Marietta College 1934; M.S. (bacter) University of Cincinnati 1935; Ph.D. (med sci) Radcliffe College 1950; D.Sc. (hon) Marietta College 1958; Medical technician, Good Samaritan and Holmes Hospitals, Cincinnati 1935-41; Instructor and lecturer (bacter) Cincinnati 1938-41; Bacteriologist, Parke Davis & Co. 1942-43; Instructor, Department Bacteriology, Harvard Medical School 1943-49; Associate Scientist, Brookhaven National Laboratory 1949-58; Scientist 1959—

OTHO D(UNREATH) EASTERDAY, PH.D. Associate Scientist

Active Duty U.S. Naval Reserve 1943-46; B.A. (chem-biol) Ball State Teachers College 1948; M.S. (pharm) The State University of Iowa 1950; Research Assistant (pharm) 1948-51; Ph.D. (pharm-chem) 1953; Associate Scientist, Brookhaven National Laboratory 1953—

LEE E(DWARD) FARR, M.D. Senior Scientist; Medical Director; Chairman, Medical Department; Chief of Staff, Hospital of the Medical Research Center.

B.S. Yale University 1929; M.D. Yale University School of Medicine 1933; Clinical Assistant, Infants and Children's Hospital, Boston 1931-32; Assistant in Pediatrics, Yale University School of Medicine 1933-34; Assistant in Medicine, Hospital of the Rockefeller Institute for Medical Research 1934-37; Associate in Medicine 1937-40; Director of Research, Physician-in-Chief, Alfred I. duPont Institute, Wilmington, Del. 1940-49; Medical Officer, Active Duty, U.S. Naval Reserve 1942-46; Deep Sea Diving and Submarine Medicine, Naval Medical Research Institute 1944-46; Senior Scientist, Medical Direc-

tor, Chairman, Medical
Brookhaven National L.

LAWRENCE V(A)

Assistant Chemist, Hospi

A.B. (chem) DePauw
organic chem) Michig
Duty U.S. Naval Re
physiol) University of
low; University of Wisc
tion, Veterans Admin
1950; Associate Scien
ratory 1951-58; Scien

WALTER Senior Scientist; Associate Chemist, Ho

S.B. (chem) Mass
1937; Ph.D. (organ
Stockholm 1937-38;
ate, Assistant Profess
1940-43; Associate P
University 1953-55; S
ratory 1955-56; Seni

STUART W(EL) Senior Scientist; Assi Chief

Hospital of
Chief, Gradu

A.B. Clark Unive
cal School 1935; A
1935-36; Instructor
Demonstrator and
search Fellow, Car
tute, U.S. Public H
42; Medical Offic
Disease Research
Department Patho
of Medicine, Seat
Brookhaven Na
1956-58; Senior S

ROBE Senior Scientist Attending Physicia

B.A. Brown U
Medical Colleg
County Hospita
Active Duty, U.S
tice 1947; Associ
haven National
Senior Scientist

JAMES S(I) Senior Scier Attending Physi

B.S. (pre-m
University of

†Effective July

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Department, Senior Physician,
Hospital 1948—

(NE) HANKES, PH.D.

Physiologist;
Hospital of the Medical Research Center.
University 1942; M.S. (biochem-
istry) University 1943; Active
1944-46; Ph.D. (biochem-
istry) 1949; Postdoctoral Fel-
low 1949-50; Chief, Allergy Sec-
tion Hospital, Aspinwall, Pa.
Brookhaven National Labo-
ratory 1959—

HUGHES, PH.D.

Division of Biochemistry;
Hospital of the Medical Research Center.
Massachusetts Institute of Technology
1941; Fellow, University of
Chicago, Research Associate, Associ-
ate (chem), Harvard University
1941; Assistant, Chemistry, Johns Hopkins
University, Brookhaven National Labo-
ratory 1957—

(TON) LIPPINCOTT, M.D.

Chairman, Medical Department;†
Physiology Service,
Hospital of the Medical Research Center;
Medical Education Program.

1929; M.D., C.M., McGill Medi-
cal Demonstrator (path), McGill
University of Pennsylvania 1937-38;
Resident (path), McGill 1936-39; Re-
search, National Cancer Insti-
tute Service, Washington, D.C. 1940-
46; Active Duty, U.S. Army, Tropical
1946; Professor, Executive Officer,
University of Washington School
1946-55; Senior Medical Associate,
Laboratory 1955-56; Scientist
1958—

(ANDER) LOVE, M.D.

Chief, Division of Industrial Medicine;
Hospital of the Medical Research Center.
University 1937; M.D. Cornell University
1942; Resident in Medicine, Kings
County Hospital 1946-47; Medical Officer,
Naval Reserve 1943-46; Private prac-
titioner, Associate Physician, Brook-
haven National Laboratory 1947-50; Scientist 1951-52;
—

(DR) ROBERTSON, M.D., PH.D.

Chief, Division of Medical Physics;
Hospital of the Medical Research Center.
University of Minnesota 1943; M.B.
Minnesota Medical School 1944; M.D.

1945; Teaching Assistant (physiol), University of Califor-
nia at Berkeley 1946-47; Assistant Physiol. 1947-50; Ph.D.
(physiol) University of California at Berkeley 1949; Medi-
cal Officer, Active Duty, U.S. Naval Reserve 1945-46;
Private practice Eureka, Montana 1946; Associate Scien-
tist, Brookhaven National Laboratory 1950-53; Medical
Officer, Active Duty, U.S. Naval Reserve, Medical Divi-
sion, U.S. Naval Radiological Defense Laboratory 1953-
55; Scientist, Brookhaven National Laboratory 1955-56;
Senior Scientist 1956—

WALTON W(ALLACE) SHREEVE, M.D., PH.D.

Scientist; Associate Attending Physician,
Hospital of the Medical Research Center.

B.A. (pre-med) DePauw University 1943; M.D.
Indiana University 1944; American Cancer Society Fel-
low (biochem), Western Reserve University 1947-50;
Ph.D. (biochem) Western Reserve University 1951;
Medical Officer, Active Duty, U.S. Naval Reserve 1945-
46; Research Physician, Veterans Administration Hospi-
tal, Cleveland 1950-52; Head, Radioisotope Laboratory,
U.S. Naval Hospital, Oakland, Calif. 1952-54; Scientist,
Brookhaven National Laboratory 1954—

ELMER E(UGENE) STICKLEY, PH.D.

Scientist;

Medical Physicist, Hospital of the Medical Research Center.

B.S. (phys) Carnegie Institute of Technology 1937;
M.S. (phys) University of Pittsburgh 1940; Graduate
Student Assistant (phys) 1937-42; Ph.D. (phys) 1942; In-
structor, Pennsylvania College for Women 1938-42; Fel-
low, Mellon Institute for Industrial Basic Research 1942-
43; Physicist (Glass Research Division) Pittsburgh Plate
Glass Co. 1943-51; Medical Associate, Brookhaven Na-
tional Laboratory 1951; Associate Scientist 1952-53;
Scientist 1954—

RICHARD D(EAN) STONER, PH.D.

Scientist;

Parasitologist, Hospital of the Medical Research Center.

B.A. (zool) The State University of Iowa 1940; Instruc-
tor 1947-49; Ph.D. (zool-paras) 1950; Active Duty, U.S.
Naval Reserve 1940-41; U.S. Army 1942; Assistant Scien-
tist, Brookhaven National Laboratory 1950; Associate
Scientist 1951-55; Scientist 1956—

DONALD D(EXTER) VAN SLYKE, PH.D.

Senior Scientist;

Chemist, Hospital of the Medical Research Center.

B.S. (chem) University of Michigan 1905; Ph.D. (chem)
1907; Sc.D. (hon) Yale University, Michigan, North-
western, Chicago, London; M.D. (hon) University of Oslo,
Norway; Research Chemist, New York Experimental
Station, Geneva, N.Y. 1906; Research Chemist, Hospital
of the Rockefeller Institute for Medical Research 1907-14;
Chief Chemist 1914-49; Senior Scientist, Assistant Direc-
tor for Biology and Medicine, Brookhaven National Labo-
ratory 1949-56; Counselor, Research Grants, Eli Lilly and
Company 1951-56 (on leave from Brookhaven); Senior
Medical Scientist (Emeritus) 1956—

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Laboratory Objectives and Program

Brookhaven National Laboratory is a national research center in which the Laboratory staff and scientists from other institutions, especially those located in the northeastern United States, carry out fundamental and applied research in the nuclear sciences and related subjects as an integral part of the nation-wide program of the Atomic Energy Commission. It was established as a cooperative venture between nine leading northeastern universities (Columbia, Cornell, Harvard, Johns Hopkins, the Massachusetts Institute of Technology, the University of Pennsylvania, Princeton, the University of Rochester, and Yale) and the government in recognition of the need for large and expensive equipments, and concentrations of scientific manpower for the successful prosecution of nuclear research. The primary objectives of the Laboratory are:

1. To seek new knowledge in the nuclear sciences and related fields with emphasis on programs that require such large-scale research tools as nuclear reactors, accelerators, and special laboratories which are beyond the scope of most or all individual institutions.

2. To encourage appropriate use of its facilities by scientists of college, university, industrial, and other laboratories.

3. To assist the Atomic Energy Commission in the solution of specific problems by utilizing the Laboratory's unique facilities or the special talents of its staff.

4. To make use of the Laboratory as an important auxiliary in the training of scientists and engineers and otherwise to assist in the dissemination of scientific and technical knowledge.

The cooperative nature of the Brookhaven program is of paramount importance. A significant and increasing fraction of the scientists and engineers directly engaged in the scientific program is comprised of visitors from other institutions who take advantage of the special opportunities at Brookhaven to carry out specific research and to gain useful knowledge and experience.

These objectives, of pioneering in research fields requiring large and specialized equipment, of making the Laboratory's facilities available to

visiting scientists, and of furthering the education and training of young scientists, exert a profound influence on the life of the Laboratory and on its planning with respect to both staff and facilities. Because of the constantly changing work and the rotation of the staff, a maximum degree of flexibility is demanded; the continuing presence of specially skilled groups and adequate and specialized laboratories and other facilities are required for the development, construction, and effective utilization of advanced scientific equipments; problems of housing, transportation, etc., are accentuated by the large number of scientists on temporary assignment, by the relative remoteness of the Laboratory from centers of population, and by the resort nature of the surrounding area. All these factors must be considered in the development of future plans.

The scientific program can be broadly divided into five general categories:

1. Fundamental studies of atomic nuclei, the particles which constitute them, and the forces involved in their structure.

2. Study and exploitation of the physical, chemical, and biological effects of nuclear radiation.

3. The use of nuclear tools such as neutrons, charged particles, gamma-rays, and isotopic tracers in all branches of scientific research.

4. Research and development not necessarily of a nuclear nature but useful in atomic energy development.

5. Useful applications of nuclear power.

The research is centered around, though not confined to, the use of several large equipments and other special facilities, which include a large, graphite-moderated, air-cooled nuclear reactor with accompanying laboratories suitable for work at low radiation levels; a small nuclear reactor for medical use; a hot chemistry laboratory for work at intermediate and high radiation levels; a proton synchrotron (the Cosmotron) which operates at approximately 3 Bev; a 60-in. cyclotron capable of accelerating deuterons to somewhat in excess of 20 Mev; a 3.5-Mev positive particle electrostatic accelerator; a 2-Mev electron electrostatic accelerator; and an 18-in. high-intensity cyclotron that

accelerates protons to 3 Mev and deuterons to 2 Mev. In mid-1960, the Alternating Gradient Synchrotron, which accelerates protons to energies of approximately 30 Bev, was completed; having undergone the necessary testing, it is now in full operation for the high energy physics research program.

The scientific work is carried on by seven departments and three divisions: The Physics, Chemistry, Biology, Medical, and Nuclear Engineering Departments, which conduct research and development in the indicated fields; the Accelerator Department, which is responsible for the design, construction, and operation of the large accelerators; the Instrumentation and Health Physics Department, which develops, constructs, and services nuclear instruments and is responsible for radiation protection throughout the Laboratory; the Reactor Division, which operates the research reactors; the Applied Mathematics Division; and the Mechanical Engineering Division.

STAFFING

The Laboratory scientific staff now includes approximately 335 "regular" members, 78 salaried and 16 nonsalaried postdoctoral research associ-

ates with tenure limited to two years, and 350 full- and part-time visitors from other institutions. Of the last group, approximately 200 spend a significant fraction of their time at the Laboratory, an average of about 100 actually being on site at any one time.

The Laboratory's mission of conducting research primarily in the more basic aspects of the atomic energy program, and in particular the objective of making its facilities available to visiting scientists including students, can be fully realized only by considerable expansion in the staff. In many of the activities in which Brookhaven engages, opportunities elsewhere are few in number or nonexistent. Implementation of existing budget requests should bring the continuing staff toward a well-rounded and effective size in many of the Laboratory's activities, as they provide for a staff in June 1962 of approximately 500 staff scientists, including 100 research associates, and 2200 supporting personnel. The average number of visiting scientists working on site will increase to over 150.

It is anticipated that with increased emphasis on basic research programs in the field of atomic energy and with the addition at Brookhaven of more advanced research tools and facilities, the scientific staff may double its present size in perhaps ten years.

The Medical Department Program

Lee E. Farr, M.D.

Medical Director and Chairman, Medical Department

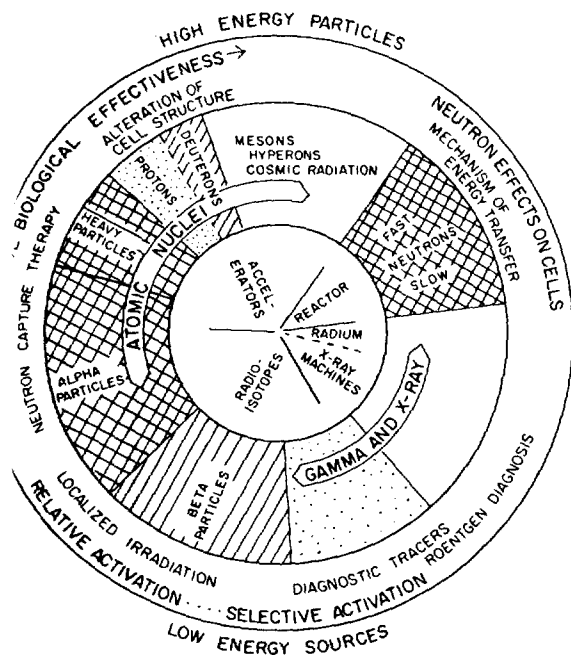
To distinguish certain efforts in the clinical and scientific practices of medicine peculiar to our times, the term "nuclear medicine" is becoming established in our lexicon. Nuclear medicine may be defined as that field of medicine which seeks to obtain diagnostic or therapeutic advantage through the utilization of the properties of particles resulting from nuclear transformation and from atomic transpositions resulting from nuclear changes. It is concerned, then, with the fundamental particles: the nucleus, the alpha particle, the neutron, the neutrino, the meson, the pion, and other identified high-energy particles. Beta and gamma emissions as manifestations of nuclear changes may be utilized. In these aspects nuclear medicine differs markedly on the one hand from radiology, which is concerned with electromagnetic and particle bombardment, and on the other hand from simple tracer techniques, which are applications or extensions of biochemistry and physiology. In many areas, however, a complete overlap may be seen. Another responsibility is to determine the effects of environmental radiological contamination upon man, to meet problems of decontamination of man, and to develop an understanding of such radiation effects in man as may need to be effectively combated.

The research program of the Medical Department concerns itself with the biological effects of radiation and in particular with particle radiation of very short range. The researches thus must inherently be concerned with studies of precise isotope localization, kinetics of distribution and redistribution, metabolism of organic compounds, functions of inorganic compounds, and the effect of excited atoms on the stability of large molecules or complexes. We, as physicians, must always concern ourselves with ultimate effects upon intact mammalian organisms, even though the experimental observations may be carried out on isolated organ systems, tissue cells in culture, or chemical reactions which occur in the body. Ad-

vantage is sought of special situations which may be applicable to medical therapy such as neutron capture therapy of glioblastoma multiforme. Isotopes used are largely those of short half-life - from a minute or less up to a few days - in order that progression through a metabolic complex can more satisfactorily be followed by judicious radioactive isotope selection and that radiation dose may be held to a minimum. Gamma and x-radiation studies are also carried out in order that similarities and differences may be closely examined in the same fashion that effects are observed in single cells and in multicelled and highly organized species. Diagnostic studies in the widest sense are carried out on suitable disease states under study in the hospital. Such studies, however, are concerned primarily with elucidation of the nature of the disturbance and the proper selection of individuals in a general population for a uniform response rather than with specific diagnostic routines for use in a large general medical clinic. These studies have great significance in permitting us to predict effects of exposure of man to various radionuclides, both elemental and as organic compounds. The entire program of the Department is integrated with each scientist having awareness of, interest in, and, frequently, participation in his colleagues' investigations.

Many of the research problems confronting medical men today are so large and so complex that a group assault is necessary. However, in all circumstances a strenuous effort is made fully to preserve for the participating research scientist complete individual freedom to find his own path toward solution of some feature of the over-all problem. The scientist must not be denied the pleasure, privilege, or responsibility of doing his own thinking. Cooperative effort is maintained on an individual basis of voluntary associations among members of the Department and also with colleagues outside the Department. By careful preservation of the individual's choice of what

[Hatched Box] FIELD OF SPECIAL INTEREST [Dotted Box] ACTIVE SECONDARY INTEREST
 [Solid Box] MAJOR ACTIVITY [White Box] PASSIVE ATTENTION ONLY



Fields of nuclear science at Brookhaven of interest to the Medical Department.

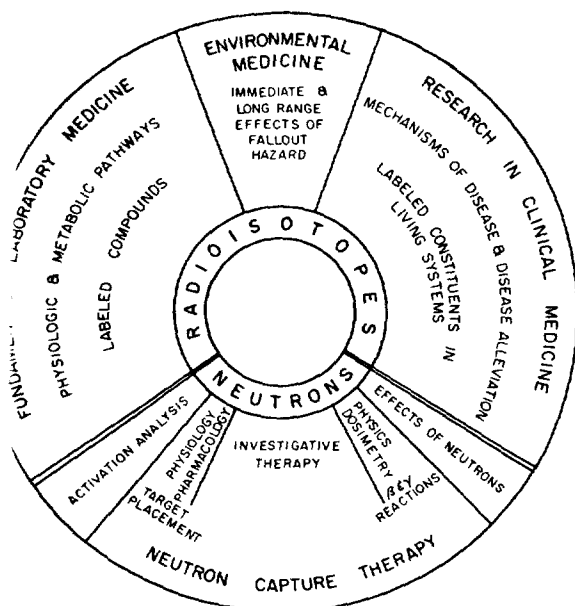
appears to him to be the path leading to the most rewarding effort, there will emerge a program achieving the most productive employment of available knowledge, skills, and equipment. The new ideas for research must come from individuals, and in turn these will derive from experimental testing of hypotheses of each scientist within his own field of greatest competence.

Although research is the primary objective of the Medical Department, various aspects of education are inextricably blended into the framework of the investigative program. The special facilities of Brookhaven National Laboratory, the objective of Associated Universities, Inc., to assist other institutions by making these intricate and expensive devices available to qualified scientists, the responsibility of the Division of Biology and Medicine of the Atomic Energy Commission and the members of the staffs of its sponsored and supported laboratories in bringing before those concerned with medical education the present status and future areas of exploration in nuclear medicine – all these put further emphasis upon the role of the Medical Department in offering educational leadership in this new field of medical science.

THE MEDICAL DEPARTMENT STAFF AND ITS ORGANIZATION

The scientific staff of the Medical Department is limited in number by policy and design to forty-eight full-time, regular staff positions. A staff of this size is large enough to provoke stimulation within itself but not so large that each person may not be well acquainted with the work of his colleagues. It is large enough that necessary facets of medical and diagnostic services can be covered responsibly in the hospital but not so large as to require organization of several services. Although the Department is administratively organized into seven divisions – the Hospital, Biochemistry, Experimental Pathology, Physiology, Microbiology, Medical Physics, and Industrial Medicine – functionally it operates as a single unit with no jurisdictional barriers impeding activities within the Department.

Since it is the policy of Associated Universities, Inc., that a large fraction of the staff shall be rotated in order that universities may benefit by having men on their faculties who have worked at Brookhaven and that Brookhaven may benefit



Distribution of investigative efforts of the Brookhaven Medical Department.

by a constant infusion of new enthusiasm brought to it from universities and institutes, there is a general policy limiting the time a man may remain on the staff at Brookhaven in its several ranks of term appointments. On term appointments a man may, if reappointed, stay up to a maximum of ten years provided he begins his experience here as an assistant or associate scientist. A man beginning his appointment as a scientist or senior scientist is limited to three or five years depending upon his individual category. It is generally expected that most term appointees to the staff will spend approximately three to five years at Brookhaven becoming thoroughly qualified in the areas for which opportunities are provided here. It is anticipated that most appointments will be of junior men who come for education, training, and experience in the field of this Department and who will later return to university faculties.

Taking into account these policies, the scientific staff of the Medical Department is organized into three categories:

I. Full-time, Regular Staff.

- A. Tenure scientists who hold their positions under terms comparable to professorial tenure in university faculties.
- B. Indefinite appointment scientists who hold their positions indefinitely for performance of a necessary function in the Department or Laboratory organization.
- C. Term scientists who hold appointments for specific terms.

II. Part-time, Temporary Staff. In a few special situations, part-time, temporary appointments are given for operational reasons to qualified persons.

III. Research Collaborator Staff.

The research collaborator staff is composed of those holding academic appointments in universities or equivalent appointments in hospitals or institutions who are given appointments to the staff of the Medical Department for terms renewable up to one year for intermittent work during those terms in collaboration, extension, or intensification of work of joint interest to the research collaborator and to a regular staff appointee in the Medical Department. Those holding fellowships from foundations or governmental agencies are generally given appointments as research collaborators in residence which permit them to be granted working privileges of the regular staff and to be integrated into the research, training, and

education programs of the Department. Brookhaven does not award fellowships. On the other hand, the Department does have a limited number of one-year term appointments as Medical Associate renewable for two additional terms of one year. This appointment is available to persons of all ranks in universities or institutes, and it is available to persons on sabbatical or other leave from universities and institutes. In some instances in these on-leave categories, appointment as a research collaborator in residence may be more appropriate.

The categories of the scientific staff previously noted are further divided into four ranks: senior scientist, scientist, associate scientist, and assistant scientist. The title medical associate carries no specified rank, and persons holding this appointment may be given privileges and assigned responsibilities of any of the ranks depending upon their training and experience.

The medical staff of the hospital and the medical supporting staff of the hospital are separately designated groups of the Medical Department scientific staff which include those who by training and experience are qualified to meet the specific clinical responsibilities of this hospital. Likewise, the hospital staff includes a separately designated group of the technical staff trained to meet specific responsibilities. Rank of a person on the medical staff of the hospital and on the scientific staff is not always identical, being adjusted rather to specific interests, qualifications, and use. Inquiries regarding staff appointments are welcomed and should be addressed to the Medical Director.

The technical staff of the Department is a career staff in the same manner as is the scientific staff. It is composed of technically qualified persons, individually selected for their interests and aptitudes, who bring a wide variety of skills and techniques to the Department's program. The technical staff is divided into several categories: scientist's assistants, technical assistants, laboratory services assistants, nursing staff to the hospital, clinical services staff to the hospital, and special services staff to the hospital. A scientist's assistant is a personal technical associate of a scientist holding a tenure appointment and is responsible directly to the scientist for performance of his duties. All other members of the technical staff are responsible to the Department as a whole through designated administrative channels to the

Medical Director. A technical assistant may be assigned to specific duties and, although still retaining his general responsibility to the Department as a whole, will act as a technical associate of specifically designated scientific staff members holding an indefinite appointment or, in special instances, a term appointment as scientist or

higher. Other types of specialized professional training and skills are represented by the nursing staff, clinical services staff, and the other variously designated categories of the technical staff.

The clerical and administrative staff furnishes those services to the Department as a whole.

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The research objectives of the Medical Department are centered on development of an understanding of the interactions between components of living cells and particles generated by physical devices. Whether or not the observations are made upon man, the information is used to evaluate known or probable reactions of man to the stimulus used. Investigation of the processes involved and the beneficial as well as the deleterious effects of the transfer, release, and absorption of energy deriving from atomic transformations or transpositions recurring in cells, tissues, and organs of mammals forms the basis for continuing studies. Particle radiation forms the core of most studies, and emphasis is on the employment of neutrons, protons, deuterons, and alpha and beta particles. Intensive exploration is being undertaken with new techniques, equipment, and devices. This is done under administrative arrangements that permit an individual scientist to carry on his research autonomously, but in association with other members of the Medical Department or with members of various departments of BNL or other medical institutions.

The unique opportunity at Brookhaven to utilize special devices that make available various kinds of heavy particles is in part responsible for the interest in reactor and accelerator radiology and the program in this field with special reference to therapeutic application to malignant tumors in man. Studies looking toward appraisal of the reactor as a useful and practical instrument for medicine are clearly dependent upon its availability and that of nuclear engineers steeped in knowledge of reactor design. In fundamental and diagnostic studies, radioactive tracer methodology forms the basis for kinetic, placement (uptake), and metabolic pathway investigations in both man and, where indicated, animals. At the cellular level the beta particles of tritium are used for labeling compounds to tag selected primordial or ancestral cells, which makes it possible to observe sequential cellular proliferation, maturation, and transformation. In the field of environmental medicine, clinical studies are concerned with the immediate and long-range effects of low level radiation with reference to both degenerative diseases and carcinogenesis. The role of the Department in assisting other institutions is primarily that of offering guidance and counsel to students, research collaborators, and physicians-in-training, and to

chairmen of departments of medical schools through conclaves covering the scientific, clinical, and administrative aspects of nuclear medicine.

Within this frame of reference specific examples of the research under way and to be developed are given below. The report is not comprehensive, and those interested in further details are referred to publications of the Medical Department.

A. REACTOR RADIOLOGY (Medical Research Reactor)

1. Reactor output in relation to power level or pulse integral (060101). Drs. E.E. Stickley, J.S. Robertson

The earliest phase of the Medical Research Reactor (MRR) was the development of design criteria in preparation for the first planning studies in 1953. By March 15, 1959, the MRR had progressed through concept, design, and construction, and was put into operation. The earlier work was carried out at the Brookhaven Graphite Research Reactor (BGRR), where the operating factors were not adjustable to the specific needs of the experiment; neutron output measurements were recorded against the power levels and the control rod patterns. From time to time major changes were made in the type of fuel and its distribution in the graphite matrix. For each device and for each change in factors affecting operation of the BGRR, new determinations of neutron output and contaminating radiations were required. Operational factors affecting radiations delivered through the medical treatment port in the BGRR included (1) rebuilding of the cone blocks to incorporate a shutter, (2) further modification of the shielding in this revised facility, (3) increases in the power level, (4) variation in control and safety rod positions, (5) change-over to a new type of fuel, and (6) alteration of the shape of the loaded zone of the reactor.

The MRR, during the first two months of operation, was used experimentally at power levels up to 1 Mw. On the basis of the initial results, permission was given to operate at power levels up to 3 Mw. In May 1960 this limit was extended to include operation at 5 Mw for periods not exceeding 10 min. To operate at this level the cooling capacity had to be increased. In the test run following this change the increased water flow under two-pump operation was found to cause intermittent fuel element displacement. For this reason

operation was restricted temporarily to 3 Mw and a single pump on the water circuit until locking devices could be fitted to all fuel elements. Operation at 5 Mw was first used only for exposures of

neutrons delivered. For these purposes the practical aspects of neutron optics are applied; materials selected for their moderating and reflecting properties are used in combination with

t critical points about the patient's head. Similar provisions were made for the various animal experiment series, utilizing in addition boron carbide and lithium fluoride packed in containers or impregnated in paraffin. The whole-body irradiation vault was fitted with a curtain and liners to minimize activation of the walls by neutron absorption. A simple pneumatic tube device and gas activation tank were installed in the northeast beam hole. Television and mirrors were added as personnel protection measures in observation rooms. A monorail was built for use in manipulating foil during activation exposures.

Development of the devices and fixtures for all irradiation sites has continued. Field-defining fixtures incorporating heavy water have been designed and have delivered a higher slow neutron flux with lower gamma-ray contamination. Improved design and construction is expected to result from work with Fiberglas-resin containers for the heavy water. Continued experimentation with the moderator element tanks in the bulk shielding led to a design which places the heavy water in the shutter and part in reflector. The primary advantage of this arrangement, which retains a certain amount of absorptivity, is better control of the fast neutron flux through the closed shutter. A complete set of safety interlocks on all exposure rooms has been installed. Attention has been given to the design of exposure holders for mice (head or thigh), rabbit central nervous system or retinal studies), the osteogenic sarcoma), pigs (ear), and man (about the head, neck, and chest).

proposed to study further the replacement of moderator and moderator components in the neutron channels by elements having heavy water as the active agent, throughout the path from core to point of irradiation. Rapid handling devices are being developed for activation analysis, pneumatic experiments, and the possible therapeutic applications of short-lived isotopes. A collimated neutron beam and cave for tissue penetrations should be provided on the north beam line. Means are to be devised for manipulating animal and phantoms in whole-body irradiation experiments. Instantly adjustable field-defining apertures will be required as part of the localizing and collimating system for use in handling patients. Advances in the design of neutron channels, structures, shields, and energy modifiers will

require refinement in the neutron optics and the application of new, especially enriched materials. These advances will also rely on extension of concepts already stated, such as the neutron hyperthermalizer suggested by Rossi. Special materials which have been proposed include plastics made with deuterium in place of protonium, Li^6F , and (for other purposes) converter plates of uranium and other substances. The further development of uses of the MRR will require additional special installations (such as refrigerated or water-cooled activation devices in the beam holes) to deliver substances for research into the diagnostic, investigative, or therapeutic possibilities of short-lived radioactivities.

3. Neutron capture therapy: Clinical and animal investigation (0609). Drs. L.E. Farr, W.G. Calvo, E.E. Stickley, J.S. Robertson, O.D. Easterday, D.N. Slatkin

Neutron capture therapy originated at Brookhaven National Laboratory, and to date all patients treated, as well as experimental animals studied, have been observed following treatment either at the BGRR or the MRR. This clinical study is one of the major projects, both in relation to basic observations in the laboratory and to clinical investigations in the hospital. Neutron capture therapy is a radiation treatment which uses energetic heavy particles created inside the disease site to be specifically treated. The localization of the radiation and the high biological effectiveness of heavy particles are two of its chief advantages. The energy of a thermal neutron is very low, about 0.025 electron volt, and its direct effect in tissue is negligible. However, such a neutron when captured by the target element creates millions of electron volts of nuclear energy, which are released.

In the actual therapeutic procedure, B^{10} is administered to the patient and is employed for the capture of the neutrons. The neutron and the B^{10} nucleus combine momentarily to form an unstable compound nucleus, which immediately breaks up into an alpha particle and a lithium particle. All the energy of both particles is absorbed within a tissue volume approximating that of one cell. Highly localized lethal cytological effects may thereby be attained. Although the primary consideration is the fact that slow neutrons *per se* have negligible effect in passing through tissue, there

are other important reactions, such as the capture of slow neutrons in nitrogen, giving a short-range but energetic proton, and the capture in hydrogen, giving a gamma-ray. Obviously the dosimetry of such a mixed radiation beam is complex.

The major studies in progress deal primarily with (1) dosimetric measurements; (2) pharmacological considerations of the element boron to be utilized for capture purposes; (3) clinical follow-up of the patients who have received varying amounts of boron, with exposures for varying time intervals to thermal neutrons of different flux; (4) the overall effect on the brain as studied at autopsy by histopathological and topographical comparison of the radiation effects occurring in the tumor only or in the normal tissue only, or the absence of any effect; (5) exploratory procedures with transplantable and spontaneous animal neoplasms to afford insight into better possible applications in man; and (6) newer dosimetric considerations determined *in vivo* with the patient in the whole-body counter, to gather better measurements on the neutrons, because neutrons cannot be detected or measured directly. Previous methods have depended upon observation of some secondary effect resulting from the action of the neutrons, since neutrons lack the electrical charge by which other particulate radiations can be detected. Secondary effects useful in the detection of slow neutrons are the radioactivity induced in a target or foil material and the fission effect that follows neutron capture in certain heavy elements. These techniques have not been abandoned but are employed in conjunction with the new refined approach for comparative purposes and total evaluation of the dose.

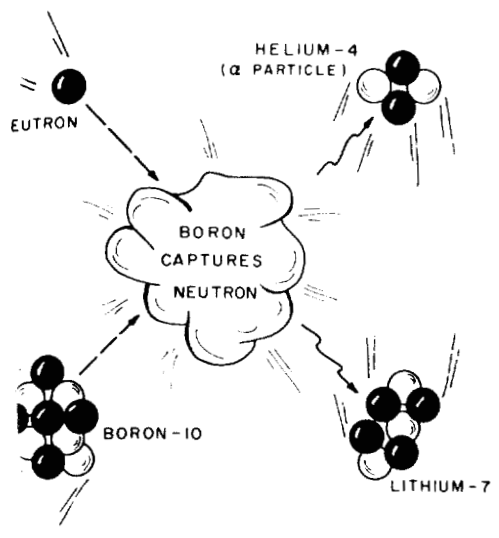
During the year clinical activities were limited because of the extensive efforts directed toward improvement of the MRR. Patients given thermal neutron capture therapy during this period were primarily those in far advanced stages of their disease. Skin flaps were turned back, and a thermal neutron exposure of the brain cortex ranging from 1.73×10^{12} to 1.21×10^{13} neutrons/cm² was obtained. No immediate adverse effects were noted from the marked increase in neutron exposure in this group of patients as compared with those treated previously. Significant practical advantages were gained by using a semipulsed type of operation of the MRR for these treatments.

In the pharmacological studies, organic boron compounds synthesized elsewhere are being studied in these laboratories. The final pharmacological testing, particularly of new compounds of Li⁶ and B¹⁰, must be done here. At present several inorganic borates that have been complexed with carbohydrates are being investigated by infrared spectroscopy. It is expected that in continuing these studies the borate-glucose complex spectra can be evaluated, and perhaps a target element that is even more suitable can be employed in the therapeutic procedure.

In addition to clinical observations on the experimental procedure, the effectiveness of neutron capture therapy has been evaluated by making a combined topographical and histopathological survey of the irradiated brains obtained at autopsy. The procedure is to embed the brain *in toto* in celloidin, and then to section and stain serial blocks so that all spatial relationships can be studied microscopically. With appropriate special stains cytologic features and arrangements of nuclei and nerve tracts are readily recognized. The purpose is to determine whether the irradiation has destroyed neoplastic cells and also whether it has affected surrounding and distant structures. Different types of cases have been studied, including (1) 70 cases with primary neoplasms of the central nervous system, in which selected blocks of tissue from the neoplasm and nonneoplastic areas of brain have been investigated; (2) 20 cases with similar neoplasms, studied for comparative purposes by the whole-brain technique; (3) 10 cases having no neoplasms, studied with whole-brain technique; (4) 40 cases of primary brain neoplasms treated by neutron capture therapy (studies completed on 26); and (5) one case of primary brain neoplasm treated with thermal neutrons only. Comparison of these cases has been useful in establishing criteria for the recognition of effects, direct and indirect, immediate and delayed, from any form of irradiation to neoplastic and normal structures in the central nervous system.

Whole-brain sections were prepared from 16 cases with intracranial gliomas and sarcomas in which the total neutron exposure ranged from 0.44×10^{12} to 6.31×10^{12} neutrons/cm² and the amount of sodium tetraborate ranged from 25 to 50 µg/kg body weight. In three of the cases with glioblastoma multiforme and one with sarcoma,

BORON-10 — THERMAL NEUTRON REACTION

NEUTRON CAPTURE THERAPY
FOR MALIGNANT BRAIN TUMOR,
AN EXPERIMENTAL PROCEDURE

Upon capture of a thermal neutron, the B^{10} atom instantaneously disintegrates (A) into an alpha particle (${}^4_2\text{He}$) and an energetic lithium particle with a large release of energy (2.4 Mev). The cytotoxic effect of the alpha particles is demonstrated by comparison of (B) biopsy from malignant cerebellar vascular neoplasm before therapy and (C) biopsy from same neoplasm 11 weeks after therapy showing complete cytonecrosis.



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necrosis of the neoplasm appeared to be present in the region of the radiation port. In the remainder of the cases no alterations in the neoplasms attributable to neutron capture therapy could be established. No damage to the nonneoplastic central nervous system structures resulting from the irradiation procedure was observed.

4. Activation analysis for physiological purposes: Concentration, distribution, and studies of compartmental exchange of trace elements (0610). Drs. G.C. Cotzias, P.S. Papavasiliou, D.C. Borg, E.R. Hughes

That trace metals are present in living matter has long been known, but the paucity of suitable precise techniques has hindered investigation of their function in human metabolism, in both normal and diseased states. Although a trace metal may be present only in minute amounts, it may be of great importance chemically if, for example, it is a specific activator of an enzyme system, or if it is present in relatively high concentration in a given type of cell, tissue, or organ. An important aspect of the physiology of such a trace element may be its exchange from one anatomical compartment to another in the course of metabolic activity. The development of tracer methodology with short-lived radioisotopes has made it possible to investigate compartmental exchange (or turnover), and the introduction of neutron activation analysis has aided in studying the concentration and distribution of microconstituents. These techniques have been applied to the study of manganese in Parkinson's disease, copper in Wilson's disease, and cadmium turnover in animals.

Parkinson's disease is a slowly progressive, degenerative disease of the central nervous system occurring in adults; it results in rhythmic tremor of resting muscles and associated stiffness and slowing of movements. This entity has been induced in man by inhalation of manganese ore dusts and by the use of some tranquilizing drugs. Such induction of Parkinsonism does not imply that these materials are the sole causes, but the fact that the disease may be produced by manganese led to studies of this metal in this disease. The investigations have centered on measurements of manganese metabolism *in vivo* both before and after response to drugs and other agents such as hormones. The specificity of the manganese pathway was first established in normal animals, and

progress is being made in verifying this pathway in man. Establishment of the normal pattern of distribution and excretion of manganese should form a basis for determining whether a distinct alteration or deviation occurs in this disease. The principal result observed following administration of a tranquilizing drug, such as thorazine, was that the pharmacological agent can bind trivalent manganese and slow down the fast disappearance rate of injected manganese salt. Because adrenal steroids are known to affect profoundly the behavior of bulk metals, their effect on the turnover rate of Mn^{54} was studied in mice. Little or no effect was found, and a similar study in man will probably have limited application.

The finding of a rapid disappearance rate of injected Mn^{54} led to animal studies which showed that the element was taken up by tissues rich in mitochondria; this was also noted in man by external scanning of patients to whom the manganese radioisotope had been given. This observation indicated the importance of the mechanism of transport, which is now under continuing study. The carrier mechanism involves the synthesis of a metallo-organic compound of manganese which is being isolated from red blood cells and liver cells. The identification of this human porphyrin containing manganese establishes a hitherto unknown transport mechanism, and its specificity should be of value in the recognition of the metal pathway and turnover patterns in Parkinson's disease.

Trace elements occur in such small concentrations in tissues that they were at first considered to be contaminants. Some, such as iron, zinc, manganese, iodine, and copper, are essential to life. Definite abnormalities of metabolism of these elements have been established in some disease states. In blood itself trace elements are present in such low concentrations that quantitative determination is made difficult because of interference by the abundant macroconstituents. Reactor neutrons are capable of activating some of these elements. The availability of the MRR makes possible the use of sensitive and specific methods of activation analysis for the minute quantities of essential trace elements in blood and plasma. These procedures have eliminated bulk element interference and will allow delineation of the physiological specificity of trace elements in man on a chemical basis. By using specific instrumenta-

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this can be accomplished when necessary without structural or constitutional alteration of biological samples. This permits anatomical as well as physiological studies on identical tissue specimens. The basic studies of manganese metabolism in man will be considered not only in Parkinson's disease but in certain collagen diseases. It is known, for example, that in the collagen disease treated by hydralazine there is marked slowing of body turnover. By using activation analysis it will now be possible to determine specific activity of the Mn^{54} in these kinetic studies.

Issue and physiological effects of reactor radiation (060101). Drs. J.S. Robertson, S.H. Cohn, E.E. Ley, J.H. Jacobson, G.B. Kara, H.W. Najac

In these studies, three basic investigations are carried out: (1) the role of neutron irradiation in cataract formation; (2) the relationship of thermal neutron exposure to electrophysiological changes in the eye in animals; and (3) dosimetry with reference to the estimation of captured gamma rays in patients given neutron capture therapy. Neutrons are used in all three investigations, but the device for measurement and the target for activation are different in each.

Cataract formation has been known to occur following accidental exposure to neutrons. The present concept of cataract formation in such cases is that epithelial cells in the germinative zone are damaged and later form faulty lens fibers, which result in cataracts. In investigating an important effect, neutrons from the MRR are being used to determine whether a cataract develops before or after the neutron-damaged epithelial cells in the germinative zone reach the anterior fold of the lens. For this study the mouse eye was irradiated *in utero* with sublethal doses of neutrons. Tritium-labeled thymidine was used to label only the lens epithelial cells in the germinative zone in order to follow the migration of the labeled cells after gamma irradiation. The technique of cell production and migration for this study was developed in the cat lens.

In another phase of this problem, the MRR serves as a primary source of neutrons, and the characteristics are modified as needed by the placement of shielding and moderating material. With use of this system, morphological and biochemical changes in the retina and the changes on the electroretinogram (ERG) in the

rabbit can be compared with electromagnetic radiation effects, as established previously with the 250-kvp x-radiation method. A large series of rabbits was exposed to thermal neutrons, and another group was irradiated with x-rays. It was noted that with 2000 r from the electromagnetic radiation the ERG response diminished to the point of extinction, and respiratory enzyme activity was also lost. It is of interest that in the early neutron exposures these same phenomena were not encountered. The correlation of destruction of tissue by irradiation with ERG studies is expected to provide information on activities in these specific layers of the eye.

In neutron capture therapy the thermal neutron is captured by the B^{10} atom. The latter promptly disintegrates into an alpha particle and an energetic lithium particle with a release of energy. All the energy of both particles is absorbed within a tissue volume approximating that of one cell. In addition, various elements in the body simultaneously capture neutrons and become activated. It is therefore apparent that dosimetric characterization of the neutron and gamma spectra is a complicated problem. One attempt to solve the latter phase is through a combination of measurements made in the whole-body gamma spectrometer, with reference to the geometry as it actually occurs in the head.

The thermal neutron dose received by the brain of patients with malignant primary neoplasms in that area in the course of neutron capture therapy has been investigated with *in vivo* gamma spectrometric measurements of induced gamma activities. Neutron irradiation produces Na^{24} as well as other radioisotopes such as Ca^{45} from the sodium and calcium in the head, and the resultant gamma activity of these isotopes as they circulated throughout the body was measured. This measurement was then used in the calculation of the effective thermal neutron dose received by the brain. The results were compared with physical dosimetry measurements obtained by placing physical receptors close to the head, or biological receptors.

B. ACCELERATOR RADIOLOGY (Van de Graaff Generator, 60-in. Cyclotron, and Cosmotron)

The study of particle effects that are or may be of medical significance is not limited to reactor

radiology. Accelerators can provide "pure" energy spectra of a variety of particles and hence are used as devices by the Medical Department to extend and diversify its program.

1. Effects of accelerator-produced monoenergetic neutrons in mammals (06010). Drs. V.P. Bond, J.L. Bateman, E.E. Stickley, H.H. Rossi

The effects of monoenergetic neutrons in mammals are being investigated for several reasons. It is important to learn more about the possible effects in man of exposure to fast neutrons in order to determine methods of protection as well as allowable exposure levels. In properly arranged experiments, additional basic information can be gathered concerning radiation damage and possible tissue recovery. Such approaches include the determination of the effects of dose rate on radiosensitivity. This information is useful in determining in man the effective biological dose in radiotherapeutic and accidental exposures. As a final factor in this program, the experiments are designed to compare "one hit" and "multiple hit" dose response patterns and to provide information on protection, the effects of oxygen in irradiations with fast neutrons, and those of particles of higher linear energy transfer (LET).

In earlier studies with neutrons, the wide spread of particle energy from reactors and accelerators made interpretation of biological results extremely difficult. For this reason, the 3-Mev Van de Graaff generator was used to accelerate protons into a tritiated zirconium target. The resultant fast neutrons were of suitable energy and flux to serve as a source of monoenergetic neutrons for the irradiation of mice. During this period special equipment was constructed to measure both depth dose and quantity of radiation in number and density of ionizing events in graded sizes of microscopic tissue-equivalent spheres. LET spectra were obtainable by utilizing this same apparatus.

Replicate experiments with this source of monoenergetic neutrons make it possible to use as a biological indicator the weight loss in spleen and thymus at 4 days postirradiation. Spermatogonia depletion in the testes of irradiated mice and their descendants has also been investigated, and appears to be a sensitive biological indicator.

In extensions of experiments reported last year, mice of different ages from those previously studied are being used, and higher energies, at

least as high as 1.80 Mev, are being utilized. In addition, testing of other biological end-points is being considered, e.g., bone marrow with its capacity to incorporate such compounds as 5-iododeoxyuridine. Investigation of the effects of oxygen is also being considered. This will permit studies directed towards determining additional features such as the role of heavy recoil nuclei in producing radiosensitivity peaks with neutrons at cross section resonance energies.

2. Effects of monoenergetic deuterons on neural growth (060101). Drs. L.E. Farr, L.I. Malis, J.E. Rose

The 60-in. cyclotron was used in a study of the effects on tissue of penetration of the cerebral cortex by a deuteron beam. A laminar lesion (sharply delimited narrow zone in which all nerve cells have been destroyed) was produced with peak doses of 15,000 to 45,000 rad. The corresponding surface and average doses are 3000 to 9000 and 5000 to 15,000 rad, respectively. Deuteron intensity ranged from 4.0 to 12.0×10^9 deuterons/cm². By appropriate maneuvers the procedure can be used to isolate a strip of cortical tissue but a few neurons thick. Doses above 45,000 rad produced necrotic foci, and at 75,000 rad complete necrosis of the irradiated region was observed.

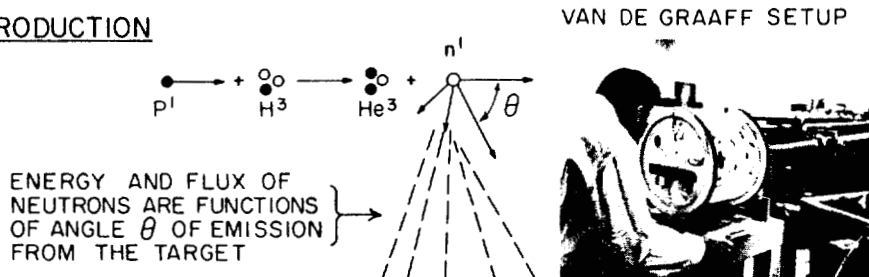
3. Methodology of widening the Bragg peak in tissue by using deuterons (060101). Drs. S.W. Lippincott, C.R. Jansen, W.G. Calvo, K.R. Rai, C.P. Baker*

Heavy particles are much heavier than electrons (deuterons are ≈ 4000 times heavier), and by virtue of their physical properties have unique and important applications in medicine and biology. Because of their mass, the angle of scattering in a given collision is reduced by about the same ratio of mass difference. They also possess a definite range of penetration in matter instead of following an exponential law, as do x-rays or gamma-rays. In passing through a material the particle loses some of its energy per unit length of path. This rate of energy loss is called the linear energy transfer (LET) of the particle in the material it traverses. The particles lose their energy to the material they traverse by means of ionization, elastic scattering, inelastic scattering, and excitation. Ionization occurring in tissue along the path of penetrating particles increases in density as the

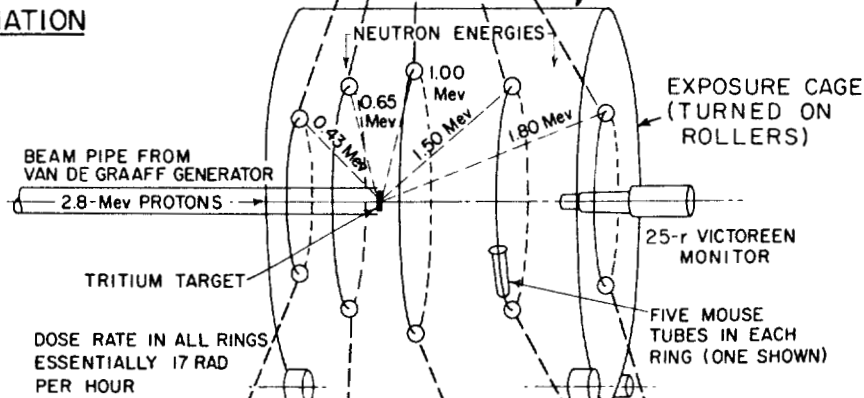
*Member of the Physics Department.

EMPLOYMENT OF THE 3-Mev VAN DE GRAAFF GENERATOR IN PRODUCTION OF MONOENERGETIC FAST NEUTRONS FOR SPLEEN-THYMUS WEIGHT-LOSS STUDIES IN MICE

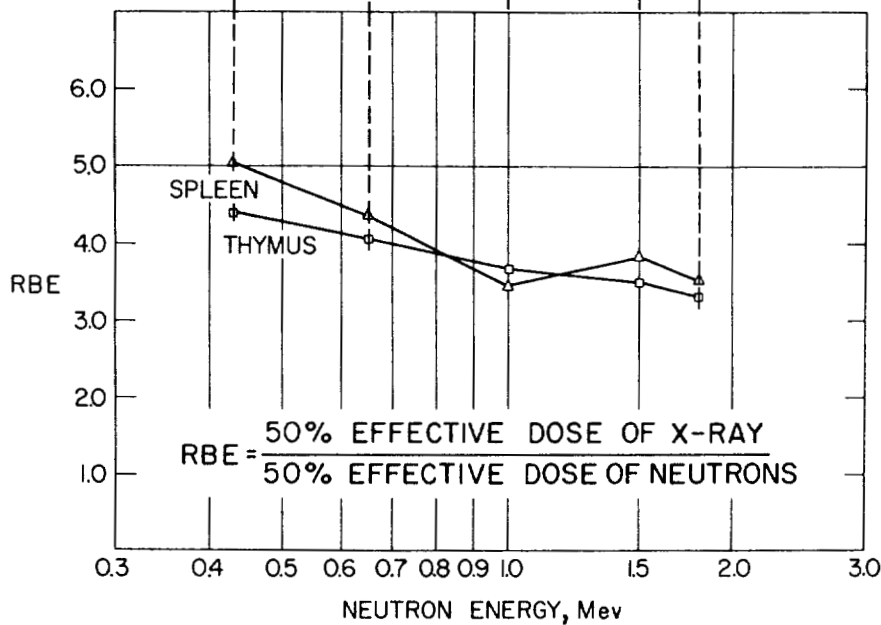
NEUTRON PRODUCTION



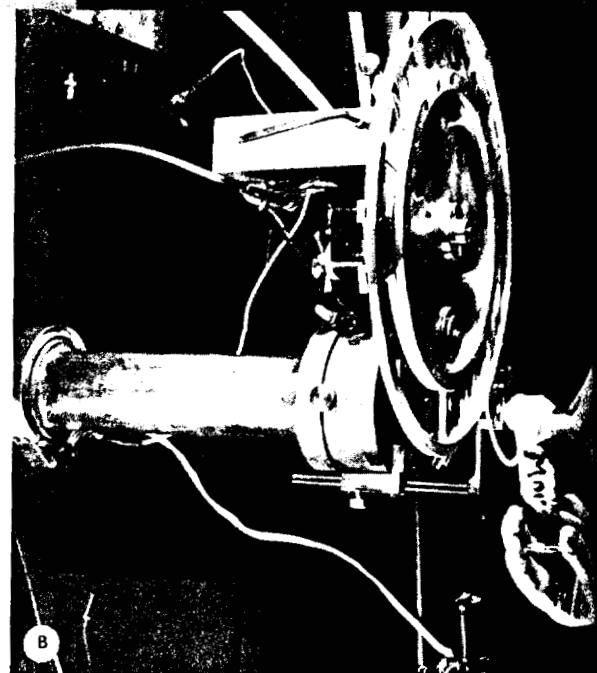
ANIMAL IRRADIATION



RESULTS

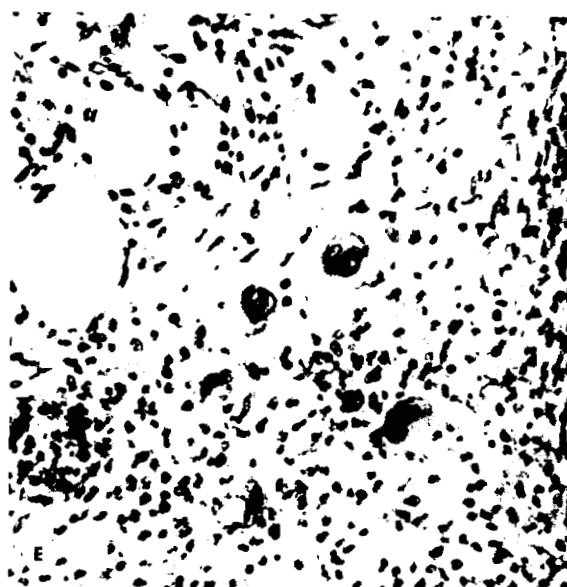
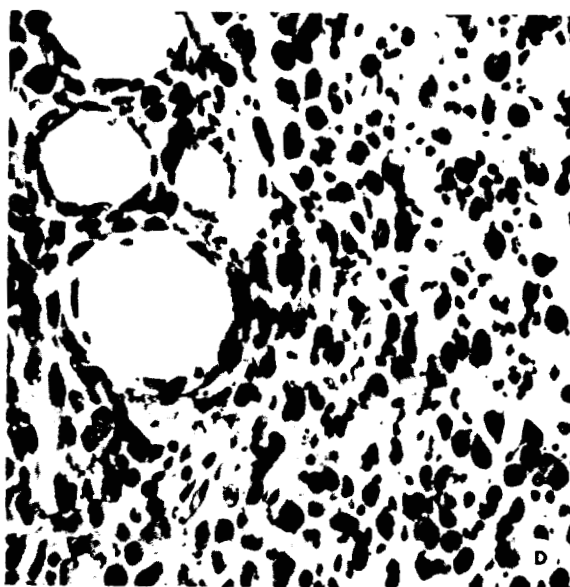
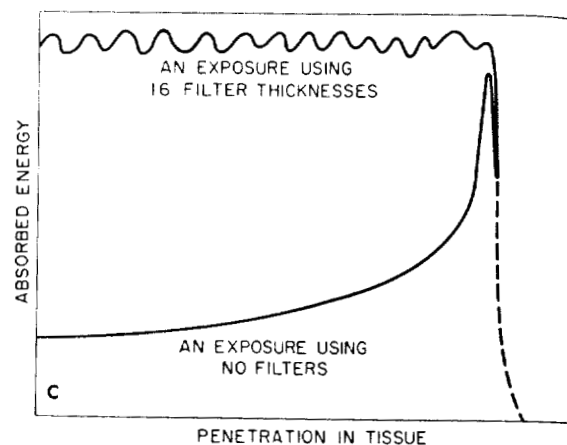


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RADIATION EFFECT OF ACCELERATOR-PRODUCED DEUTERONS ON TRANSPLANTABLE NEOPLASMS

The 60-in. cyclotron (A) is the source of highly energetic deuterons. A beam-filtering wheel (B) was developed to control the amount and location of energy (deuterons) absorbed in tissue (C). The uniformly malignant character of the cells in a transplantable neoplasm is shown (D) before radiation with deuterons. Six days postradiation, the transplanted neoplasm shows only inflammatory cells and nonproliferating tumor giant cells (E).



particle continuously loses its energy. In the final portion of the path, the energy given up per unit path length rises to a peak (Bragg peak) just before the end of the path is reached.

The objective of the present studies was effectively to widen the Bragg peak in depth in the path of the charged heavy particles through tissues in order to allow study of the biological effects of a certain number of particles in the beginning of their track compared to the effects of an equal number of particles at the end of their track. The cyclotron at BNL accelerates deuterons to energies of 20 Mev; a current density of 1.83×10^{-11} A/cm² has normally been used. With this beam $\times 10^8$ deuterons/cm²-sec is delivered. In all studies the introduction of an aluminum foil of appropriate thickness into the deuteron beam decreased the energy of the beam and resulted in the production of a Bragg peak at a certain range in the tissue. To produce many Bragg peaks at different depths throughout the tissue, so close to each other that all the tissue would be in this intense ionization area, it was not possible to interrupt the exposure at short intervals and to introduce successively thicker aluminum filters between the radiation port and the tissue.

It was necessary to introduce 16 different apertures to achieve this objective. This made it necessary to deal with such short exposure times that could not be measured accurately, apart from the fact that the procedure was time consuming. These difficulties were obviated by introducing a rotating filter (wheel) driven by an electric motor mounted in front of the radiation port. The wheel consisted of heavy aluminum 30 cm in diameter with apertures of accurately determined width on its periphery. In each of the apertures an aluminum foil of appropriate thickness was clamped. The wheel was driven by a synchronous motor at 1600 rpm. Each foil therefore passed the beam five times each second. One-fifth of a second was very much compared to the shortest exposure time used, so that a good averaging was achieved. This facilitated the production of charged energetic heavy particles in the production of adjacent or separated Bragg peaks within the range of the particles in two or more layers of intense ionization at different depths separated by layers of less ionization. Tissue were produced. A cylinder of uniform ionization that cuts off sharply in depth in tissue could be produced.

4. Giant cell formation in neoplasms resulting from heavy particle radiation (060101). Drs. S.W. Lippincott, W.G. Calvo, L.E. Farr, C.R. Jansen

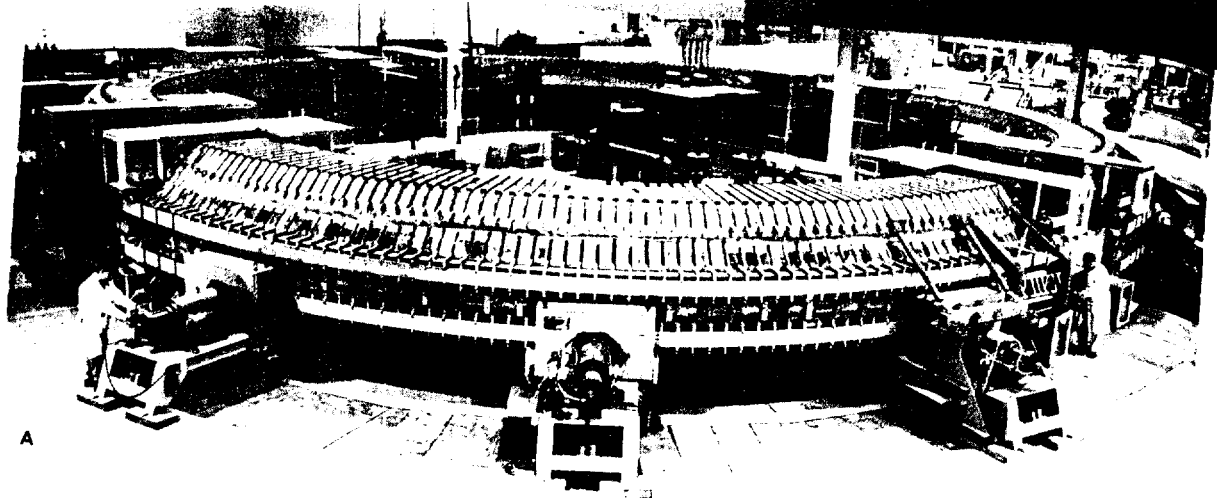
A series of experiments was made in which implants of mouse sarcoma 37 were exposed to heavy particle radiation from deuterons produced in a 60-in. cyclotron at an energy of 20 Mev. The beam was circular and 2 cm in diameter. The integrator measured one count when the cyclotron delivered 2.08×10^8 deuterons/cm². The range used was from 2.5 to 312.5 counts. Sarcoma 37 was selected because of a constant 100% transplantability and essentially similar type of proliferating neoplastic cell as seen microscopically.

One-mm cubes of viable neoplasm were transplanted into mice as controls. Cubes of neoplastic tissue of the same size were irradiated *in vitro* by deuterons as indicated above and then transplanted immediately. Animals were sacrificed at from 1 to 10 days. After radiation, during the follow-up period, it was noted that neoplastic cells lived for a period of time but apparently failed to multiply. With decrease of cellularity of these cells, bizarre giant cells developed (from malignant cells). These residual giant cells failed to multiply, and the transplant failed to invade or to survive. This raises the important question of whether giant cell formation in neoplasms indicates simply development of a cell type no longer capable of reproduction rather than of one which yields a clue as to the degree of malignancy of the neoplasm.

5. Use of cyclotron-produced I^{124} , a positron emitter. (060101). Drs. S.W. Lippincott, C.R. Jansen, K.R. Rai, L.E. Farr, W.H. Sweet*

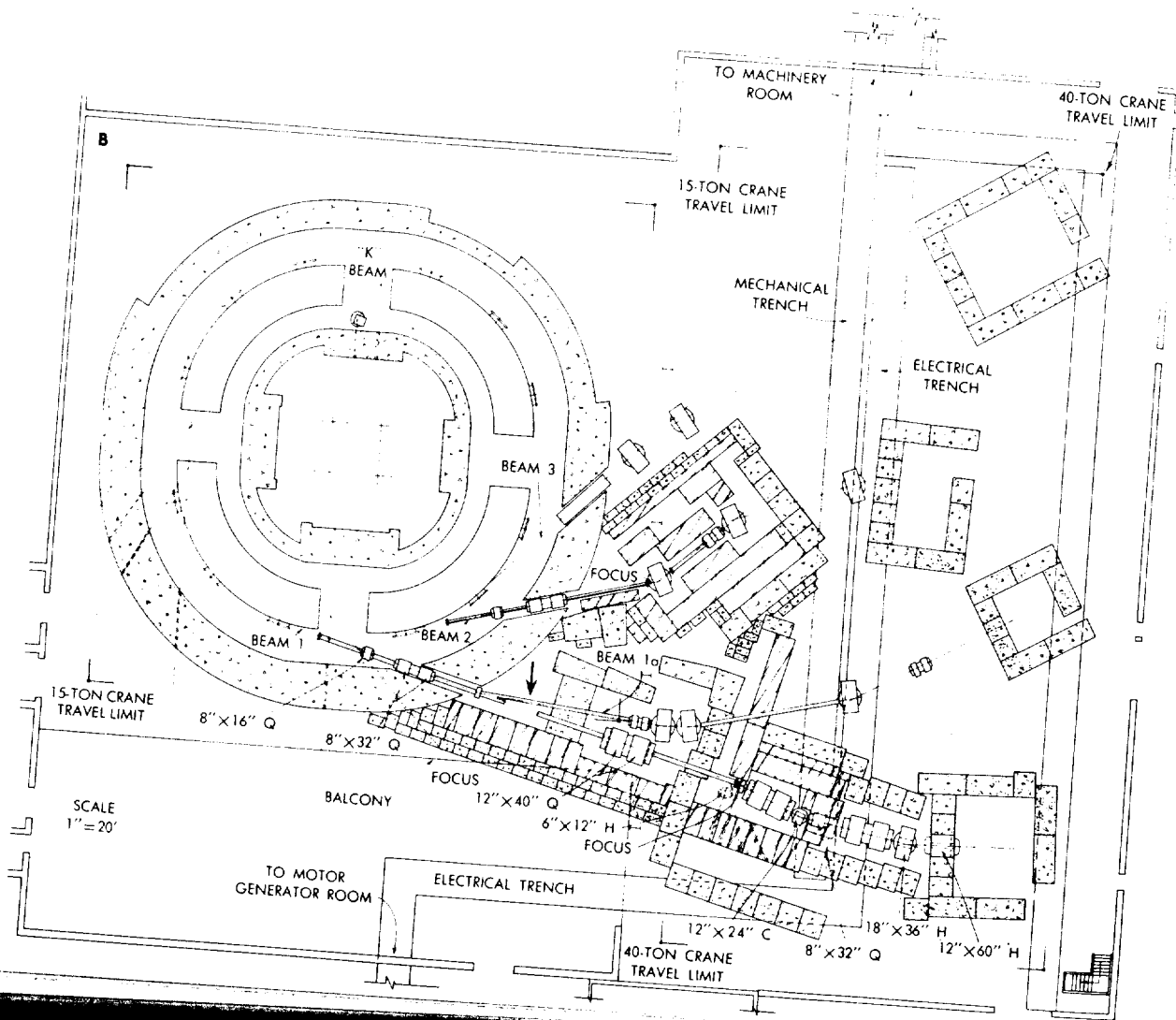
During the year, I^{124} (a positron emitter) was produced at the cyclotron by bombarding an antimony target with alpha particles. The I^{124} was then separated in the Hot Laboratory. Successful iodination of gamma globulin was achieved. The first patient to whom the labeled globulin was administered had a primary brain neoplasm, and the use of a positron scanner showed that a greater concentration of the globulin was located in the neoplasm than in the intact brain. The diagnostic possibilities of utilizing the site of degradation of the protein as a marker will be investigated not only in the brain but in other sites.

*Massachusetts General Hospital, Boston, Mass.



EFFECTS OF HIGH ENERGY PROTONS PRODUCED BY THE COSMOTRON

The Cosmotron (A) is a synchrotron that accelerates protons in a circular path to speeds approaching the velocity of light. The protons attain an energy of 3 Bev and are directed as a beam towards a target, as shown in (B). In the experimental area at the rear of the Cosmotron mice with growing tumors are being arranged (C) prior to radiation with 3-Bev protons to study the therapeutic effects of these high energy particles.



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Preliminary studies on the pathology of particle radiation of high energy protons produced by the Cosmotron (060101). Drs. S.W. Lippincott, C.R. Jensen, K.R. Rai, W.G. Calvo, L.E. Farr

Investigations utilizing the 60-in. cyclotron as a source of 10-Mev protons and 20-Mev deuterons irradiate both intact animals and mice with implantable neoplasms are being extended by using the Cosmotron as the source of particles. The Cosmotron is a proton synchrotron in which injected protons may be accelerated to an energy of Bev. The external beam delivers 1.25×10^{10} particles per pulse over a 3-cm² surface area. It is also possible to obtain 2-Bev π^- and π^+ -mesons in a satisfactory beam giving 3×10^7 particles per pulse. A pulse occurs every 5 sec, so that by varying the period of exposure the total number of rads suitable for radiation experiments may be obtained. The homogeneity of the beams can be determined by irradiating plastic foil squares of various sizes superimposed on one another (centrally placed) and measuring the activity, as for example in the conversion of C^{14} into C^{11} . As part of an overall departmental activity concerned with the pathology of high energy particle radiation, these studies are being carried out to determine the effects of protons and mesons on (1) whole-brain irradiation of mice and partial-brain irradiation of rabbits, (2) conventional and refined histochemical techniques used to evaluate results, (3) transplantable neoplasia, and (4) relative biological effectiveness.

C. ENVIRONMENTAL MEDICINE AND RADIATION EFFECTS

In vivo measurement of radioactive materials in (060102). Drs. S.H. Cohn, J.S. Robertson, Lippincott, R.A. Love

General demographic studies of populations that have received continuous low level radiation internally deposited radioactive materials are of interest because it is possible to estimate the activity from the amount remaining in the body at different times, and to relate it to the resultant biological effects. The retention of Thorotrast by a certain population is of particular interest, since the internal emitter deposits itself in liver, spleen, and bone marrow, rather than other viscera. Resultant fibrotic lesions have been reported in these organs of thorium deposition. Although the tissue

dosimetry for the Thorotrast study is extremely complex, the whole-body gamma spectrometer offers a promising approach for making the necessary identification and quantification of the gamma-emitting residual daughter products in the decay chain.

Dosimetric experience has been gained through studying five patients. Three of these patients were terminal cases, and Thorotrast was administered to them so that the absolute levels of their body burdens could be counted and compared with a calibrated amount of Th^{232} in the liver and spleen of a plastic phantom of standard man. Analysis of the material injected is under way by alpha pulse-height analysis; this is necessary for the calibration of the counting apparatus for measuring the thorium dioxide from the daughters. In addition, two patients who received Thorotrast for diagnostic purposes (7 and 21 years ago) were measured, and estimates of their thorium dioxide body burdens were obtained. These individuals had local infiltration at the site of injection, which somewhat complicated the calculations. However, by measuring individuals at different periods extending over years, it may be possible to correlate the low level radiation with the ultimate biological result.

Further studies on radioactive body burdens, already under way and to be continued for several years, are concerned with a population of BNL employees working in areas in which they may be occupationally exposed to radionuclides. The base lines for the levels of Cs^{137} , Zn^{65} , and K^{40} are being established. The principles of dosimetry and calibration and the use of the plastic phantom are the same as in the other studies. In the initial measurement of more than 200 BNL personnel, Zn^{65} was identified for the first time in a group of reactor workers. The techniques are thus applicable to the study of any population whose members have low levels of internal contamination. Surveillance of this population with respect to internal contamination is a project of increasing importance at BNL, and such studies will become increasingly important as industrial nuclear reactors increase in number and scope in this country.

A program that will continue for three to five years has been initiated with studies in which tracer doses of Sr^{85} have been administered to outpatients. These individuals have been studied by use of the *in vivo* whole-body counting technique. Cs^{137} and Sc^{46} have been administered for the

same purpose to other individuals. In addition to these long-term projects, relatively short-term studies of Ca^{47} uptake are under way. The combined short and long-term studies of strontium and calcium metabolism in man are being applied to patients with various kinds of skeletal diseases to learn more about the body pool, accretion rate in bone, and long-term net results in the patient.

2. Studies of various radioprotective agents in irradiated animals (0603). Drs. V.P. Bond, E.P. Cronkite

A series of related investigations is under way in which various aspects of combatting the detrimental effects of radiation will be explored. It is well known that intensive radiation produces damage at the organ, tissue, and cellular levels. These experiments are being designed to encompass these biological levels and to consider certain of the known resultant damages, prior to administration of biological and chemical components that may help to combat the disastrous effects of radiation. For example, it is known that hemorrhage occurs and that it is related to platelet production, so the formation of platelets must be investigated. The possibility of giving whole marrow for protective purposes is being explored. Tritium-labeled cells are being followed during cell formation before radiation and cell destruction after radiation. Other complications such as the gastrointestinal tract disturbances that result in several physiological alterations (e.g., serious loss of fluids and electrolytes) are being investigated.

In basic studies of platelets in certain normal and induced radiation states, the first essential is quantitative determination of the number of platelets involved. The Coulter electronic counter is being employed in the development of an accurate method for counting platelets in clinical and animal research. Progress has been satisfactory. In relation to the problem of bleeding, investigations are under way to determine whether the platelets interact directly with capillary endothelium of the vasculature, or intermediately by initiating the slow intravascular deposition of fibrin on capillary endothelium, the latter being a possible part of the process mediating coagulation at the surface of the endothelium. A projected step in the current investigations may be actual use of platelets in the control of radiation effects. A comparison of the effect of fresh and preserved platelet administration has been undertaken. It has been demonstrat-

ed clearly that only fresh platelets prevent the commencement of bleeding in the fatally irradiated animal, or stop the bleeding once it has commenced in the thrombopenic irradiated animal. Lyophilized and frozen platelets were of no value.

The final phase of the platelet study, which is to be continued, is concerned with the homeostatic regulation of platelet production. The platelet count can be varied by suppression with radiation or by hypertransfusion of platelets, which makes it possible to study alterations in platelet levels. These procedures have been used in an attempt to determine whether a thrombopoietic stimulating factor and an inhibitory factor exist, and, if so, how the relationship between them is maintained. If these factors can be isolated and characterized, they may be useful in combatting the irradiation syndrome.

In this long-range work, as in the case of platelets, other components of the hematopoietic system must be considered. The current method is to study the fate and function of blood cells that can be labeled *in vitro* with tritiated thymidine, and also to study the effects of tritiated cells existing in the bone marrow, with reference to using a mitotic index to demonstrate the rate and type of proliferation. As an outgrowth of these studies of cells in their primary source, the marrow, and in their circulation in the blood stream, studies were initiated to determine whether some hazard to these cellular populations might result from use of these labeled cells. Finally, the information obtained on cellular formation, movement, and proliferation has made it possible to initiate studies on the actual effects of radiation on cells in systems such as the bone marrow.

In this area, continuing studies based upon preliminary investigations will be concerned with (1) alterations in elements existing within the bone that can be studied by *in vivo* counting; (2) administration of living cells (leukocytes instead of platelets), and (3) the radioprotective possibilities of certain chemical compounds, such as vitamin E. In the studies of elements occurring in bone, it has been found that 2000 r of local x-irradiation resulted in the tibia in a decreased accretion rate of certain of the radioactive materials injected, such as Sr^{85} . The accretion rate and exchange capacity for elements such as calcium and strontium in various bones may be of considerable importance in the chemical dynamics of skeletal metabolism

the individual before and after any form of radiation, and may indeed affect response, aging, and longevity. Because of the great importance of the application of infection in the radiation syndrome, studies have been initiated and will be extended to determine whether transfusion of peripheral leukocytes into animals undergoing a radiation-induced leukopenia will alter the response of these animals to challenge doses of infectious organisms, and thus reverse the normal postirradiation-induced infection pattern. This should indicate whether the induced resistance to infection is a radiation time-dependent factor and should constitute a better basis for selection of compounds that may conceivably combat the inflammatory reactions occurring following radiation. The only compound immediately under study as a radioactive agent is vitamin E. The preliminary results have demonstrated a protective action in animals given 950 rad; 10% lethality was obtained as compared with 45% in the control group.

izing radiation effects upon immune mechanisms (060101). Drs. R.D. Stoner, V.P. Bond. Ionizing radiation appears to have a specific effect upon immune mechanisms whereby the normal immune responses are suppressed in proportion to the radiation delivered. The capacity to produce antibody is therefore greatly inhibited or destroyed in irradiated animals. A study is in progress to determine the effects of radiation on antibody production with reference to natural resistance and to active and passive immunity to bacterial and parasitic infections. The source of radiation is a Co^{60} gamma irradiation device, and the animals used are pathogen-free mice.

ion from the above source, in this type of experiment, greatly inhibited or prevented antibody production under certain conditions, such as after administration of influenza virus vaccine and tetanoid. Radiation also enhanced susceptibility of mice to anaphylaxis.

It is necessary to know more about radiosensitivity with reference to the primary and secondary effects of antibodies that occur following antigenic stimulus and at different intervals following exposure. By injection of dye stuffs it is possible to study the effects of dose and time of injection on inhibition of the secondary antibody responses. Emphasis is be-

ing placed on histological studies in an attempt to identify the cells concerned with these responses.

A natural extension of these immunological investigations is concerned with the immune mechanism in homologous and heterologous studies, particularly with reference to the significance of postradiation treatment. Under such experimental conditions it is possible to determine the result of postradiation transfusion of mouse and rat bone marrow as protective agents for recipient mice against varying levels of whole-body radiation, including the specifically lethal. Recovery of the hematopoietic system is being studied in mice protected with homologous or heterologous marrow, as is the role played by secondary loss of weight and wasting in the animals studied until death occurs. The final extension in this series of animal investigations is concerned with the protective effect of transfused marrow and the ability of the donor marrow to produce antibody in irradiated mice.

4. Radiation-induced neoplasia in the rat (060101). Drs. V.P. Bond, E.P. Cronkite, R.A. Conard, C.J. Shellabarger, E.A. Tonna

Early studies indicated that the female Sprague-Dawley rat, following whole-body radiation with doses of ≈ 400 r, developed a high incidence of breast neoplasms. The objective of the continuing studies has been to extend these experiments to determine under what conditions the neoplasms occur, and to elucidate the basic mechanisms involved. It was shown that normal ovarian function is necessary for maximal incidence of induced neoplasia, and that the neoplasms did not arise from direct irradiation of the ovaries, pituitary, or other endocrine organs. The histologic types of neoplasms obtained – adenocarcinoma, adenofibroma, fibroadenoma and fibrosarcoma – did not appear to vary with the procedure used. Male rats also developed these types of neoplasia following exposure, but in smaller numbers.

Neoplasms arose only in areas directly exposed to the beam, i.e., no "abscopal" effect occurred. This was shown by partial-body irradiation and by irradiation of only the skin or the body of the animals, whose skin had been virtually completely removed under anesthesia and later reconstituted. The dose-effect response was approximately linear over the range of 25 r to 400 r, with the curve appearing to go through zero dose at zero response.

No data were obtained below 25 r; the linear response did not hold above ≈ 500 r. These results suggest that both initial irradiation damage and a suitable endocrine balance must exist for this carcinogenic process to take place.

The effects of whole-body radiation with electromagnetic sources do not constitute the complete scope of studies on induced carcinogenesis in animals. Preliminary studies are under way in which rodent skin is irradiated with Sr^{90} plaques utilizing doses up to 10,000 rep, after which the animals are sacrificed serially over a period of months to allow the material to be examined microscopically in order to determine, by conventional histologic techniques as well as those involving certain enzyme systems, what important cellular, tissue, morphologic, and chemical alterations may occur during the development of the malignant neoplasms.

Studies of Japanese children exposed at Hiroshima and Nagasaki and of Marshallese children exposed in the accidental fallout of 1954 have indicated some impairment of growth and development which may possibly be due to radiation exposure. Since the doses involved were lower than would be expected to produce retardation of bone growth by direct irradiation, studies are being carried on to elucidate the part that indirect mechanisms might play and the dose dependence of such effects. The methodology consists of determining the effects of x-irradiation on bone growth by roentgenographic measurement of tibial bone lengths at various times after irradiation. Shielding procedures already tested indicate that direct and indirect effects of irradiation on bone growth are dose dependent. Further studies are planned to test (1) the effect of lead shielding of various parts of the body during exposure, (2) for organ or hormonal deficiencies, and (3) for effects of ablation of organs and replacement therapy.

D. TRACER STUDIES WITH TRITIATED COMPOUNDS AT THE ORGAN, TISSUE, AND CELLULAR LEVELS

1. Cell identification, proliferation, migration, and differentiation (0604). Drs. W.L. Hughes, V.P. Bond, E.P. Cronkite, R.M. Drew, R.D. Stoner, L.B. Feinendegen, S.C. Spraragen, E.A. Tonna, S.A. Killmann, T.M. Flidner

In the past a number of attempts have been made by many investigators to tag or label cells

in order to determine their origin, rate of division, growth, and fate. Initial methods were unsatisfactory because the label did not remain in the cell long enough or was toxic to the cell, or because the amounts of tissue required were too large for ease in handling. In this department a number of investigators in various disciplines have selected as the locus for labeling a component occurring regularly in cells and concerned with one or more major functions. This constituent is deoxyribonucleic acid (DNA), which is found solely in the nuclei of cells. It is a chemical carrier of heredity (the main constituent of genes and chromosomes) and remains stable and unchanged in any given cell. New DNA is made only for the formation of new cells preceding cell division. From other laboratories reports had come that N^{15} -labeled thymidine could be used for the same purposes. From these observations came the background for the technique developed in this department, in which the beta particles of tritium (H^3), with a maximum energy of only 18 Mev, are used to label thymidine. This offered the highest resolution obtainable in an autoradiograph of a cell, giving a range of little more than a micron in the photographic emulsions. This permanent label has been used as an identifying marker in cells in a series of studies and will be used in a long-range program concerned with bone marrow, peripheral blood, and the skeletal system in normal and diseased states, as well as with effects of factors outside the living body, as in tissue culture, and with processes such as inflammatory and neoplastic reactions at organ, tissue, and cellular levels.

The original work was concerned with finding suitable compounds as precursors to DNA metabolism which could be tritiated and for which sufficient resolution in the autoradiograph was obtainable. Thymidine, cytidine, and deoxyuridine are among the chemical constituents that have proved to be useful. The materials labeled have included bacteria in cultures, living cells in cultures, living cells in blood, bone marrow, and other normal structures in animals, and, finally, cells, tissues, and organs under various responses, such as inflammation, neoplasia, and radiation. For example, radiation has been used, like certain chemicals such as cortisone, to study the effects on uptake; both have been found to be inhibitors. In an extension of the work with iodine, reported last year, the incorporation of deuterium and bromine in suitable com-

unds has been investigated in an attempt to learn more about the process of replication. Additional metabolic analogues are being constantly sought, with the intent of expanding these techniques to other systems. If such components become available as labeled constituents, it may be possible to study reactions occurring at the organ, tissue, and cellular levels following exposure to particles from the reactor, i.e., neutrons, and to those from accelerators such as the cyclotron, i.e., protons, deuterons, and alpha particles.

In the initial studies of labeled cells, bone marrow precursor cells as well as mature cells were studied. It is well recognized that morphological and cytological considerations alone are not adequate for characterization of the development and progress of cells in certain systems such as the hematopoietic system. For this reason these techniques have proved to be invaluable in determining the total DNA content of certain precursor cells, in establishing the rate of DNA synthesis from grain-count data, and in obtaining additional information on the generation times of the various kinds of cells studied under normal and abnormal conditions.

The role of hyperplasia in the development of atherosclerotic-like lesions in the rabbit aorta and coronary vessels has been studied, following cholesterol feeding, by labeling and identifying the proliferative process in the cells related to the lesion. Thus, information has been gained as to whether proliferation is of primary or secondary importance in the etiology and development of the disorder. This is a necessary consideration in the case of simultaneous or succeeding chemical alterations which may occur and extend or alter the course of the atheromatous lesion.

Through study of DNA synthesis it has been shown that the percentage of labeled cells increases in patients with certain disorders, such as chronic mononucleosis. This was established first observing that the number of labeled cells in the peripheral blood normally is very low, in the order of <1000 per nucleated cell. In the case of leukemic patients treated with Myleran, the number of cells showing label was found to decrease with the total white count. This result indicates a depressive effect of the drug on the process of DNA synthesis or on cells capable of synthesizing DNA. A series of continuing studies by various investigators in the Department has been undertaken in

the following areas: (a) study of the source of cells participating in inflammatory reactions of animals; (b) role of cell proliferation and transformation in antibody formation; (c) DNA synthesis in homograft tissue reactions; and (d) metabolism of DNA in mammalian cell cultures under normal and neoplastic conditions. In the first area the primary objective is to determine whether cells of the histiocytic, macrophagic, and fibroblastic groups participate in inflammatory reactions due to infection or sterile inflammation and whether they originate *in situ* or migrate into the area from the blood. In the latter case, a secondary consideration is to determine the type of migrating cells.

The question of which cells participate in the production of antibodies has long been investigated; opinions differ as to whether lymphocytes, plasma cells, transitional cells, or reticulum cells serve as the site of antibody formation. The specific objectives of this research, therefore, are to determine which cells, if any, undergo proliferation and/or transformation to another type of cell in the primary and secondary stages of antibody formation. It is hoped that by using a combination of procedures it will be possible to determine the cellular site of deposition of antigens, their interactions with cells, and the role of cell proliferation.

In connection with DNA synthesis in homograft reactions, the objective is to discern in homologous strains of mice whether perturbations exist in DNA synthesis accompanying the cellular exchanges in the homograft reaction between host and donor cells in tissue transplants, especially those involving the skin. It should be possible to learn much about skin grafting, because it has already been demonstrated in this department that tritiated thymidine is an excellent indicator of established vascularity between host and grafted tissue; that labeled epithelial cells in autographs appear to occur in the same manner as in wound healing; and that in the homograft invading host cells label as actively as do the cells of the vessels of perivascular regions and those in relatively avascular areas.

In the field of neoplastic disorders, observations made in tissue culture studies will be extended by using the HeLa strain of human cancer cells to obtain more precise information about DNA metabolism and mitosis. This will also provide a basis for designing experiments to study the effects of external irradiation on the DNA synthesis cycle

and abnormal metabolism. Thus far it has been possible to define the total DNA synthetic time, the pre- and postmitotic resting phases, and the generation time of this strain of human cancer in tissue culture. The greatest variability was found in the premitotic phase of the cell cycle; some cells remained in this resting phase between DNA synthesis and mitosis for only 2 hr, while others lasted as long as 8 hr. This information explains, in part at least, the inherent asynchrony in tissue cell culture populations. In this connection, preliminary studies of radiation effects are being carried on; the initial study, using 500 r of x-irradiation, suggests that the predominating effect of x-irradiation is that of inducing the cells to remain in DNA synthesis for an abnormally long time.

The use of suitable radioisotopes in initial studies of fibroblasts and their reactions suggests that metabolic pathways may be traced during and subsequent to cell interactions. Specific comparisons of such factors as radiosensitivity of given cellular volumes and localization of irradiation effects can also be made by this technique. For example, the localization of tritium within the cell nucleus should result in almost exclusive irradiation of this radiosensitive volume because of the very short range of the resulting beta radiation. H^3 -cytidine, on the other hand, incorporated into the ribonucleic acid of the cell showed radioactivity concentrated chiefly in the cytoplasm. Cells in culture were used to establish and compare the lethal and cytological effects of intracellular and cytoplasmic irradiation by tritium, and in the future it will be possible to irradiate various kinds of cells in tissue culture with different agents and to determine their comparative effects on tissue type.

The studies described thus far are concerned with comparing existing normal states with certain altered states, as in infection and neoplasia. Another extremely important area is gerontology, because of the increased numbers of people living to older ages. Studies have been undertaken on a rather large scale of the effects of aging on bone, a tissue suitable for study in simultaneous histochemical and autoradiographic investigations. Aging in any tissue is a complex cellular and biochemical process that has not yet been well characterized. The specific objective of these continuing studies is determination of the metabolic and cytological changes taking place with age

within the cells of the periosteum and bone in general. Histochemical, cytologic, electron micrographic, and autoradiographic procedures are used for determination of the contents of mucopolysaccharides, respiratory enzymes, and metabolically important enzymes, and for finding the mineral relations and the relationships of the fibrous structure to the crystal structure. As one example of the importance of this approach, the relationship of the fibrous bundles of collagen to the nonorganic bone structure has been established. The pattern of deposition and interlacing directly determined demonstrates that the stress structural patterns of bone deduced years before by earlier investigators are essentially correct. In this same tissue it has been demonstrated that the osteogenic cells of the periosteum participate significantly in the remodeling of the bone in longitudinal growth in addition to growth at the cartilaginous plate. The proliferative potential of the periosteum diminished rapidly from birth to ≈ 8 wk of age in animals, while that of the epiphysis maintained an initial high level of proliferation up to 5 wk; the epiphysis then followed a course similar to that of the periosteum. A further example of research in this area is the study of the origin of osteoclasts, which are so important in resorption of bone and maintain the balance between bone deposition and removal. It has been shown clearly that the osteoclasts arise from fusion of osteoblasts.

In addition to aging in the bone, the growth processes in early age periods are being studied, and techniques utilizing tritiated thymidine are being used in the developing mouse embryo. The objective is to study the growth rate of different tissues in the growing embryo at different stages of development. Thus far the degree of incorporation into the embryo, uterus, and placenta has been determined. The decidua cells of the placenta showed good uptake at the beginning, and the greatest degree of uptake was seen in the endothelial cells. Embryonic tissues did not show noticeable uptake until the ninth day, and then only in the outer membrane tissues of the trophoblast cells. On the tenth day incorporation occurred mainly in the blood and mesenchyme system cells. On succeeding days more incorporation was found in other embryonic tissues. The nervous system did not incorporate thymidine until the fourteenth day. These differential time periods in

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ling of cells and tissues may make it possible to undertake studies to determine the nature of congenital deformities or even genetic effects caused by radiation from intranuclear radiation.

, rate of division, growth, and fate of tritium-labeled cells (0610). Drs. E.P. Cronkite, V.P. Bond

In the previous section the pertinent reasons for using tritiated compounds as cell markers were discussed. The studies discussed in this section utilize the same techniques, but some of the purposes of the experiments extend beyond those described previously. The studies under way are concerned primarily with cell proliferation in man and are also concerned with such important factors as (a) prediction of life span, function, and progeny of labeled cells; (b) cell proliferation in human malignant disease; (c) metabolic events associated with tritiated thymine and other pyrimidines in man during the course of the labeling process and subsequent

The chief results of using tritium-labeled thymine in man have been to demonstrate the effectiveness of labeling with a specific DNA precursor and the movements of the autoradiographically detectable label from proliferative to nonproliferative compartments could be established by observing the diminution in the grain count of the labeled cell with time. The analogue computer IBM 614 are now being used to elucidate the analysis of the data, although certain observations have been adequately covered by conventional methods and appear to indicate some of the kinetic time parameters concerned with cell division, life span of mature cell entities, and migration paths in mammalian tissues of certain types of mature cells after the steady state has been reached. For example, in man the generation time of the erythroblasts appears to be ≈ 24 hr, the turnover time of the orthochromatic orthoblastic nonproliferative cells that become labeled by migration of the label into this compartment is ≈ 20 hr. In the neutrophilic series the generation time varies from ≈ 24 to 54 hr, depending on the stage of granulocytopoiesis in the bone marrow. The average stay of the neutrophils in the peripheral blood is of the order of two days. Turnover time of the megakaryocytes has been shown to be considerably longer, i.e., ≈ 10 days. In addition, studies have been initiated to determine whether a defect in cell proliferation

exists in certain human malignant diseases, especially those concerned with the hematopoietic tissues. Initial observations indicate that the generation time of cells of both solid and diffuse neoplasms is longer than anticipated from previous studies by other techniques. This statement is based on observations with labeled cells in such diseases as chronic lymphocytic and granulocytic leukemia, glioblastoma multiforme, carcinoma of the breast, and multiple myeloma. In the evaluation of the data to be obtained in further studies, particular attention will be paid to whether or not there is a metabolic defect in the malignant cell that prevents thymidine from being a satisfactory DNA label with reference to rates of cell proliferation in some of the neoplastic entities. Such studies will be carried out with other pyrimidine precursors such as cytidine and uridine. These studies may have specific implications in respect to therapeutic considerations and particularly with reference to the development of new chemotherapeutic agents, if only a small fraction of the population of these cells is at any time in DNA synthesis.

The establishment of the ability of tritiated thymidine and other tritium-labeled pyrimidines to label RNA and DNA in mammalian cells, particularly in normal hemopoiesis and in certain of the malignant neoplasms of this system, requires investigation of further metabolic considerations. Preliminary work is already under way to determine the plasma clearance, urinary excretion, and degradation of these pyrimidines in human subjects. Apparently rapid plasma clearance of tritiated thymidine is associated with incorporation of the labeled compound into the newly formed DNA of proliferating cells. The labeling process is effectively complete within ≈ 20 min, and thymidine is not detectable after ≈ 30 min. It is degraded in part to β -aminoisobutyric acid and to water, both detectable by chromatographic and radioisotopic techniques. In addition to the metabolic findings it is important to know whether tritiated thymidine can be given safely to selected individuals. Indications are that it can, and it is hoped that further observations will demonstrate that apparent interference with hemopoiesis does not take place. It is planned to extend these metabolic studies to further observations in certain of the neoplastic diseases and to include other precursors such as cytidine before and after therapy

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in neoplastic disorders of the hematopoietic system as well as in certain of the well-known blood dyscrasias.

E. RADIOACTIVE TRACER METHODOLOGY: MATHEMATICAL, BIOCHEMICAL, PHYSIOLOGICAL, AND CLINICAL APPLICATIONS

1. Theory and interpretation (060102).

The use of radioactive elements as tracers to give information on rate of movement and fate of the studied constituent in a mixture largely or almost entirely nonlabeled is the field of widest general application of radioactive isotopes in medicine. In principle it is possible to deduce the kinetic properties of steady-state systems by mathematical analysis of families of curves chosen as representative of the behavior of the exchangeable substances in the systems. In practice, however, this pure mathematical reasoning must be combined with analysis of experimental data to determine the best fits. Computers both analogue and digital thus come into play for data analysis long before the definitive mathematical relationship has been completely clarified.

2. Development of a new positron multidetector scanner (060602). Dr. J.S. Robertson

The use of radioactively labeled substances that concentrate in neoplasms is being investigated in the development of diagnostic procedures. Typical scanning methods, however, use only one or a pair of detectors. The localization of positron emitters depends upon the principle that annihilation of the positron produces two gamma-rays which are emitted in opposite directions. Therefore, two detectors can see these two gamma-rays in coincidence and establish a line along which the source is localized. Multiple detectors shorten the scanning time because (1) multiple areas are seen simultaneously, and (2) emissions in many directions from a given point are detectable. Keeping track of coincidence counts occurring between one detector and any of several other detectors poses several problems not encountered when only paired detectors are used. Data acquisition problems include determination of optimal placement of the detectors to insure full coverage of the volume of interest with minimal redundancy, and balancing of the response of the detectors to give a uniform response to a uniform source. The

placement problem is being explored with the use of the IBM 704 computer. Data storage will require the use of a 4096-channel pulse-height analyzer. The problem of data reduction or interpretation may require invention of an appropriate digital-to-analogue converter.

Three-dimensional models for various possible distributions of the detectors have been built and examined for quality of volume coverage. Preliminary results indicate that 48 crystals 1 in. in diameter can be placed to give resolution of localization good to 1 ml in a 2000-ml volume. Further systematic study of this phase of the problem will be programmed for machine computation, which will not only answer the questions of expected volume coverage but give the geometrical efficiency of counting to be expected from each point source. Ten crystals are on hand for experimental checking of the computed expectations.

When the design criteria are sufficiently well established, a working model of the proposed system will be constructed and tested. Methods for displaying the data quickly and in suitable analogue form will be developed. Ideally, the physician should have a picture from two or more views or through several planes of interest upon completion of the scan. This may require construction of a special computer to be installed in the counting room. One of the ultimate goals of this project is to develop an instrument that would produce a scan as nearly instantaneous as possible with a minimum of equipment so that copies could be used in other institutions. There are many tracer problems being studied in the Department in which an improved method of scanning is needed, and it is anticipated that such a machine would be used extensively, although it is difficult to predict exactly how. If the scanning time can be shortened sufficiently, it may be feasible to conduct kinetic studies involving changes in distribution occurring in correspondingly short times.

3. Metabolism of labeled amino acids and vitamins in neoplastic diseases (0609). Dr. L.V. Hanks

These studies are concerned with the isolation and analysis of tryptophan metabolites present in urine. The kynurenine pathway of tryptophan degradation appears to proceed by oxidation of the indole nucleus, as shown with C¹⁴ labeling in specific positions of the benzene ring. Clinical

udies in the literature indicate that in some neo-
astic diseases elevated levels of these metabolites

tumor-bearing mice. In an extension of this work,
 β -alanine-2-C¹⁴ is being studied as a precursor of

phan and glycine properly labeled; in a parasite occurring in the tissues of an animal; and in the determination *in vitro* (usually with P^{32}) of the rates of disappearance from the circulation and/or the rate of excretion of catabolic products. Proteins studied thus far have included albumin, gamma globulin, α -lipoprotein, and ribonuclease. Mechanisms investigated have included the immune reaction in animals following administration of suitable antigens as well as glomerular filtration and absorption of reticulo-endothelial cells.

Among the investigations carried out with labeled amino acids are those concerned with the mechanism of formation of hydroxylysine from lysine in collagen. Collagen, which forms 30 to 40% of the protein constituents of mammals, is unique in containing the amino acid hydroxylysine reportedly absent in other proteins. Previous work with C^{14} in this department has shown that the hydroxylysine in collagen is formed from lysine which becomes hydroxylated during or after incorporation into the collagen. By using labeled amino acids to determine the origin and formation of certain protein constituents occurring in mammalian tissue, the effects of various agents (e.g., radiation) upon such processes as collagen synthesis may be determined. A further application of this technique is to determine the permanence of a protein constituent in the mammalian body. In this connection, C^{14} -labeled lysine has been used in young animals to follow the permanence of collagen once it appears in a given area in the body. A specific application of this information, which may be investigated in the future, is one of great importance to the surgeon, namely, learning more about unusual destructive or formative factors that either aid or prevent wound healing in man.

Labeled amino acids are also used to study the problems of protein formation in disease processes, for example, those involving parasites. Parasitic diseases constitute major problems in many segments of world-wide society. The particular parasite selected for study was *Trichinella spiralis*, and its larvae have been investigated by *in vitro* metabolic studies of tryptophan-2- C^{14} and glycine-2- C^{14} as well as by studies to be carried out in more detail in the future concerning the incorporation of thymidine-labeled tryptophan by this same organism. The present objective is to study the metabolism of various C^{14} -labeled amino acids in experimental trichinosis in mice. This involves a

study of the metabolism of amino acids in the host as well as in the *Trichinella* larvae. When mice infected with *Trichinella* larvae were administered C^{14} -labeled amino acids, the encysted larvae incorporated measurable amounts of C^{14} . Of the C^{14} incorporated *in vivo*, 76 to 78% was found in the proteins. During culture *in vitro*, an increase of several per cent in the protein-incorporated C^{14} and a decrease in glycogen- C^{14} took place, which indicated incorporation of C^{14} from glycogen into protein. The changes in the lipid and nonprecipitable C^{14} were small and variable. Such basic studies of rates and sites of incorporation and comparisons between *in vitro* and *in vivo* metabolism should be useful in future studies of the metabolism of the invading agent and the host reaction, and therefore be important in therapeutic considerations.

The studies of plasma protein metabolism are being extended, particularly in the field of catabolism. Renal catabolism of serum proteins is being studied in detail, and attention is also being directed to extrarenal sites of catabolism, particularly the reticulo-endothelial sites in the liver that may be important cellular areas for degradation of proteins. It has been possible to label ribonuclease with iodine, and a study is under way to determine the extent of its concentration in the rat's kidney after injection. As already mentioned, the proteins are frequently bound in the blood to certain other constituents (e.g., carbohydrates), and in a series of investigations under way protein polysaccharide complexes are being studied. In addition to macromolecules that are definitely proteins or carbohydrates, many hybrids exist that contain both amino acids and carbohydrates and possess intermediate properties. Studies here are involved with the mucins excreted as a protective coating for epithelium and the glycoproteins which are frequently increased nonspecifically in certain diseases. Effort is being directed toward isolation and characterization of such substances obtained from various tissues to learn more about their modes of origin, and towards elucidation of their structures to help understand their functions. The latter effort is becoming increasingly dependent upon the discovery of bacterial enzymes that specifically split certain linkages, for example, those in the mucoproteins. The isolation of mucins from certain disease states, such as cystic fibrosis, is revealing physicochemical abnormalities that

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may help to explain some of the pathological features of the disease.

5. Radioactive tracers in studies of protein metabolism in cancer (0609). Drs. S.W. Lippincott, S. Fine, C.R. Jansen, K.R. Rai, S.H. Cohn, S. Korman

The present studies are a continuation of clinical investigations begun elsewhere several years ago. The objective is to determine the physicochemical properties and functions of the serum proteins in neoplastic diseases. Should any characteristics exist for a given protein fraction distinguishing its nature or behavior from a similar fraction in normal subjects (or those with various nonneoplastic diseases), a basis might be established for a diagnostic test for cancer. The first approach in this long-range program was the use of techniques involving immunochemical procedures, electrophoresis, ultracentrifugation, and infrared spectroscopy. In addition, serial observations have been made of the turnover rates of radioactively labeled proteins in neoplastic diseases. From the latter, fundamental information concerning protein catabolism in multiple myeloma has been gained, and a distinct metabolic difference in the turnover rates of normal and aberrant protein in cancer of the breast has been noted.

Aberrations of protein metabolism in multiple myeloma have been studied by a number of investigators to ascertain whether the globulins in the blood consist of excesses of normal globulins, of chemically abnormal globulins, or both. In this study, certain fundamental aspects of protein metabolism have been investigated by determining the turnover of I^{131} -labeled normal gamma globulin in patients with this disease. In patients with a beta-type electrophoretic pattern the mean half-life is 16 days, and for those with a gamma-type pattern it is 7 days. Similar results were obtained in the turnover of autologous and homologous labeled gamma globulin in this disease.

In clinical studies of the metabolic behavior of radioactively labeled proteins, the turnover or degradation rate is usually determined from serum concentration curves which entail multiple blood sampling. In the present experiments, the turnover of I^{131} -labeled proteins is being determined not only by the conventional method of blood sampling but also by a new technique utilizing the whole-body gamma spectrometer. This device

permits *in vivo* measurement of very low levels of an internally deposited gamma emitter (in this case, I^{131}). The procedure provides an excellent method for measuring retention of labeled albumin and globulins over long periods of time and is now the method of choice.

An extension of the turnover studies in patients with multiple myeloma utilizing beta globulin is under way. The present study compares the metabolism of labeled myeloma beta globulin with that of normal and myeloma gamma globulin. The turnover of beta globulin is far more rapid in patients with a beta-type serum electrophoretic pattern than in those with a gamma-type pattern. The hyperproteinemia of patients with multiple myeloma is thus found to be due to an accelerated rate of synthesis of the anomalous protein, which more than compensates for the accelerated rate of catabolism of these abnormal proteins.

In patients with metastatic cancer of the breast, turnover studies of gamma globulin prepared from healthy normal donors and of aberrant gamma and beta globulins from patients with multiple myeloma have been initiated. To date 34 patients have been investigated, and the series is to be extended to 75. The shortest period of observation is ≈ 2 months and the longest, > 2 years. The mean half-life for normal gamma globulin is ≈ 11 days and for the aberrant proteins ≈ 7 days. This differential metabolic recognition of two types of globulin in the same individual may have significant application to the diagnostic problem if the site of accelerated catabolism should prove to reside within the growing neoplastic mass.

For possible localization of this accelerated catabolic process, cyclotron-produced I^{124} is being substituted for I^{131} for labeling. The technique for this has been successfully worked out. I^{124} is a positron emitter giving off gamma-rays at 180° . For detailed scanning and localization it is necessary to use a positron scanner which with a collimated beam may help to locate the site(s) of catabolism, and thus the presence and anatomical position of the neoplasm. In a joint study with Dr. W.H. Sweet, preliminary scanning is under way at the Massachusetts General Hospital in Boston, where a positron scanner capable of covering the head region (now in use for detecting Ar^{74}) is being tested for adaptability to measure the activity of the I^{124} -labeled proteins in the brains of patients with neoplastic lesions.

6. Study of metabolic processes in man by the use of C^{14} -labeled compounds (0610). Drs. W.W. Shreeve, R.C. De Meutter

Metabolism in man may be considered broadly as the total physical and chemical processes by which the living cells of tissues and organs maintain life. The entire breadth of such multiple biochemical activities cannot at present be measured and studied simultaneously. Individual phases, however, can be investigated by selection of appropriate radioactive isotopes such as C^{14} which has been rather widely used in animals and is now being employed in the study of diabetes in man. In this disease a disorder of carbohydrate metabolism results in an excessive amount of sugar in the blood and loss in the urine. With serious advance of the disease abnormalities of protein and fat metabolism also occur.

The current research in this department began with an investigation of the pathways of carbohydrate formation in subjects with presumably normal metabolism and has been extended to various types of diabetic patients. The technique used is based upon determining the isotopic distribution of glucose in subjects given 1- C^{14} -acetate. The amount of C^{14} converted to glucose has strongly suggested the overproduction of glucose, particularly in acute ketotic diabetes. C^{14} -acetic acid is also being used in studies of lipid metabolism to derive information on controversial problems in fat metabolism, and the turnover of cholesterol in plasma red cells is under investigation with C^{14} -mevalonic acid. Such studies indicate how quantitative differences in rates of reactions, rates of transfer between metabolic and cellular compartments, and selection of alternate routes of metabolism may be observed in health and disease.

Emphasis in this department has been placed on the measurement of respired $C^{14}O_2$ as an index of the oxidation of various substrates by patients with diabetes and other metabolic disorders, together with delineation of control of oxidation by hormones. Breath, arterial, and venous concentrations of C^{14} in carbon dioxide have been compared simultaneously to detect the extent and rate of mixing with nonlabeled carbon dioxide in the tissues. At the same time Evans blue dye and Na^{24} -labeled sodium chloride have been used to define rates of mixing in plasma (T-1824) and extracellular fluids respectively. Two diabetic

patients were studied with the three simultaneous tracers. Bicarbonate was found definitely to mix in a larger space and with a larger pool than would be contained in the extracellular compartment of the peripheral tissues (forearm). $C^{14}O_2$ was measured by proportional counting, Na^{24} by well-type solid scintillators, and T-1824 by colorimetry.

The oxidation of organic hydrocarbon compounds in the body provides energy for life processes, and the channeling and control of supply of this energy is governed by factors such as hormones, enzymes, vitamins, and other nutrients. The rate or extent of total oxidation of any particular organic compound can be followed by examining the appearance of radioactive C^{14} in the expired carbon dioxide after administration *in vivo* of the C^{14} -labeled compound. C^{14} activities in carbon dioxide of breath and glucose of blood were compared after administration of C^{14} -labeled glucose to diabetic and other patients. In nondiabetic and moderately diabetic patients, 20% of the total expired air derived directly from glucose, whereas in severe diabetic patients the value was 10%. $C^{14}O_2$ production from labeled lactate was compared with conversion to glucose in three diabetic patients. Insulin or glucose administration increased moderately the appearance of $C^{14}O_2$ in the breath, and diabetic acidosis markedly decreased (to one-half) the apparent oxidation. A concomitant increase in the appearance of C^{14} in glucose suggested the diversion of lactate to gluconeogenesis and away from oxidative pathways. The finding bears on the nutritive value versus the gluconeogenic hazard of sodium lactate in the treatment of diabetic acidosis.

Gluconeogenesis has been widely studied *in vivo* in diabetes by comparison of hepatic arterial-venous differences in glucose concentration and by measurement of blood glucose renewal rates, as shown by changes in activity of C^{14} -glucose. A new approach has been instituted in this department by administering C^{14} -labeled precursors of glucose and analyzing the amount of C^{14} converted to blood glucose. C^{14} -labeled pyruvate showed about the same amount of conversion to blood glucose as C^{14} -lactate in diabetic patients. One nondiabetic patient showed a lower conversion of lactate than any diabetic.

The amount of C^{14} appearing in blood glucose after administration of labeled precursors is an indication of the rate of gluconeogenesis, and the

ccessive intermediate chemical reactions in this process can be elucidated by examining the pattern of C^{14} among the carbon atoms comprising the molecule of glucose. The studies under way are expected to provide a knowledge of the reaction sequence that may be helpful in understanding or predicting the effect on gluconeogenesis of hormone, a drug, a certain dietary regimen, a genetic trait, and even a pathologic process. The main outcome of this work is expected to be a demonstration of whether or not the formation of glucose is biologically the reversal of its catabolism (at least in man). The metabolism of blood ketocids in diabetic man constitutes a study in progress. An estimate at this point of the total C^{14} in β -keto acids has indicated that 1.5 to 3% of the injected C^{14} -acetate is so accounted for in mild diabetics, and 5 to 8% in severe diabetic patients. The magnitude of turnover rate indicated by serial analyses suggests that not more than twice as much keto acid is formed from acetate in the first hour. This finding bears on the role of keto acids as a major metabolic fuel in diabetic acidosis.

1. Kinetics of sodium and labeled hormones in human and experimental hypertension (0610). Drs. J.K. Dahl, L. Silver, M.G. Smilay, I.L. Schwartz, A.F. Lebovitz

Chronic arterial hypertension (high blood pressure) is one of the most common diseases in this country, and the chief causes of death in this entity are due to complications of atherosclerosis (degenerative alterations) in the vessels of the heart, brain, and kidneys resulting in such conditions as coronary thrombosis, apoplexy, and renal failure. The cause or causes of hypertension and of atherosclerosis have been explored from different points of view in animals and in man by many investigators. In certain animals, feeding of excess salt can provoke the appearance of hypertension, usually without development of atherosclerosis. Numerous studies of essential hypertension in man have produced some evidence that an aberration of sodium metabolism is associated with this disease. In view of all these observations, detailed long-time studies of the role of sodium in hypertension in man and animals have been under way in this department for several years and will be continued for several more.

The use of relatively unpurified sea salt as a condiment by racial groups among which hypertension is common formed the basis for an experi-

ment in which a number of rats were fed sea salt, and an equal number were fed plain salt. The results suggested that rats fed sea salt had an increase in both the incidence and severity of hypertension. In a colony of beagles that have been fed added salt for >4 years there has been an elevation of cholesterol (and possibly other plasma lipids) in the absence of an increase in blood pressure; none of the animals have been sacrificed for pathological study, so it is not known yet whether atherosclerosis is developing. This chemical finding is of interest because blood cholesterol is elevated in many patients with atheromatosis, and an increase also occurs in the cholesterol and phospholipid content of the atheromatous aorta, the largest of the blood vessels.

It was thought that, if high fat and high salt intakes are important in the development of atherosclerosis and hypertension, respectively, it might be of value to study an adult population in a Japanese farm village to compare the clinical effects of hypertension in these people with those in people studied in this country. From the American viewpoint, the Japanese people examined had a primarily vegetarian, low fat, high salt diet. The clinical picture of hypertension in these Japanese was found to differ significantly from that observed in this country in that the Japanese showed strikingly little evidence of the usual cardiac complications found so commonly in hypertensives in Western adult populations.

For operational purposes in man the program continues to be developed on the thesis that a derangement of sodium metabolism is basic to the hypertensive process. Furthermore, it is believed in this department that excess dietary consumption of sodium as sodium chloride is the most common mode of effecting this derangement. The primary objective of the continuing studies is to test this thesis by the addition and subtraction of dietary sodium, primarily as sodium chloride; by subjecting the organism to stress in this way it is hoped that the area of abnormality will be revealed. The concomitant administration of various isotopes, e.g., Na^{24} , Na^{22} , or K^{42} , allows study of the dynamic effects of dietary changes in salt intake. The whole-body counter is essential in carrying out these detailed studies.

The results noted to date in a small group of rats fed sea salt warranted an extensive experiment in which, in addition to studies of blood pres-

sure and lipid content of serum, detailed autopsy studies are being carried out to determine whether atherosclerosis has been produced. A beagle colony studied for six years in relation to salt intake, both normal and excess, will continue to be followed clinically, and studies will be made at autopsy to determine whether or not excess salt has been a factor capable of producing hypertension in these animals. Factors known to affect either hypertension or sodium turnover will be further tested systematically with radioactive isotopes. For example, some workers have suggested that prolonged sodium restriction might be harmful to the organism by virtue of interfering with adrenal cortical function. Since this was incompatible with the extensive clinical experience at BNL, quantitative biochemical measurements of adrenocortical function, after prolonged sodium restriction, are being made on three patients and will be continued in a larger series over a prolonged period of time.

In another approach to this problem the genetics of labeled vasopressin in human and experimental hypertension will be studied. The objective is to determine the possible relationship of the posterior pituitary hormone, vasopressin, to human hypertension. This hormone is concerned with the homeostasis of body water and electrolytes and has a marked constrictor action on the effector organ involved in hypertension, namely, the smooth muscle of the arteriole. Purified vasopressin has been labeled for the first time with tritium or I^{131} by techniques developed in this department. It will now be possible to estimate vasopressin activity at the site of localization more specifically than heretofore.

8. Iron, cobalt, and chloride kinetic studies in normal and diseased subjects (0610). Drs. E.P. Cronkite, D.C. Price, J.S. Robertson

Radioactive tracers are used to label compounds for study of physiologic metabolic pathways and also to label constituents designed to elucidate the mechanisms involved in the development and alleviation of various diseases. The selected tracer is a substance in labeled form; the label makes it detectable by the observer without affecting its behavior in the system being studied. The transport of a labeled substance into and out of anatomical or physiological compartments makes it possible to study either chemical synthesis or degradation. With this general principle in

mind, studies have been concerned with (1) vitamin B_{12} and its binding sites and turnover rates; (2) extrathyroidal metabolism of halides; and (3) the metabolism, turnover, and fate of orally and parenterally administered radioactive iron in normal and diseased subjects.

Vitamin B_{12} is essential for the metabolism and proliferation of all living cells. Deficiencies of this material result in disease processes related to the hematopoietic organs, the gastrointestinal tract, and the central nervous system. The studies under way are concerned with labeling vitamin B_{12} with cobalt, utilizing the whole-body counter, and studying plasma clearance, gastrointestinal absorption, excretion, and turnover rates of retained material administered both orally and parenterally. Observations thus far indicate that when vitamin B_{12} is administered intravenously plasma clearance and mixing of vitamin B_{12} proceed simultaneously. In autopsy material from patients receiving the labeled material, the tissue concentrations of detectable label were found to vary widely. In three years of study, labeled vitamin B_{12} has not come into equilibrium in the various body compartments, and therefore the studies must be extended for at least one to three years. Lack of equilibrium indicates the possibility of a changing distribution of the radiovitamin with time. Specific application will be made of these observations in evaluation of such matters as the absorption effects on a broad clinical scale. Models are being constructed and tested for analysis of the turnover data obtained or to be obtained from a series of twelve patients by utilizing the analogue computer. This problem of equilibration of vitamin B_{12} is concerned with binding sites, and studies under way indicate that a tight immediate binding of vitamin B_{12} by plasma tissues and body fluids does occur. However, the nature of the binding and its variation in disease must be considered. Specific reference will be made to the plasma protein to which the radiovitamin is bound and the chemical nature of the binding site.

Radioactive tracer studies in another area have been initiated with an investigation of the extrathyroidal metabolism of halides. The initial work was carried out with I^{131} in rats to study the gastric secretion of iodine. It was discovered that 50% of the injected dose was recovered in the stomach at ≈ 1 hr after injection. Fed animals secreted several times as much iodine into the stomach as did

ing animals, but the amounts of radioactive iodine found were not appreciably different in the two groups. A few trial extensions of these studies to patients have been made, and indications are that the role of the stomach in iodine metabolism in human beings is probably much less significant than it is in the rat. A suitable clinical procedure is expected to be developed for using radioactive halides as possible diagnostic tools in diseases affecting the stomach. Further work with animals will be directed towards clarifying the relative roles of the competing rates of secretion and reabsorption. Such studies may also assist in furthering the understanding of the mechanism of gastric secretion of hydrochloric acid.

A study on a small scale of another important element is expected to be expanded to include as many as 200 subjects. This study is concerned with iron metabolism, turnover, and fate of orally and parenterally administered radioactive iron in normal and in diseased subjects. Methods for determining iron absorption, deficiency, turnover, and its excretion in the body have in the past been very inaccurate and dependent upon some perturbation of the normal steady state. The purpose of these continuing studies is to determine the efficiency of absorption of iron from the gastrointestinal tract, its modification by changing the chemical environment, the turnover of iron, and its fate as established by using the sensitive whole-body gamma spectrometer. It is already known that with this instrument a relative iron deficiency can be detected with as little as $1 \mu\text{C}$ of Fe^{59} , an amount much smaller than is usually necessary to measure iron retention by ordinary radioisotopic methods in feces.

F. SPECIAL PROJECTS

Medical studies of the people of the Marshall Islands accidentally irradiated by fallout (060101).

R.A. Conard, S.H. Cohn, A. Lowrey, L.M. Meyer, W. Sutow, B.S. Blumberg, J.W. Hollingsworth, H. Lyon, W.H. Lewis, Jr., H.E. MacDonald,* A.A. Jaffe* In March 1954, following detonation of a nuclear device, 239 Marshallese were accidentally irradiated by fallout. Medical studies of these people and of control populations have been carried out on an annual basis by teams of physicians under the auspices of the Division of Biology and

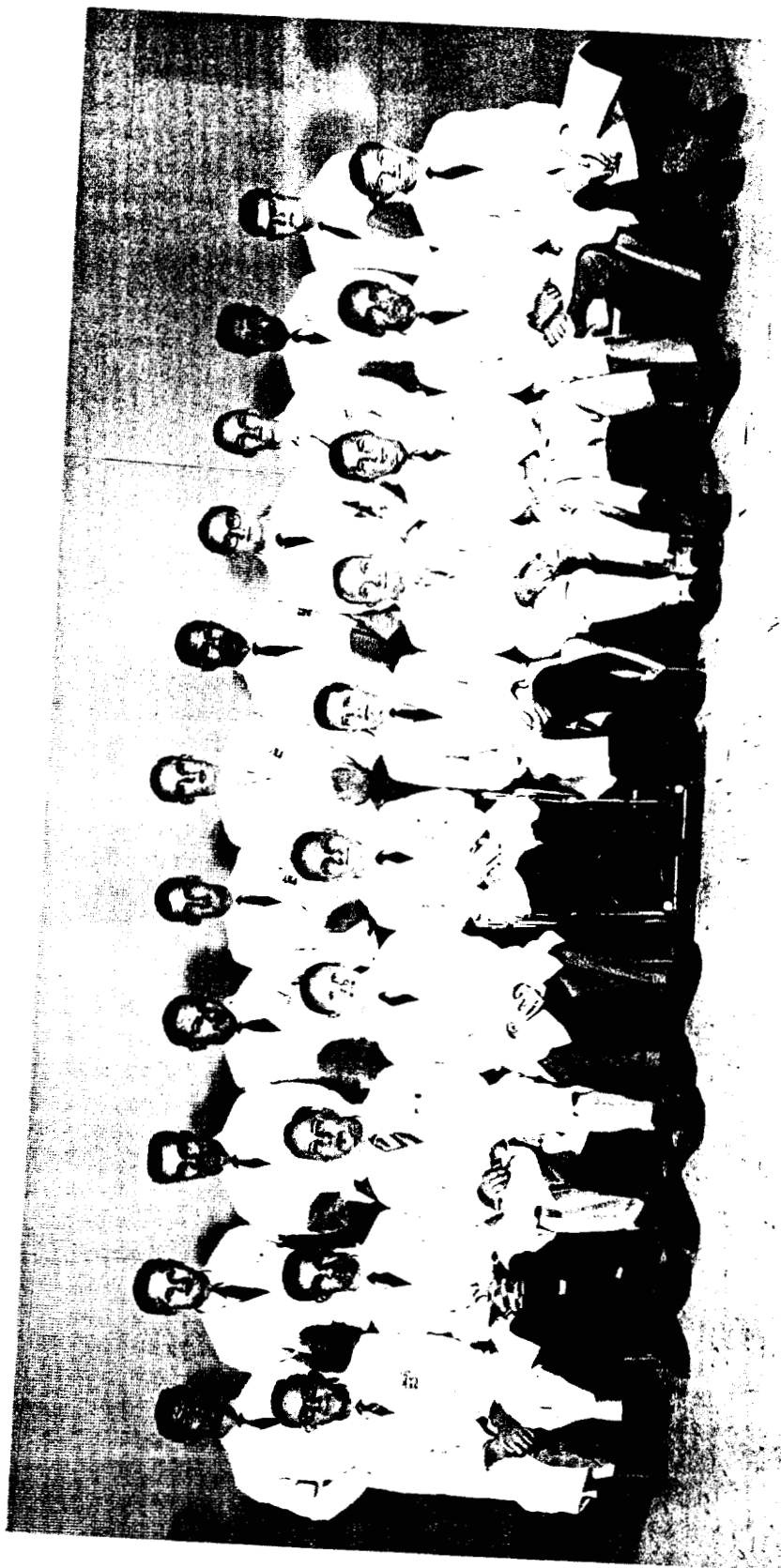
Medicine of the United States Atomic Energy Commission and under the direction of the Medical Department of Brookhaven National Laboratory. Research collaborators from many institutions take part. The objective of these surveys is to study the acute and long-term effects of the exposure of the Marshallese people to fallout in regard to whole-body gamma exposure, beta irradiation of the skin, and internal contamination. In addition, an evaluation of the ecological aspects of persisting low levels of radioactivity on the people of Rongelap Island is an important part of the studies. The surveys involve complete medical histories and physical examinations, including examinations of the skin, hematological studies, radiochemical urine analyses, and whole-body gamma spectroscopy for evaluation of body burden of radionuclides.

Considerable knowledge has been gained from these studies on the effects of fallout radiation on human beings. In addition the surveys have afforded valuable experience in carrying out medical surveys of populations under field conditions. Results of these studies show that gamma radiation is the most serious consequence of such exposures; beta burns of the skin, although not so serious, may be moderately disabling; internal exposure resulting from the absorption of isotopes appears to be the least serious of the hazards; the low level residual contamination of Rongelap Atoll is reflected in the marine, plant, and human cycles.

A combined five and six-year postexposure report is being prepared in which appendices of raw data gathered during fiscal 1961 will be incorporated. Data will include (1) observations on the possibility of acceleration of aging in this population due to fallout; (2) the degree of internal radiation contamination in these subjects from Sr^{90} and Cs^{137} as indicated by radiochemical analysis of body fluid specimens; and (3) the *in vivo* measurement of the body burdens of fission products and neutron-induced activities as determined by the portable whole-body gamma spectrometer.

It is expected that further annual medical surveys will be carried out. From experience with the exposed Japanese, the next several years are expected to be important for observations of possible late effects of radiation, particularly leukemia and cancer. An alternating schedule with special examinations is planned so that the scope of the surveys and the number of personnel involved will be reduced.

*Department of Public Health, Trust Territory of the Pacific Islands.



FACULTY AND STUDENTS IN SUMMER PRECEPTORSHIP PROGRAM IN NUCLEAR MEDICINE

Reading from left to right, FRONT ROW, FACULTY: Marcel Patterson, Jesse Steinfeld, Lee Farr, Walton Shreeve, Martin Schneider, Harold Burlington, Thomas L. Wright, Marvin Loring, James Strickler, and Herman R. Haymond. REAR ROW:

STUDENTS: James Lu-Meng, William R. Hazzard, John T. Celentano, Stanley J. Wacksman, Dennis D. O'Keefe, James A. Allums, Ed F. Bayouth, John P. Board, Jr., Alva E. Jackson, William T. Stubenbord, and Richard Portnoy.

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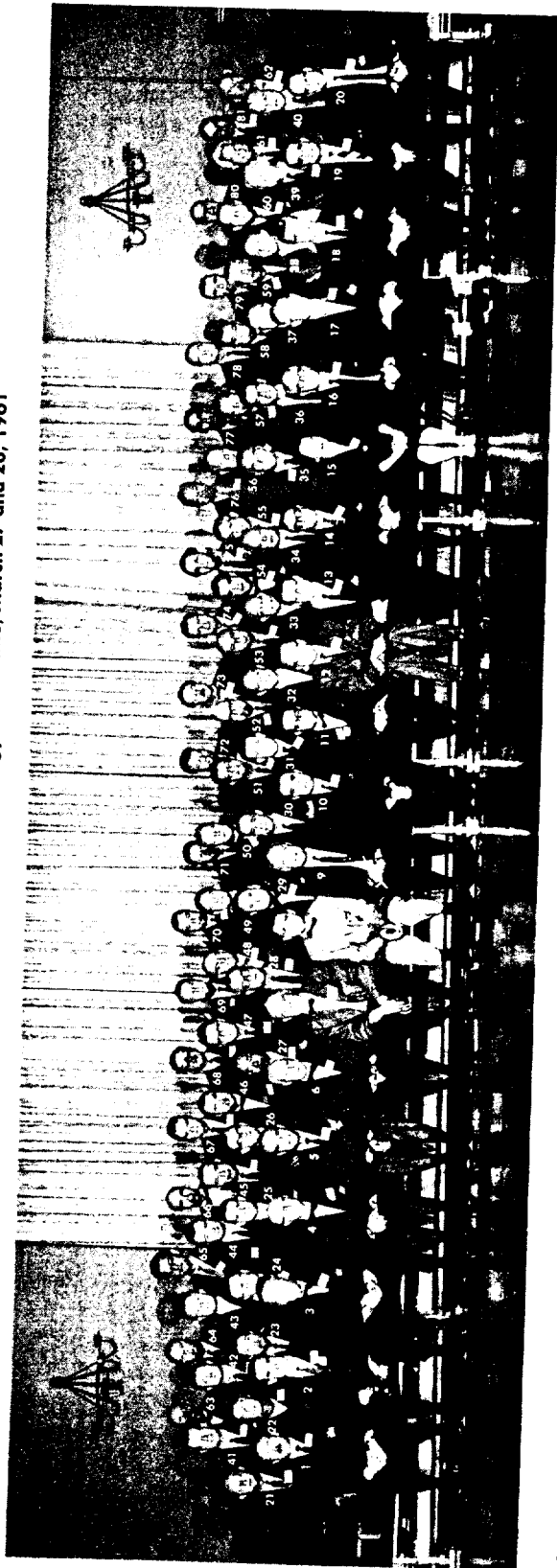
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Fifth Conclave in the Series on Nuclear Energy in Medicine, March 27 and 28, 1961



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| 2. A. Ross | 26. C.W. Daeschner | 38. J.W. Gerrard | 50. R.V. Platou | 62. T.C. Panas | 74. F.H. Wright |
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| 12. C.C. Fischer | 36. S. Krugman | 48. J.C. Peterson | 60. B.E. Batson | 72. W.F. Stanage | |

2. Research preceptorship in nuclear medicine methodology and practice (060101). Drs. L.E. Farr, W.W. Shreeve

The purpose of this project is to give a few selected medical students in association with a few members of their medical faculty special experience in the developmental aspects of the new field of nuclear medicine. Medical schools at present have no systematic instruction in this subject, and the experience at Brookhaven may serve to organize in the minds of present medical educators and future leaders of the medical profession the needs, responsibilities, and opportunities in this area, and to promote the interest of future physicians in the field of nuclear medicine.

The activities during one month include ward rounds, laboratory demonstrations, and conferences conducted by the senior staff members of the Medical Department and their associates. They include laboratory sessions in which the special facilities of the Brookhaven Medical Center are demonstrated and used - the MRR, whole-body counter, autoradiographic equipment, Tri-Carb spectrometer, and other counting devices. Medical faculty and students participate actively in these exercises. Opportunity is afforded for informal discussions among visitors and staff.

A few introductory lectures and demonstrations emphasize basic physics, mathematics, and methodology. However, most of the available time is spent in current research activities with emphasis on methodology to indicate future trends in the field and to help instill an appreciation of the intensive investigative approach in medicine.

The idea for this joint endeavor came from discussions at a conclave at Brookhaven in December 1958 for deans of medical schools, entitled "The Impact of Atoms on Medical Science and Education." The University of Texas volunteered for a pilot program. Three faculty members and eight students beginning the senior year were selected. In preliminary consultations at Brookhaven between visiting faculty and Brookhaven staff, the structure of the program was outlined. Eight sessions of morning ward rounds were scheduled. Basic lectures and demonstrations by the University of Texas faculty were supplemented by special lectures and demonstrations by Brookhaven staff members.

This year a five-week program will again be held, but it will include two or three faculty mem-

bers and three students from each of four medical schools. The University of Texas, University of Southern California, University of Cincinnati, and Cornell University will participate. A week of orientation will again be held. In accordance with suggestions from previous faculty and students, a new formula for laboratory participation by visiting faculty and students will be tried. Exercises planned and supervised by Brookhaven staff will be conducted largely by the visitors with the special facilities and equipment of the Medical Research Center.

For the next several years this endeavor may be viewed partly as an attempt to fill a gap in the medical school curriculum through BNL contacts with medical students (if only a very few). The basic training and orientation of the visiting faculty is important, therefore, so that schools may sooner help to fill the gap. Advanced research instruction will have to be accompanied by some primary education in the fundamentals of nuclear medicine. Later the program may become more intensified along advanced research lines if the students already have had basic experience.

Details for rotation of participating medical schools have not been worked out, but in principle this should be done. Some lectures and symposia may be held at medical schools with Brookhaven staff members participating in order to further dissemination of information about developments in the field of nuclear medicine.

3. Conclaves on nuclear medicine for departmental chairmen of various disciplines in medical schools of the United States and Canada (060101). Drs. L.E. Farr, S.W. Lippincott

Although research is the primary objective of the Medical Department, various aspects of education are inextricably blended into the framework of the investigative program. In this particular effort, the Medical Department is attempting to bring before those concerned with medical education the present status and future areas of exploration in nuclear medicine. Apart from the program devoted to the training of young physicians, research collaborators, and students, a special general educational endeavor is concerned with the chairmen of the departments of the various disciplines in American and Canadian medical schools. Annually a conclave is held; its general purpose is to consider the present and future

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and place of nuclear medicine in each of the lines represented. During the two-day symposium, the medical applications of the atom and the progress of the program are discussed, especially in connection with the large devices producing particles, the instrumentation used in counting them, the application of such equipment to investigative fields of ionizing radiation. The program is designed to give the participants a review of the current status of nuclear medicine, the problems studied to date, and the problems anticipated as the major fields in the future. In March 1961 the fifth conclave in the series on nuclear energy in medicine was held on the theme "Pediatricians, the Child, and Atomic Energy." The program is given below.

SESSION I

Chairman: LEWIS K. DAHL, M.D.
*Chief of Medical Service, Medical Department,
 Brookhaven National Laboratory*

National Laboratory and Associated Universities: GERALD F. TAPE, PH.D., *Deputy Director,
 National Laboratory*

Energy Commission and Its Division of Biological Sciences: CHARLES L. DUNHAM, M.D., *Director,
 Biology and Medicine, Atomic Energy Commission*

Medical Considerations of the Atom:
 - Concepts of Structure and Energy: SAMUEL OSWALD, PH.D., *Senior Scientist, Physics Department,
 Brookhaven National Laboratory*
 - Effects of Radiation at the Cellular and Tissue Level: VICTOR P. BOND, M.D., PH.D., *Senior Scientist,
 Department, Brookhaven National Laboratory*
 - Application of Nuclear Energy to Problems in Medical Research: STUART W. LIPPINCOTT, M.D., *Senior Scientist,
 Medical Department, Brookhaven National Laboratory*

Research Purposes of Special Facilities at Brookhaven National Laboratory. Tours and Demonstrations:
 Research Reactor - ELMER E. STICKLEY, *Senior Scientist, Medical Department*
 Cyclotron - CORNELIUS R. JANSEN, M.B., CH.B., *Associate, Medical Department*; CHARLES P. BARNES, PH.D., *Senior Scientist, Physics Department*
 High Energy Gradient Synchrotron - ERIC B. FORSYTH, *Senior Scientist*; CARL R. FLATAU, B.S.; PAUL MANDEL, B.S.; *the Accelerator Department*

SESSION II

Coordinator: W.A. FINN
 Group Demonstrations and Group Discussions
 at Brookhaven National Laboratory
 Medical Department Scientific Staff

1. Radioactivity Counting Techniques and Types of Devices Available - Scintillation, Proportional, Geiger, and Ionization Chamber Instruments: JOHN L. BATEMAN, M.D., *Medical Associate*; LUDWIG E. FEINENDEGEN, M.D., *Medical Associate*; LAWRENCE V. HANKES, PH.D., *Scientist*
2. Gas Counting Techniques in Metabolic Research: WALTON W. SHREEVE, M.D., PH.D., *Scientist*; ROGER C. DE MEUTTER, M.D., *Medical Associate*
3. *In Vivo* Measurement of Isotopes by Whole-Body Gamma Spectrometer: KANTI R. RAI, M.D., *Medical Associate*; DANIEL N. SLATKIN, M.D., *Medical Associate*
4. Clinical Research at the Medical Reactor: LUCAS Y. YAMAMOTO, M.D., *Medical Associate*; OTHO D. EASTERDAY, PH.D., *Associate Scientist*; WENCESLAO CALVO, M.D., PH.D., *Medical Associate*; PAUL S. PAPAVASILIOU, M.D., *Medical Associate*
5. Radioactive Decontamination Principles and Practices: ROBERT A. LOVE, M.D., *Chief Industrial Physician*
6. Human Bone Marrow and Peripheral Blood Cell Radioautographic Analysis: EUGENE P. CRONKITE, M.D., *Senior Scientist*; HANS COTTIER, M.D., *Medical Associate*; DAVID C. PRICE, M.D., *Medical Associate*; EDGAR A. TONNA, PH.D., *Medical Associate*
7. Hormone Receptor Demonstration by Activation Analysis: ALBERT F. DEBONS, PH.D., *Medical Associate*
8. Electronic Analogue Computer for Tracer Kinetics Interpretations: JAMES S. ROBERTSON, M.D., PH.D., *Senior Scientist*
9. The Facilities in Which Nuclear Medicine Enables Each Patient To Become a Clinical and Basic Science Laboratory: GEORGE C. COTZIAS, M.D., *Senior Scientist*

SESSION III

Completion of Laboratory Demonstrations
 and Group Discussions

SESSION IV

Chairman: HERBERT C. MILLER, M.D.
*Professor and Chairman, Department of Pediatrics,
 University of Kansas School of Medicine, Kansas City, Kans.*

Current Basic and Clinical Investigation
 in Pediatric Research With Radioactive Isotopes

Neutron Capture Therapy in a Child With a Malignant Cerebellar Neoplasm: LEE E. FARR, M.D., *Chairman,
 Medical Department, Brookhaven National Laboratory*

Radiation Exposure in Children Undergoing Diagnostic Studies for Congenital Heart Disease: MADISON SPACH, M.D., *Associate in Pediatrics, Duke University School of Medicine, Durham, N.C.*

Adrenocortical Hormones and Tracer Metals: EDWIN R. HUGHES, M.D., *Medical Associate, Medical Department, Brookhaven National Laboratory*

The Embryological Development of Specific Tissue Immunity: ROBERT L. BRENT, M.D., PH.D., *Clinical Professor of Pediatrics, Jefferson Medical College of Philadelphia, Philadelphia, Pa.*

Erythrocyte Metabolism in the Young Infant: RUTH T. GROSS, M.D., *Associate Professor, Department of Pediatrics, Albert Einstein College of Medicine of Yeshiva University, New York, N.Y.*

The Use of Chromium-51 in the Study of Hemolytic Anemias: WILLIAM KRIVIT, M.D., PH.D., *Associate Professor, Department of Pediatrics, University of Minnesota Medical School, Minneapolis, Minn.*

SESSION V

Chairman: ROBERT A. ALDRICH, M.D.,
*Professor and Chairman, Department of Pediatrics
University of Washington School of Medicine, Seattle, Wash.*

Should the Pediatric Resident Have Training
in the Use of Radioisotopes for Clinical
and Experimental Pediatrics?

NATHAN SMITH, M.D., *Professor and Chairman, Department of Pediatrics, University of Wisconsin Medical School, Madison, Wis.*

WILLIAM M. WALLACE, M.D., *Professor and Chairman, Department of Pediatrics, Western Reserve University School of Medicine, Cleveland, Ohio.*

NORMAN KRETCHMER, M.D., PH.D., *Professor and Chairman, Department of Pediatrics, Stanford University School of Medicine, Stanford, Calif.*

G. RESEARCH HOSPITAL AND INDUSTRIAL MEDICINE CLINIC OPERATIONS

All patients admitted to the Hospital for participation in research endeavors must be referred by their own physicians, who continue to be responsible for them. The function of the staff is to consult with the referring physician concerning procedures best carried out at BNL. The medical profession has been most cooperative in carrying out this type of joint program. The diseases under investigation and treatment are not listed here because of their wide variety, the common factor being suitability for our research program. The appropriateness of any given patient will depend on the status of the project. Therefore, physicians are encouraged to submit data on patients in writing, so that staff members may give adequate consideration to their suitability for study.

During the past fiscal year there were 249 admissions to the Hospital compared with 202 in fiscal 1960. A total of 172 inpatients were admitted in fiscal 1961, compared with 117 in 1960. These data indicate a steady increase in use of the Hospital.

A novel extension of services developed during the past several years shows great promise. In the treatment of a number of conditions, the collaborative procedure most beneficial to a patient has proved to be admission to the Hospital for observation as a research ambulatory patient rather than as an inpatient. Except for special visits of a few hours each, the patient remains in the hospital of origin or at home, under his own physician's care. The administration of isotopes of appropriate radioactivity and half-life insures the safety and mobility of the patient. At stated intervals the patient is examined with necessary scans, counts, and laboratory tests carried out during the course of the day. During the past year, a regular weekly transportation schedule has been maintained between Brookhaven and a metropolitan hospital. A Medical Department Research Collaborator was in charge of the patients in that hospital or at home so that visits could be planned to make maximum use of Brookhaven's facilities. While this type of expansion and study has definite limitations, it provides a means of securing necessary breadth of observations at a cost concomitant with furtherance of the project. During the past year 1443 visits to the Research Ambulatory Clinic were made by 171 patients.

Visits to the Industrial Medicine Clinic during fiscal 1961 increased from 13,650 to 14,353, primarily because of the services of an additional physician. Total x-ray examinations were 2691; of these, 2082 originated in the Industrial Medicine Clinic. The total number during the previous year was 2236.

Routine examinations of employees continue to be made in the whole-body counter to record and observe body burdens of radioactive nuclides, including the naturally occurring radioactive isotopes. Because this heavily shielded facility is in great demand, the scheduled examinations of employees in the whole-body counter have not proceeded as rapidly as planned. Designation this spring of a specified time interval for employee scans should prevent further delays in carrying out the schedule.



The Medical Research Center

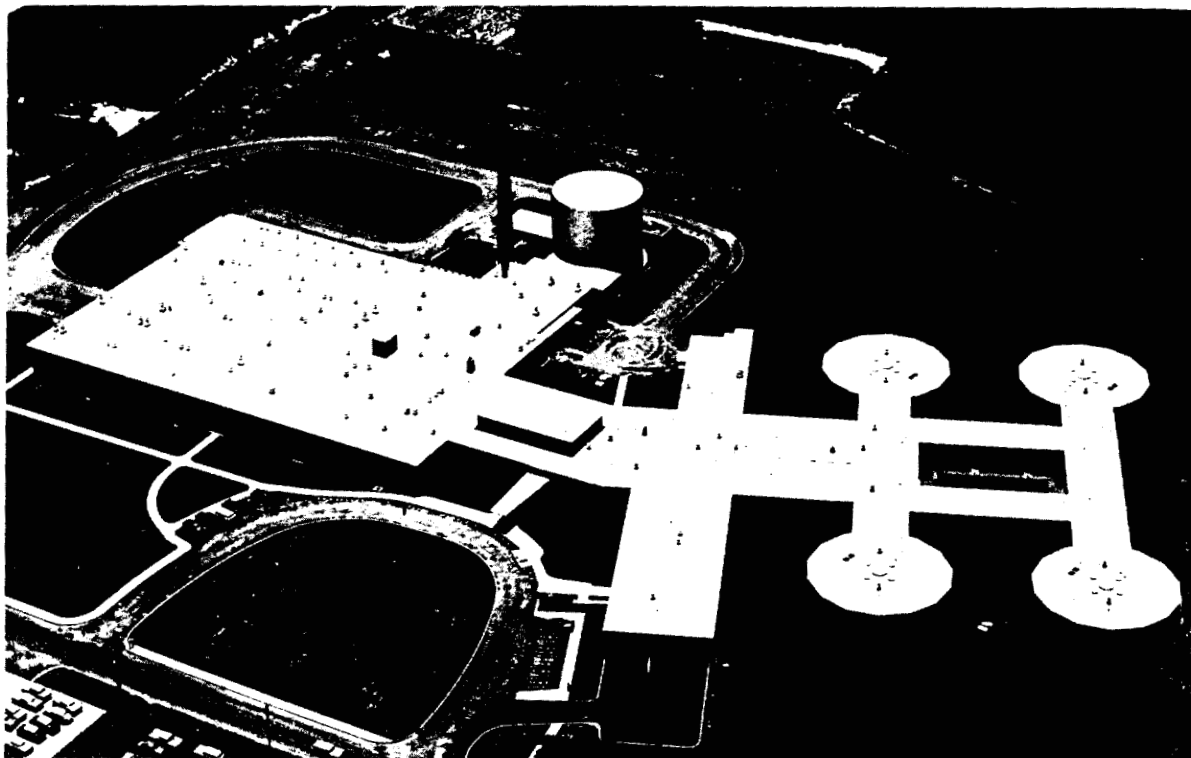
The Medical Research Center is described under two headings: (1) The Physical Plant and (2) Special Devices, including the Medical Research Reactor, the whole-body counter, and the decontamination suite

PHYSICAL PLANT

Although all the special facilities of the Laboratory are available to the scientists of the Medical Department, most of the research activities in the field of nuclear medicine are carried on in the Medical Research Center. Dedicated December 16, 1958, "to the abatement of man's ills through the application of knowledge of nuclear physics to medicine," the new building has been occupied for a year and one-half, and its design has proved to be particularly suited to the research program.

The design criteria for this building were based on three objectives: (1) The rendering of improved professional services to the patient in accordance with the precepts of modern scientific medical usage, thereby assuring the best possible care of the ill. (2) The provision of services and facilities inexpensively adaptable to the changing requirements of scientists engaged in fundamental research. (3) Economical maintenance. The unorthodox design of the building resulted from attempts to meet the functional requirements of the various activities of the Medical Department under a single roof.

The project was made possible by a congressional appropriation of \$6.5 million for the modification of existing utility services and plants and the construction of the Medical Research Reactor and its containment building and a one-story



Aerial view of the Medical Research Center.

ding housing the Hospital, Industrial Medicine Clinic, Laboratory Wing, and Central Administration Service Area.

Oriented to take maximum advantage of the sun and weather conditions, the Hospital is at the west end of the building; it has a 44,000-ft² and a capacity of 48 beds. Each of 4 identical nursing units or pavilions consists of 12 individual patient rooms on the periphery of a 72-ft circle, in the center of which is the nurses' station. This arrangement minimizes the amount of walking by nurses in the course of their duties, and makes each bed visible from the nurses' station.

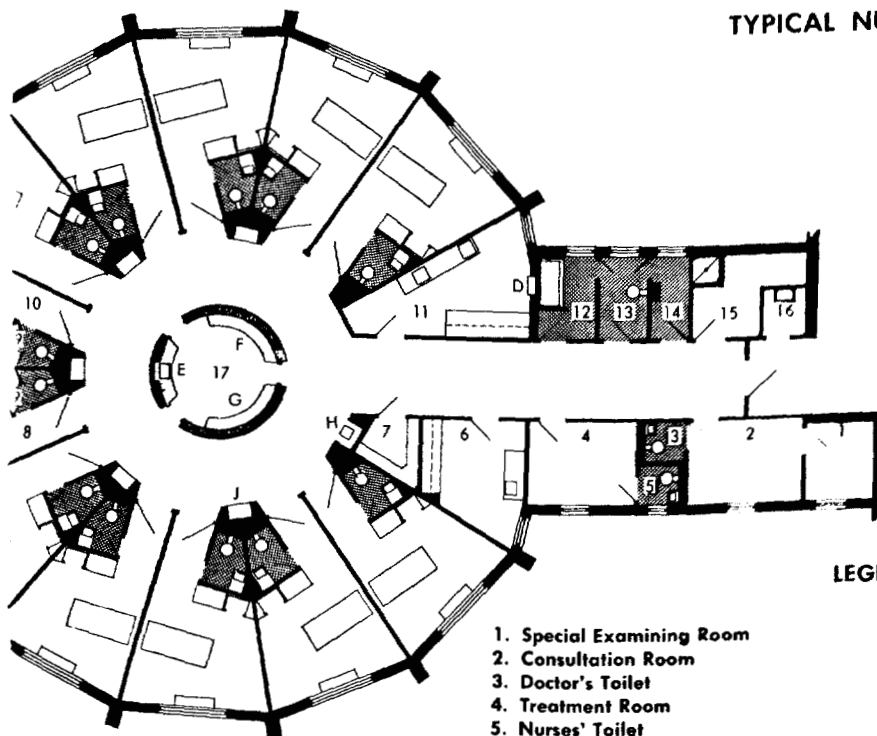
Each patient's room contains a built-in ward-robe and bureau, its own air-conditioning unit, and a private lavatory. An Executone call system permits two-way conversation connects each patient's room with the nursing station, utility room, and treatment room. It is also connected to each of the other three nursing units so that no one unit must be briefly left unattended, the

other nursing units maintain verbal contact with it. Each of the four units also has its own utility, treatment, and consultation rooms, supply and storage space, a bath and shower room, and a special toilet for wheel-chair patients.

For ambulatory patients a sitting room is provided in each pavilion. Arranged around a landscaped patio are separate dayrooms and visiting rooms for each pavilion and a chapel, patients' library, and sun porch for use by all units. Because the average stay is approximately three months, and patients come from all parts of the United States, areas for patient activities are larger and better equipped than those usually provided.

Although the hospital does not offer surgical service, a completely equipped emergency operation unit is located in the ancillary service area. The x-ray suite contains two machines for diagnostic x-rays, one of which has fluorographic attachments including an 8-in. image amplifier for minimizing patient exposure. Pharmacy, central

TYPICAL NURSING UNIT



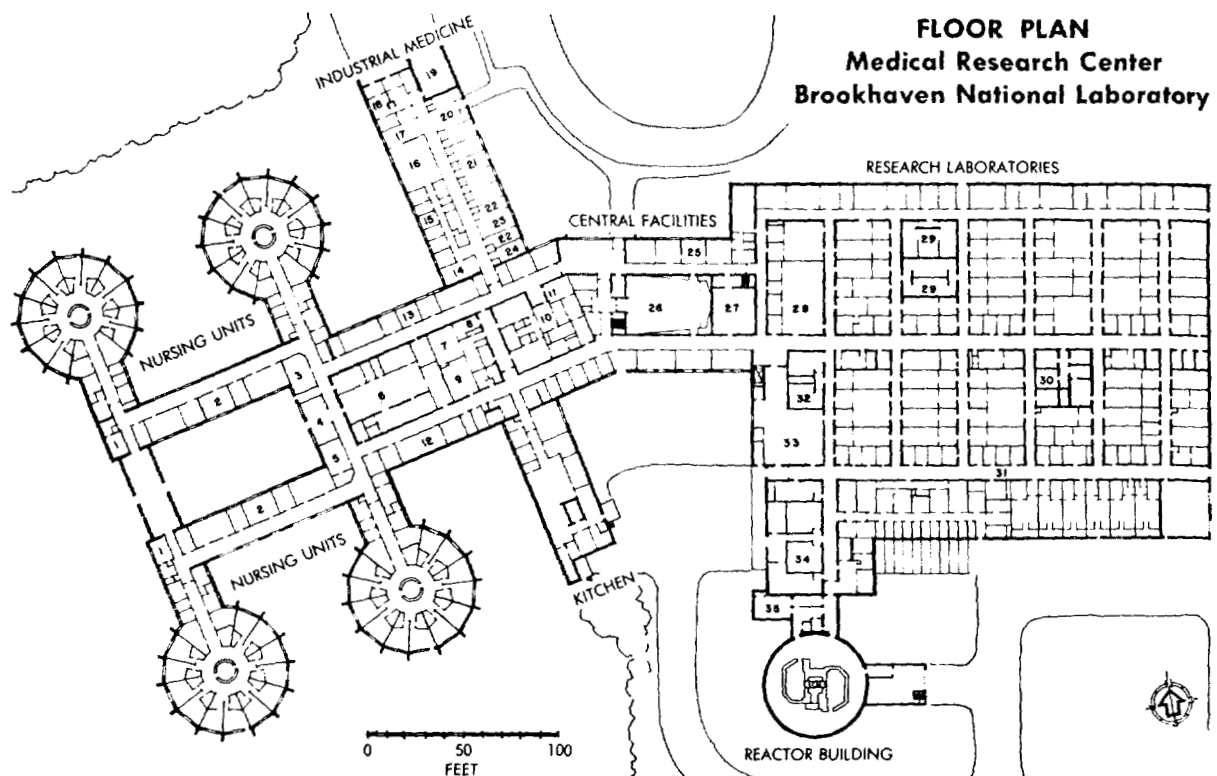
LEGEND

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| 1. Special Examining Room | 11. Utility Room |
| 2. Consultation Room | D. Bed-pan sterilizer |
| 3. Doctor's Toilet | 12. Patients' Bathroom |
| 4. Treatment Room | 13. Toilet (wheel-chair patients) |
| 5. Nurses' Toilet | 14. Patients' Shower Room |
| 6. Pantry | 15. Storage Room |
| 7. Linen | 16. Janitor's Closet |
| 8. Patient's Bedroom (typical) | 17. Nurses' Station |
| A. Heating, ventilating, air conditioning unit | E. Medicine section |
| B. Dresser-wardrobe unit | F. Chart desk |
| 9. Patient's Toilet (typical) | G. Clerical desk |
| 10. Patient's Bedroom (usable as Day Room) | H. Drinking fountain |
| C. Emergency exit | J. Storage closet (typical) |

sterile supply, occupational therapy suite, physical therapy gymnasium, medical photography room, visitors' waiting room, dressing and locker rooms, and a dietary wing complete the hospital service areas.

At the Industrial Medicine Clinic all employees receive pre-employment, termination, and annual physical examinations. Emergency first aid is also provided. A unique and particularly important feature of this wing is the radiation accident suite, used only for treating persons contaminated by radioactive material. The suite contains two identical units of three rooms, one for immediate

showering and scrubbing of the skin, another for examination and first aid treatment, and a radioactively "clean" rest area where the patient may await further processing or discharge. Another unique feature is the whole-body counting room, especially constructed with 6 in. of steel plus a thin layer of copper, cadmium, and lead on four sides and on top and bottom. By means of a sodium iodide crystal within the shielded area and a 100-channel pulse height analyzer attached to recording equipment, the counting of an individual's internally deposited gamma emitters can be completed in a few minutes with minimum back-



LEGEND

RESEARCH HOSPITAL

1. Resident Quarters
2. Day Rooms, Visiting Rooms
3. Hospital Waiting Room
4. Patients' Library
5. Medical Photography
6. Occupational and Physical Therapy
7. Emergency Operating Room
8. Anaesthesia Room
9. Central Sterile Supply
10. X-Ray Suite
11. Pharmacy Suite

12. Hospital Staff Locker Rooms
13. Hospital Offices

INDUSTRIAL MEDICINE

14. Hematology Laboratory
15. Special Testing Rooms
16. Treatment Room
17. Clerical Station
18. Decontamination Suite
19. Ambulance Garage
20. Lobby
21. Examining Rooms
22. Outpatients' Toilet
23. Urinalysis Laboratory
24. Dishwashing Room

CENTRAL FACILITIES

25. Administrative Offices
26. Seminar and Conference Room
27. Medical Library

LABORATORIES

28. Clinical Chemistry Laboratory
29. Sample Counting Rooms
30. Special Temperature Rooms
31. Animal Quarters
32. In vivo Counting Rooms
33. Stockroom
34. Isotope Receiving, Preparation, Administration

REACTOR BUILDING

35. Patient Preparation and Operating Suite

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ound influence. Already the room has been used not only for employees and patients in the hospital, but for area residents who have possibly been subjected to contamination.

The central area of the Medical Research Center contains a lobby, cloakroom, telephone switchboard room, a seminar room with a seating capacity of 130, and a medical library which now contains 3149 books and 4079 bound volumes of journals.

The Laboratory section of the Medical Research Center building provides an area $\approx 58,000$ ft² on the main floor for laboratories, offices, and special service facilities to accommodate a full-time staff of 48 scientists and a number of visiting scientists and research collaborators. A basement under this section provides space for the mechanical and electrical ducts and connections. The layout of these rooms and the final selection of a basic module of 11×11 ft resulted from eight years of experience in modifying the temporary structures previously used by the Medical Department to meet the continually changing needs of the scientific staff.

Each senior scientist with his scientific associate and scientist's assistant is assigned one unit consisting of an 11×22 -ft laboratory and an 11×11 -ft adjoining office, or equivalent space in one of the other laboratories. In addition to this work area, there are available for scheduled use by each scientist many departmental facilities such as controlled temperature rooms with wide ranges of temperature and humidity; cold rooms, one with an adjoining subzero room; humidity-controlled space and instrumentation rooms; veterinary service rooms; areas for special equipment such as centrifuges, electrophoresis apparatus, and x-ray and gamma source rooms; glass-blowing rooms; sample and *in vivo* counting rooms; dark rooms; special rooms for photographic work and tissue culture; and special rooms for receiving, processing, and using radioactive materials too active for general laboratory use. Each of the special departmental facilities is assigned to a scientist or group of scientists responsible for scheduling its use and supervising care of equipment involved. Committees of scientists develop appropriate rules and regulations governing, for example, the use of veterinary services, and the use of radioactive material so that activities in adjacent areas are compatible. Throughout the laboratory area, a laboratory culture module of 3 ft was used to enhance eco-

nomical interchangeability of furniture and equipment. Each Laboratory has 18 ft of installed bench-top surface and wall-hung cabinets, varying underbench cabinets, an underbench refrigerator, and a two-compartment sink. Laboratories have either a 6-ft hood or an additional 9-ft workbench area, and all have from 12 to 16 ft of free wall area for special equipment such as centrifuges, ovens, etc., as may be required. A large stock and receiving room is located in the center of the building.

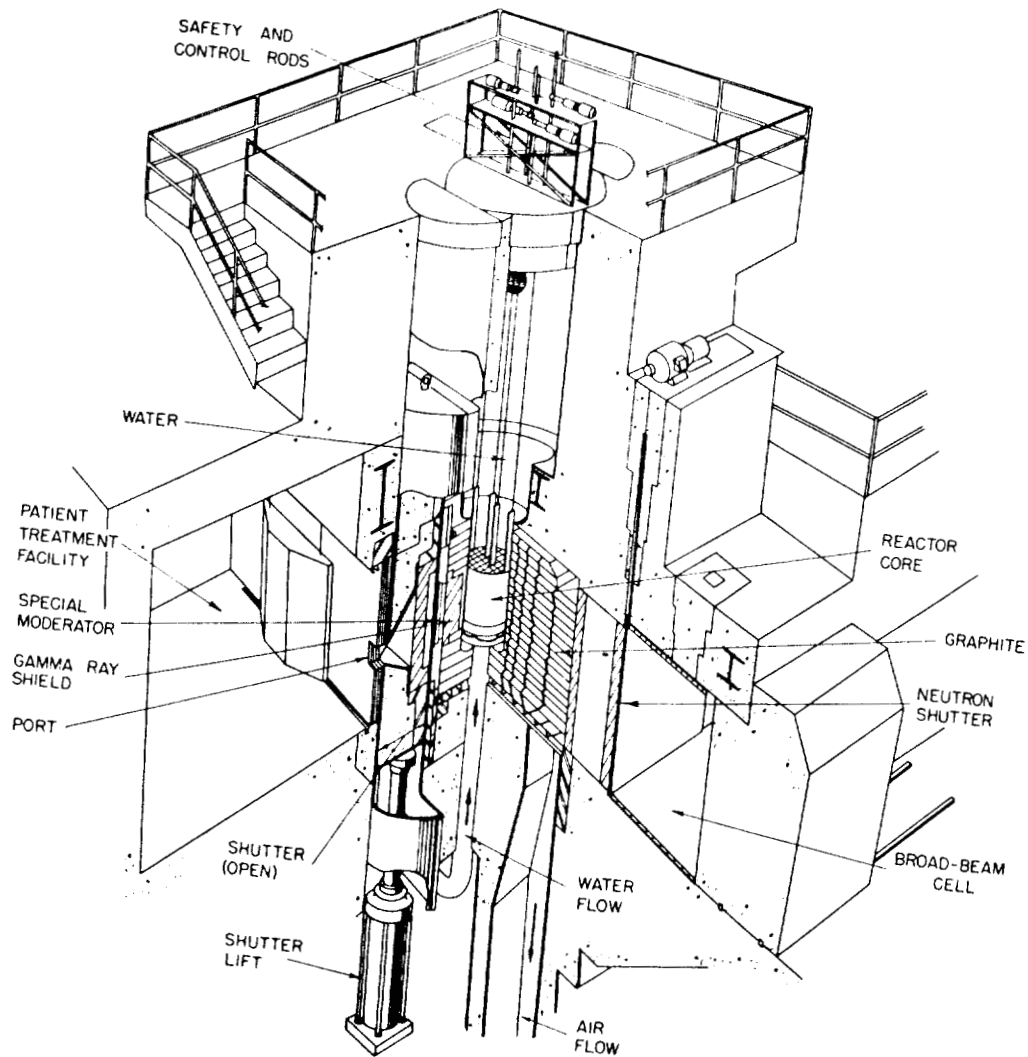
SPECIAL DEVICES

Three unique features of the Medical Research Center are here described, the Medical Research Reactor, the whole-body counter, and the decontamination suite or personnel decontamination units.

The Medical Research Reactor

The Medical Research Reactor (MRR) is one of the major experimental devices of the Medical Department; it has been built as an integral part of the laboratory and hospital in Brookhaven's Medical Research Center. This reactor was planned jointly by staff members of the Medical Department and scientific personnel from the Nuclear Engineering Department and Reactor Operations Division. It was constructed for the sole purpose of exploring the possible applications of nuclear reactors in the study of man and the diseases of man; each salient feature of its engineering and design was considered in relation to its use for therapy or diagnosis, in studies leading to these ends, or in the advancement of basic medical science. (A detailed description of the MRR may be found in BNL 600, by J.B. Godel.)

The criteria of specific orientation toward medical problems satisfied by the MRR include: (1) maximum clinical convenience of the surrounding arrangements and service features, including the contiguous hospital; (2) control of program schedule and operation, both as to time and power level, directly on the basis of demands of the medical research program; (3) basic design and flexibility of the core and reflector to provide the required quantity and quality of radiations in desirably short time intervals; (4) shielding, shutters, and other radiation control elements for adequate delivery and limitation of radiation fields in the treatment vaults; and (5) provision of isotope pro-



Cutaway diagram of the Medical Research Reactor.

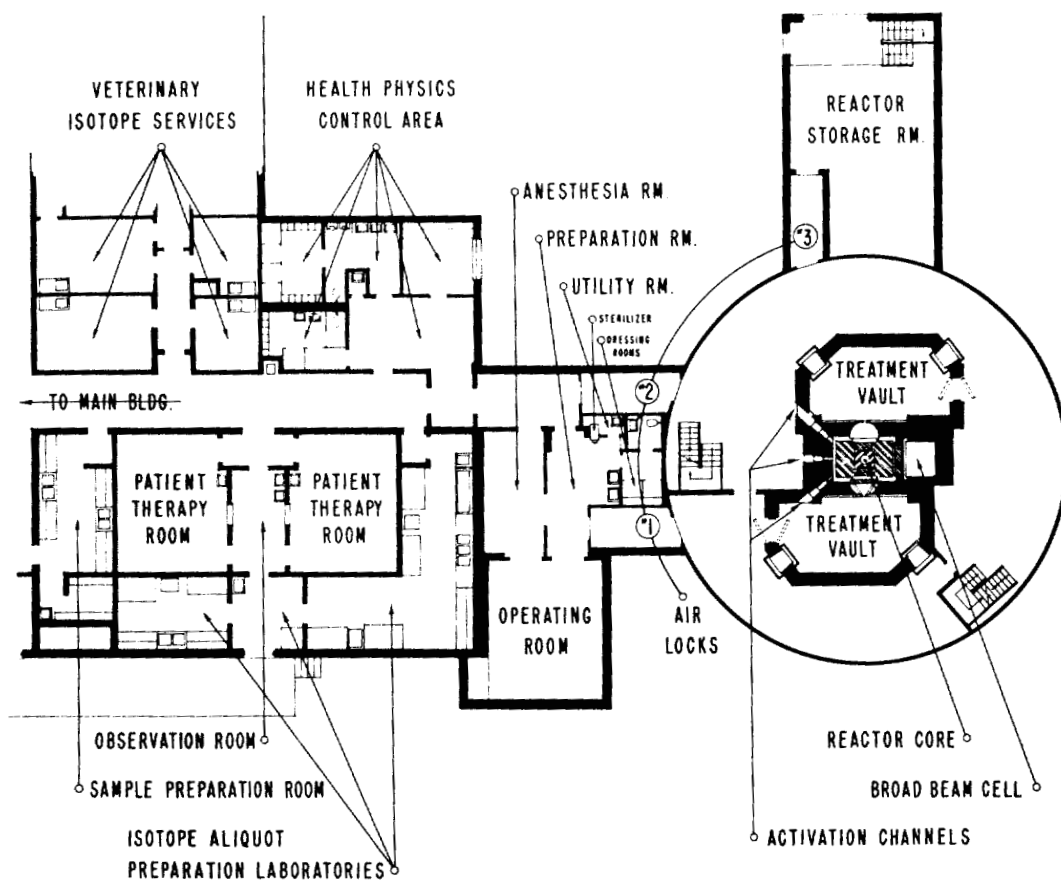
duction tubes for the instant use of short-lived radioactive materials *in vivo* or for activation analysis of biological materials. Since the goals are subject to continual change and modification, as indicated by the course of experimental results, eventual advance to entirely new concepts may well be expected.

Many of these applications could be partially realized by providing special arrangements and equipment as appurtenances on a general research reactor. Indeed, the background of experience which underlies the development of this first medical research reactor is founded upon eight years of such work with Brookhaven's original general purpose research reactor and its staff. Neverthe-

less, the limitations met in pursuing these pioneering studies in nuclear medicine have in themselves served to establish the criteria mentioned above.

In approaching these criteria, the reactor and its component parts are as standardized as possible, making full use of well-established nuclear engineering principles and technology. The fuel elements are of the standard Bulk Shielding Reactor design, the electronic control circuitry was developed and tested in the first Brookhaven reactor, and the safety features were patterned after those used in the reactor exponential testing laboratory. Thus the planning, design, and testing stages of the MRR project called for the specialized talents of the Nuclear Engineering Department, the Re-

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Floor plan of the Medical Research Reactor and adjacent facilities.

rations Division, and many other groups Brookhaven staff. Their experience and operation in the earlier medical research the large research reactor have resulted specialized medical research reactor design lead to an extensive range of applications in a unique field. The day-to-day operation and maintenance of the MRR remains the responsibility of the Reactor Operations Division, and in program planning, the design of experiments for the actual utilization of the various facilities under complete control of the Medical Research Reactor.

The design of this reactor was fully studied and every phase of its preliminary design was completed. Test series were made with each of the various assemblies, successive approximations to the final design. Advantage was taken of the various experimental assemblies to compare a variety of different arrangements for the reflector and control and directing elements along the

path of the neutron stream. This work and subsequent investigations during the first year of operation provided the present optimum configuration, pointing to the areas of greatest sensitivity with regard to capture gamma-ray production for better control of this factor. This continuous improvement makes it obvious that the MRR design has not yet reached a final optimum state, and indeed a pattern of further advance through progress in design and technology is anticipated.

The Brookhaven Medical Research Reactor had originally a nominal design power level of 1 Mw for continuous operation. Subsequent to the initial testing program, the AEC Reactor Safeguards Committee granted permission for routine operation at levels as high as 3 Mw. After a year of experimental use, permission was granted to operate at 5 Mw for periods as long as 10 min, when especially scheduled. The limitation on excess reactivity was raised from 1.0% to 3.0%; typical operation is at 1.85%. The enriched U^{235} used in 18 fuel

elements totals ≈ 2.52 kg. The core is cooled by natural water. Neutron moderation in the core is provided by the water and by graphite fillers. The moderator and reflector extend beyond the core container as an air-cooled graphite layer one yard thick. In the direction of neutron flow toward the treatment vaults the reflector is fitted with special sections to control radiation quality. To reach the irradiation port, the neutrons must pass through a succession of graphite, heavy water, and bismuth sections, in part surrounded by thick plastic reflector surfaces, with an outer boundary of boral and heavy concrete to prevent radiation leakage into protected areas.

Previous experience had demonstrated that the improvement most needed was an increase in the external neutron flux for the dual purpose of delivering larger quantities of neutrons in a shorter period of time. In addition, the need for enlarging

arately to learn their distinctive contributions to the total complex of radiation effects. This is a new approach to a field that is difficult but important; its purpose is to improve the understanding and management of the organic damage that will be a medical problem in future radiation incidents.

Exposure holes and tubes leading inside the reactor make possible investigation of such matters as the induction of radiation effects in biological materials and the tagging of biological materials by the neutron activation principle or by radiation catalysis. Certain of these experimental sites are amenable to research on the physical and geometrical factors that control the penetration of the several radiations and their patterns of energy deposition in tissues.

The control room and the electronics instrumentation for the MRR are located on a mezzanine overlooking the entire reactor research area.

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Whole-Body Counter: Gamma Spectroscopy in Clinical Medicine

A whole-body counting system has been in operation at BNL since May 1959. The design is based on a "portable" prototype built in 1958 to permit direct measurement of internally deposited gamma-emitting fission products in the Japanese people exposed to radioactive fallout from the March 1954 nuclear weapons test. This instrument was based on the system designed by E. Miller and built at Argonne National Laboratory.

The whole-body counting system is designed to detect very low concentrations of internally deposited gamma-emitting material and is built around a scintillation spectrometer. The counter is a NaI (Tl-activated) 4×8-in. crystal and is connected to a 100-channel pulse height analyzer. The crystal detector is located in a 6×7×9-ft room constructed of 6-in. steel and lined with lead, cadmium, and copper for shielding against the low energy components of background radiation. The heavy shielding effectively reduces gamma radiation to the detector from both outside and building materials and increases the signal-to-noise ratio for the system.

The scintillation counter utilizes the fact that certain substances emit a short-lived pulse of light when excited by energy from gamma rays.

This scintillation is detected by a photomultiplier tube which converts it to electrical energy. The resulting electrical pulse is amplified and sent to a pulse height discriminator. The output pulse produced is then proportional to the energy from the original incident gamma-ray. A 100-channel analyzer sorts the pulses according to height and thus produces a spectrum of energy. A particular element may then be identified by its distinctive energy spectrum. The number of pulses in any channel of the spectrum provides a quantitative measure of the amount of the radionuclide present.

Applications of the whole-body counting system can be generally grouped into two classifications: environmental studies and clinical studies.

Because of natural radioactivities and of fission products from nuclear weapons testing, every person has deposited in his tissues small amounts of radioactive materials. The levels of these concentrations are rising as the radioactive debris from the stratosphere returns to earth. During this period, when the body burdens of fission products have increased but are still low, it is absolutely essential that the base lines, that is, the average amounts of internally deposited radioelements, be determined for the population, particularly with respect to age and geographic location. Large numbers of persons must be checked in order to provide an adequate sampling for valid statistical analysis. Once such base lines are determined, it will then be possible, by continued measurement, to detect any significant increase in the deposition of fission products associated with increased use of atomic energy. Whole-body counting is an excellent way to detect and evaluate world-wide fallout contamination. The fission product Cs^{137} is very widespread, and, as a gamma emitter, is readily detected by the whole-body counter. This element provides an index of the level of human internal contamination.

Persons who have received radioactive materials in the course of medical treatment constitute another group of interest. For example, a substantial number of people have been treated with thorotrast (thorium dioxide) as an x-ray contrast medium. Over a long period of time, the continued internal radiation from this material may produce carcinogenesis. A study of persons known to have been treated with this material will yield valuable data on the relation between dose and observed clinical effects.

Another valuable use of the scintillation counter derives from its ability to measure neutron-induced gamma activity in people therapeutically or accidentally exposed to neutron irradiation. By proper calibration, it is possible to quantitate the neutron dose to which an individual has been exposed. Studies along this line are under way as part of the neutron therapy research program.

A slight modification to the system – the addition of a collimator – makes it possible to localize the isotopes in a particular organ such as the lung. The lung is of interest as the focus of deposition in cases involving inhalation of a radioactive aerosol, particularly insoluble aerosols that may be retained in the lung for long periods of time. Since spectrometric properties permit identification of

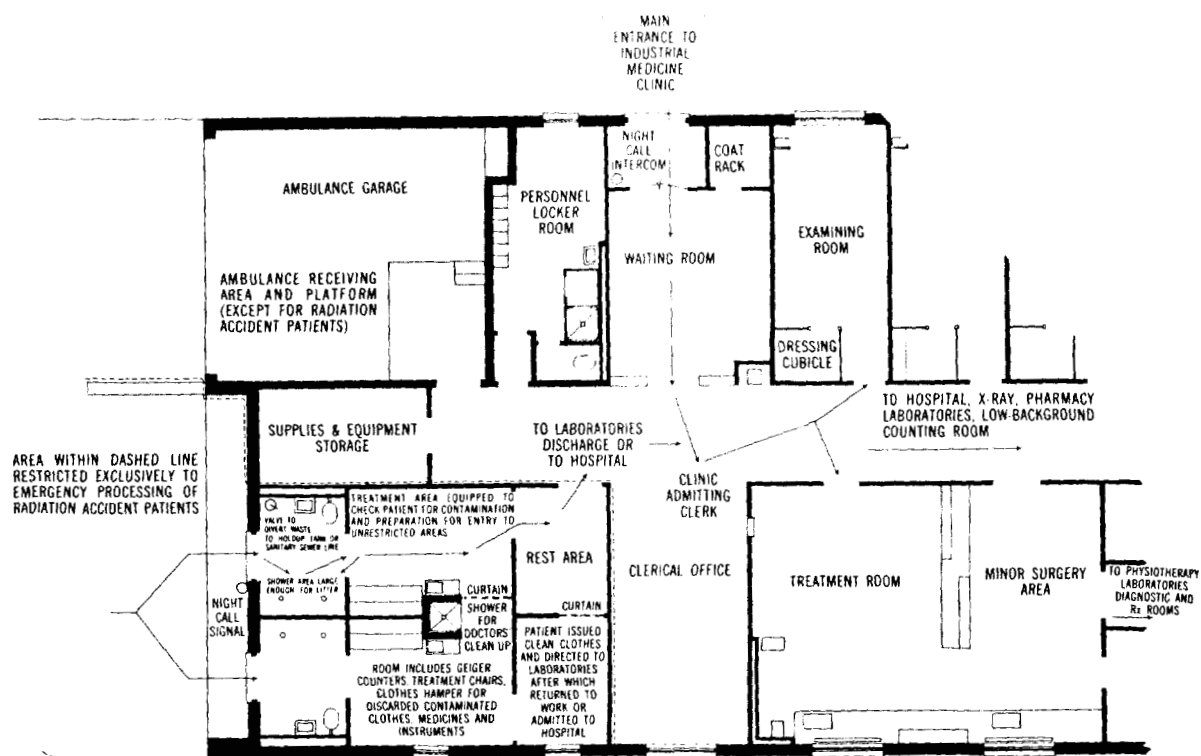


Diagram of personnel decontamination unit at Brookhaven National Laboratory.

primary energy quanta as distinguished from scattered rays, the collimated NaI(Tl) crystal is obviously the detector to determine the site of localization of very small amounts of radioactive material in the intact body.

The high quantum counting efficiency for gamma radiation makes this scintillation counter valuable for applications involving small amounts of radioactively labeled material. It is particularly suitable for administration to patients for metabolism studies. The fact that some chemical compounds concentrate in certain tissues may also be exploited. Ultrasensitive gamma detection equipment has many valuable clinical applications, particularly in the study of very slow metabolic processes in the human body. The direct *in vivo* measurement eliminates the tedious procedures of radiochemical analyses of the excreta of large numbers of patients for the determination of turnover rates of particular elements. Accurate data can be obtained on clearance rates for a particular organ, as well as elimination rates from the whole body. For example, accurate measurements of the biological turnover of fission products are needed

in order to establish or check the MPC values set up by the ICRP, which in most cases are extrapolations from animal data. Clinical studies to date have produced results at variance with the published data.

The advantage of a system with the sensitivity and the heavy shielding provided by the whole-body counting system lies in the high signal-to-noise ratio which affords the opportunity of using very low levels of tracer activity, of the order of $1 \mu\text{C}$ with a counting time of only 10 min. This is of obvious value in studying various physiological problems in patients, particularly children, as well as in long-term studies, where administration of large amounts of tracers is undesirable. Some of the problems being studied involve the determination of the rate of albumin and globulin degradation in various clinical studies with I^{131} -labeled albumin and globulin; electrolyte balance studies with K^{42} , Na^{22} and Na^{24} ; and kinetic bone studies in normal persons and patients with various bone dyscrasias, with Sr^{85} , Ca^{47} and Zn^{65} . It is also quite feasible to conduct multiple tracer experiments with this instrument with little more effort than is

ired for a single tracer experiment. A long-study is in progress to determine simultaneously the biological turnover of Co^{60} -labeled vitamin B_{12} administered parenterally and Co^{58} -labeled vitamin B_{12} administered orally.

Decontamination Units*

an installation operating large nuclear reactors such as Brookhaven National Laboratory, where there is a potential danger of contamination of many persons with radioactive materials, it is essential to have the means of coping with a radioactive contaminating accident. As part of the method of meeting such a problem, if it should arise, a decontamination suite was incorporated in the construction of our new medical clinic center. It is located at the far end of the wing with a separate entrance so that contaminated persons do not enter through the regular door. This reduces the chances of spread of contamination to the clinic proper or the hospital where such contamination might severely restrict or prohibit normal operations. The purpose of the decontamination suite is to reduce contamination capable of being considered inconsequential or manageable quantities so that necessary medical and internal decontamination procedures will not be hampered.

The decontamination suite consists of two identical units plus a separate shower for use by personnel who may have to wash after caring for contaminated patients. The duplication permits the women to use the unit while the men use the other or alternatively provides twice the capacity. If only a few patients and a large number of men are involved, as the women have been processed, both units become available for decontamination of the patients. Access to each unit is directly from the outside to a room in which the fixed equipment consists of two showers, a sink, and a toilet. The walls of the room are covered with an impervious plastic coating to prevent contaminating materials from soaking in and to facilitate cleaning if contamination of the walls occurs.

Other than separate shower stalls, the shower is completely open without a partition between the two shower heads, which project out from opposite walls seven feet apart at such an angle that the sprays, which can be varied in intensity and size of the streams, overlap at the level of a patient on a litter. This makes it possible to roll a seriously injured or unconscious patient on a litter under the shower heads where he can receive surface decontamination. A Stokes stretcher is quite suitable.

Under ordinary circumstances the waste water from the showers flows directly into the main sewer system. If the anticipated radiation level of the waste water is high, the flow can be diverted to a hold-up tank by means of a valve situated in the shower room. After the decontamination procedure, the water in the hold-up tank may be released into the main sewer system if the radiation level is low, or it may be stored for decay if the contaminating materials have a short half life, or it may be pumped into a tank truck and processed by some other means to remove the radioactive elements or to concentrate them to a smaller volume for future disposal.

Each unit contains a clothes tree and a large radiation clothes hamper where contaminated clothes can be deposited. The various items can at a later time be separated and handled in various ways according to the amount and type of substances they are contaminated with. If the clothing is contaminated with an element that has a short half life, it may be stored until the level has fallen and then the clothes may be returned. Clothes with longer-lived isotopes may be washed in the hot laundry and returned if, after cleaning, the radiation level is below the acceptable levels. Some articles that are heavily contaminated and that might be difficult to decontaminate, such as leather shoes, may have to be disposed of directly with the hot waste materials.

An attempt is made to keep contaminated wastes separate from noncontaminated wastes by having separate receptacles for the two types of materials. Paper towels used by a contaminated person are discarded in the container marked for radioactive wastes, while paper towels used by a noncontaminated person working in the room are thrown in the ordinary waste disposal can. This cuts down the volume of material that has to be screened for radiation levels before it is disposed of by appropriate means.

The second room of the suite is primarily a treatment room where patients are treated after all the loose external contaminating materials have been removed by the showers or by scrubbing in the sink, if only the hands are contaminated. Here simple débridement and wound irri-

gation No. 312.

gation can be carried out, dressings applied, and other such procedures done.

The fixed equipment in this room consists of a clean sink, which is kept free of contamination, and cabinets for storage of supplies and instruments. The movable equipment consists of such things as radiation detection counters, a table, a dressing chair, and a high chair used in nasal irrigations after inhalation of contaminating materials.

The cabinets are stocked with such things as solutions for skin decontamination, nasal catheters and syringes for nasal irrigation, instruments for minor surgical procedures, hair clippers for removal of hair contaminated with materials that will not wash out, rubber aprons and gloves for use by personnel who may have to decontaminate unconscious or seriously injured patients, paper slippers, and clean coveralls to issue to subjects after completion of the external decontamination procedures.

The third room contains a litter and a cot and serves as a dressing room. Here the patient is issued clean coveralls and paper slippers, which he puts on prior to leaving through the door into the clinic corridor. He may now be directed or taken to any of the medical department facilities such as the low-level counting room, the room where

blood is drawn for various laboratory examinations, the x-ray department, or, if necessary one of the rooms in the hospital for admission.

The flow of traffic through the unit is in one direction from the contaminated to the clean section. The patient enters the shower room directly from the outside and proceeds through the unit without retracing his steps over contaminated regions until he steps through the door from the third room into the clinic, at which time he should be free of all loose, external, nonfixed radioactive materials.

With the increasing use of radioactive materials and the possibility of contamination in case of war, serious thought should be given to having such a unit or modification of it in our general hospitals. Most emergency rooms are not specifically equipped to handle this type of problem. Without some thought as to how such an incident would be handled, radiation contamination could easily be spread throughout a hospital. While existing facilities can readily be adapted to provide such a unit, it is more difficult to have personnel specially trained and then maintained at a high pitch of efficiency by drill and practice in minor accidents.

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